Second Edition

PHARMACOLOGY FOR AND PHYSIOLOGY FOR ANESTHESIA

FOUNDATIONS AND CLINICAL APPLICATION

Hugh C. Hemmings, Jr.
Talmage D. Egan

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To my wife, Katherine, and daughter, Emma,
whose support and understanding were essential to the
completion of this book; and to my mentors and students
who have taught me so much and
from whom I continue to learn.

H.C. Hemmings, Jr.

To my wife, Julie, and our children, James, Adam,
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you are the wind beneath my wings.

T.D. Egan

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Preface to the Second Edition

We are delighted to present the updated and revised Second Edition of *Pharmacology and Physiology for Anesthesia: Foundations and Clinical Application.* Like its predecessor, this new edition's primary aim is to bridge the gap between introductory texts and comprehensive reference books by providing an in-depth overview of pharmacology and physiology for anesthesiology, intensive care, and pain medicine specialists, whether in training or practicing. The topics are chosen to cover fundamentals included in training and recertification examinations by bridging scientific principles and clinical practice.

The Second Edition has been thoroughly updated. Each revised chapter includes the latest advances in clinical science along with relevant, novel basic science discoveries. Hundreds of new segments, figures, and references have been added to provide essential information for trainees and practicing anesthetists alike.

This thoroughly revised edition includes extensive new content. New chapters on special populations (e.g., anesthetic pharmacology in obesity, geriatrics, and pediatrics), oral and non-intravenous opioids, thermoregulation, physiology and pharmacology of obstetric anesthesia, chemotherapeutic and immunosuppressive drugs, and surgical infection and antimicrobial drugs were commissioned and written by recognized experts in these fields.

Two entirely new features have been incorporated into the Second Edition to provide essential basic information in relevant areas of physics, anatomy, and imaging. The Physics sections, edited by Dr. Kai Kuck, review essential physics and engineering concepts important in anesthesia practice. The Anatomy and Imaging sections, edited by Dr. Jeffrey D. Swenson, outline practical anatomic and imaging concepts that are now indispensable in modern anesthesia. Interspersed throughout the book, these new sections are beautifully and copiously illustrated.

The Second Edition also benefits from all the enhancements that are part of the "Expert Consult" platform at Elsevier, including the "eBook" feature that enables portability and searchability on most common electronic devices; the book's full text and all the other assets are available anywhere on your mobile device. Shareable social media features also augment the Second Edition's utility.

We are grateful to the authors for their contributions to the Second Edition; their high-level knowledge and expertise are evident throughout. We also express our appreciation to the dedicated professionals at Elsevier; special thanks are due to Sarah Barth, William Schmitt, Joan Ryan, and Sharon Corell for their collective experience and hard work. We are confident that the newly updated and expanded *Pharmacology and Physiology for Anesthesia: Foundations and Clinical Application* will build your understanding of the fundamental concepts underpinning anesthesia practice and thereby improve your ability to deliver outstanding care to your patients.

Hugh C. Hemmings, Jr.
Talmage D. Egan

Excerpts from the Preface to the First Edition

The successful practice of the art of anesthesia, critical care, and pain medicine demands a sound understanding of core scientific concepts founded in physiology and pharmacology. The importance of physiology and pharmacology to anesthesiology is recognized in postgraduate anesthesia training programs and certification examinations worldwide because a thorough understanding of these disciplines is essential for graduation, certification, and successful clinical practice. Although this scientific foundation is available from a number of sources, the necessary level of detail is often insufficient in introductory texts and perhaps too esoteric in specialized monographs targeted to academics. The goal of *Pharmacology and Physiology for Anesthesia: Foundations and Clinical Application* is to bridge this gap between introductory texts and comprehensive reference books by providing a detailed overview of these fundamental subject areas for anesthesiologists, intensivists, and pain practitioners, both in training and in practice.

Pharmacology and Physiology for Anesthesia: Foundations and Clinical Application is intended to be a definitive source for in-depth coverage of these core basic and clinical sciences in a single text. Focusing on physiology, pharmacology, and molecular-cellular biology, the text's approach is integrated and systems oriented, avoiding the artificial boundaries between the basic and clinical sciences. The book is divided into eight sections: Basic Principles of Pharmacology; Nervous System; Cardiovascular System; Pulmonary System; Gastrointestinal and Endocrine Systems; Immunity and Infection; Fluid, Electrolyte, and Hematologic Homeostasis; and Blood and Hemostasis.

Recognizing that no single author possesses the necessary breadth and depth of understanding in all the core subject areas, each chapter is authored by an expert representing many of the finest institutions of North America, the United Kingdom, Europe, and Asia. This allows an international presentation of current anesthesia science presented by recognized experts at the cutting edge of anesthesia research and education.

A number of features significantly enhance the use of *Pharmacology and Physiology for Anesthesia: Foundations and Clinical Application* as a tool for learning, teaching, and review. These include access to the online text via the Expert Consult platform, including a complete, downloadable image bank. Recognizing that graphics are often the most expressive and effective way of conveying concepts, full-color illustrations facilitate use of the book as a learning aid and make it enjoyable to read. The text is copiously illustrated; all figures having been drawn or redrawn by the superb artists at Elsevier.

Each chapter stresses the scientific principles necessary for the understanding and management of various situations encountered in anesthesia practice. Detailed explanations of clinical techniques are avoided because this information is available in many comprehensive and subspecialty clinical anesthesia texts and handbooks. This book is not intended to provide a detailed review of specialized research areas for the scientist. Rather, the fundamental information necessary to understand essential concepts and principles is stressed, and basic science concepts are related to relevant clinical anesthesia applications. Chapters are self-contained with minimal repetition and include a short list of key points for review and key references to stimulate further exploration of interesting topics. The expertise and hard work of the contributing authors is evident in the quality of each chapter. We are confident that *Pharmacology and Physiology for Anesthesia: Foundations and Clinical Application* will help solidify your understanding of core anesthesia topics and thereby improve the safety and effectiveness of the care you render to your patients.

Hugh C. Hemmings, Jr.
Talmage D. Egan

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PHARMACOLOGY AND PHYSIOLOGY FOR ANESTHESIA

FOUNDATIONS AND CLINICAL APPLICATION

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1

Mechanisms of Drug Action

ALEX PROEKT AND HUGH C. HEMMINGS, JR.

CHAPTER OUTLINE

The Receptor Concept
- Historical Beginnings
- Modern Development

Pharmacodynamics
- Drug Binding
  - *From Drug Binding to Physiologic Effect*
  - *Efficacy*
- Full Agonists, Partial Agonists, and Inverse Agonists
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- Identification of Drug Targets
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- Cell Signaling
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Novel Antidotes

Understanding the basic principles of pharmacology is fundamental to the practice of medicine in general, but is perhaps most relevant to the practice of anesthesiology. It is now widely accepted that cells contain a host of specific receptors that mediate the medicinal properties of drugs. Although the use of plant-derived medicinal compounds dates back to antiquity, the mechanisms by which these drugs act to modify disease processes remained mysterious until relatively recently. As late as 1964, de Jong wrote, "To most of the modern pharmacologists the receptor is like a beautiful but remote lady. He has written her many a letter and quite often she has answered the letters. From these answers the pharmacologist has built himself an image of this fair lady. He cannot, however, truly, claim ever to have seen her, although one day he may do so."[1]

This chapter briefly reviews the history of the receptor concept from the abstract notion alluded to by de Jong to the modern view of receptors as specific, identifiable cellular macromolecules to which drugs must bind in order to initiate their effects. Also introduced and defined are basic concepts that describe drug-receptor interactions such as affinity, efficacy, specificity, agonism, antagonism, and the dose-response curve. Finally, the evolving discipline of molecular pharmacology is discussed as it relates to modern drug development. Mathematical representations of the concepts are included in the form of equations for the reader seeking quantitative understanding, although the explanations of key concepts in the text are intended to be understood without reliance on mathematics.

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The Receptor Concept

Historical Beginnings

The specificity of drugs for a particular disease has been known since at least the 17th century. The best known example of this is the efficacy of Peruvian bark, the predecessor of quinine, in the treatment of malaria.[2] Sobernheim (1803–1846) first applied the concept of selective affinity to explain the apparent specificity of drugs. He believed, for example, that strychnine had an affinity for spinal cord while digitalis had affinity for the heart.[1] Blake (1814–1893) first demonstrated that inorganic compounds with similar macroscopic crystalline structures exert similar effects when administered intravenously.[3] This triggered a vigorous scientific debate at the turn of the 20th century regarding whether it was the chemical structure or physical properties of drugs that endow them with medicinal properties.[4] This debate was particularly relevant for the theories of actions of general anesthetics because it was believed until recently that their relatively simple and diverse chemical structures precluded the possibility of a specific drug-receptor interaction.[5]

The term *receptor* was first coined in 1900 by Ehrlich (1854–1915) as a replacement for his original term "side chain" *(Seitenkette)* that he used to explain the specificity of the antibacterial actions of antitoxins (antibodies).[6] Ehrlich did not originally believe that specific receptors existed for small molecules such as medicinal compounds because they could easily be washed out of the body by solvents. This belief was at odds with the remarkable experimental findings of Langley (1852–1925), who was investigating whether the origin of the automatic activity of the heart resided in the heart muscle itself or was imposed on the heart by the nervous system. He demonstrated that the effect of the plant-derived drug jabonardi—bradycardia—occurred even when innervation was blocked, and that this effect was reversed by applying atropine directly to the heart. He went on to show that the relative abundance of the agonist (jabonardi) over its antagonist (atropine) determined the overall physiologic effect. This observation led Langley to

Abstract

Understanding the basic principles of pharmacology is fundamental to the practice of medicine in general, but it is perhaps most relevant to the practice of anesthesiology. It is now widely accepted that cells contain a host of specific receptors that mediate the medicinal properties of drugs. Although the use of plant-derived medicinal compounds dates back to antiquity, the mechanisms by which these drugs act to modify disease processes remained mysterious until relatively recently. As late as 1964, de Jong wrote, "To most of the modern pharmacologists the receptor is like a beautiful but remote lady. He has written her many a letter and quite often she has answered the letters. From these answers the pharmacologist has built himself an image of this fair lady. He cannot, however, truly, claim ever to have seen her, although one day he may do so."[1] This chapter briefly reviews the history of the receptor concept from the abstract notion alluded to by de Jong to the modern view of receptors as specific, identifiable cellular macromolecules to which drugs must bind to initiate their effects. Also introduced and defined are basic concepts that describe drug-receptor interactions such as affinity, efficacy, specificity, agonism, antagonism, and the dose-response curve. Finally, the evolving discipline of molecular pharmacology is discussed as it relates to modern drug development. Mathematic representations of the concepts are included in the form of equations for the reader seeking quantitative understanding, although the explanations of key concepts in the text are intended to be understood without reliance on mathematics.

Keywords

receptor
agonist
affinity
efficacy
potency
antagonist
signal transduction

propose that competition of the two drugs for binding to the same substance explained their antagonistic effects on the heart rate. However, the key experiment that led Langley to formulate his receptor concept came 30 years later in 1905, when he showed that the contractile effect of nicotine on skeletal muscle can be antagonized by curare. From the observation that even after application of curare the relaxed muscle contracted following direct application of electric current, he concluded that neither curare nor nicotine acted directly on the contractile machinery. Instead, Langley argued that the drugs interacted with a "receptive substance" that was essential for the initiation of the physiologic actions of the drug.[7]

Modern Development

Langley's concept of "receptive substance" forms the basis of the modern concept of a receptor, but it was not accepted without debate. It took years of work by Clark (1885–1941) and Gaddum (1900–1965), among others, to solidify the receptor concept. Clark demonstrated that the relationship between drug concentration and the physiologic response formed a hyperbolic relationship (the familiar sigmoidal dose-response curve; see later). Clark concluded that the relationship arose from equilibration between the drug and its receptor and argued that the effect was directly proportional to the number of drug-receptor complexes.[8] Ariëns (1918–2002) elaborated on Clark's theory and showed that the *affinity* of the drug for the receptor is distinct from the ability of the drug-receptor complex to elicit a physiologic response.[9] This distinction was further elaborated by Stephenson (1925–2004), who mathematically defined and quantified *efficacy*—the propensity of a drug to elicit a response.[10] Through his investigation of sympathomimetic compounds, Ahlquist (1914–1983) found that responses in various tissues occurred with two distinct orders of potency. This led him to propose multiple types of receptors for the same drug (α- and β-adrenergic receptors in this case), and the concept of *specificity,* which was finally published in 1948 after multiple rejections.[11]

Ahlquist's work is the foundation of modern pharmacology, including the development of the first and still widely used receptor-specific drugs—β-blockers—by Black (1924–2010), who also developed H_2-histamine receptor blockers used to diminish stomach acid production in the treatment of peptic ulcer disease. Since Black's fundamental discovery, many receptors have been identified, structures of many drug-receptor complexes have been solved using x-ray crystallography and nuclear magnetic resonance (NMR), and the concept of drug-receptor interactions is now universally considered as the basis of the physiologic actions of drugs.

Pharmacodynamics

Drug Binding

Pharmacodynamics is broadly defined as the biochemical and physiologic effects of drugs. Proteins constitute the largest class of drug receptors, but other biomolecules can also be targeted. Proteins and other complex macromolecules can exist in a number of different conformational states. For simplicity, assume just two receptor conformations: physiologically active and inactive. In the case of an ion channel, for instance, the active conformation is an open conformation that allows ion permeation across the membrane, and the inactive conformation is the closed ion channel.

The following equation describes the relationship between the active and inactive states of the receptor (R):

[1]

$$R^I \underset{k_i}{\overset{k_a}{\rightleftharpoons}} R^A$$

R^I denotes the inactive (closed) ion channel and R^A denotes the active (open) ion channel, and k_a and k_i are rate constants for the forward and reverse conformational changes, respectively. In this example, rate k_i is higher than k_a (shown by arrow thickness) to illustrate a situation in which the channel is mostly closed in the absence of drug. The equilibrium relationship between the active and inactive conformations can be written as the ratio of the rate constants:

[2]

$$\frac{[R^A]}{[R^I]} = \frac{k_a}{k_i}$$

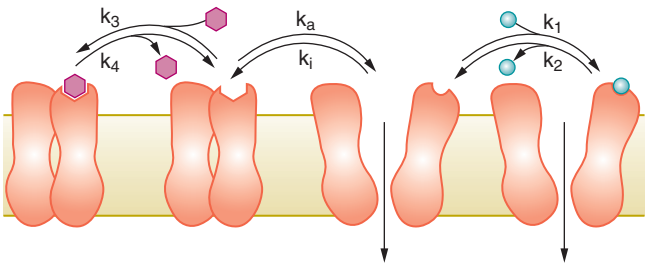
To initiate its pharmacologic action, a drug (D) first needs to bind its receptor"

[3]

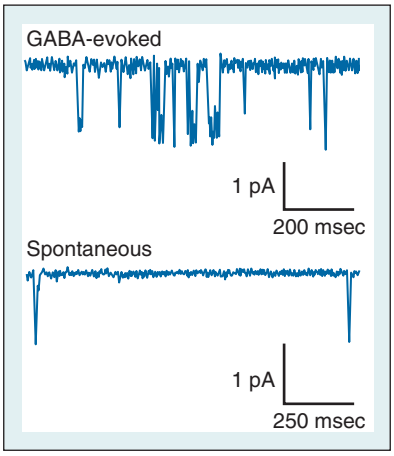
$$R^I \underset{k_i}{\overset{k_a}{\rightleftharpoons}} R^A + D \underset{k_2}{\overset{k_1}{\rightleftharpoons}} R^A * D$$

In this example, drug D binds an active form of the receptor (R^A) to form the complex R^A*D. As in the first example, this binding reaction has two rate constants, k_1 and k_2, that dictate the rates of drug-receptor complex formation and dissociation, respectively. The equilibrium constant for this binding reaction is therefore the ratio of the rate constants (k_1/k_2). The net effect of drug binding is an increase in active receptors as drug selectively binds the active conformation and thus prevents it from converting to the inactive conformation. This type of interaction of drug with a receptor is called *agonism* (discussed later). Fig. 1.1 shows a more general case, in which one drug (agonist) binds to an active (open) form of the ion channel while another drug (antagonist) selectively binds the closed form.

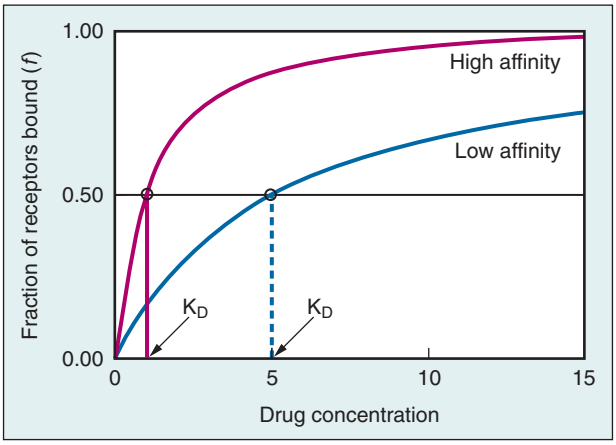
Although it might seem at first counterintuitive that even in the absence of agonist a receptor can be found in its active form, modern experimental methods such as single-channel patch clamp recordings can show this directly.[12] An example of such a recording is shown in Fig. 1.2.[13]



• **Fig. 1.1** Illustration of an ion channel in a lipid bilayer in equilibrium between two conformational states. The abundance of active (open) and inactive (closed) conformations is dictated by the rate constants k_a and k_i. An agonist *(aqua circle)* selectively binds to the open conformation of the ion channel, whereas an antagonist *(magenta hexagon)* selectively binds to the closed conformation. In both cases, drug binding stabilizes the receptor conformation: open in the case of an agonist and closed in the case of antagonist. The equilibrium for drug binding is dictated by the ratio of the rates k_1/k_2 and k_3/k_4 for the agonist and antagonist, respectively.



• **Fig. 1.2** An example of agonist elicited and spontaneous formation of the active form of a receptor. A single γ-aminobutyric acid $(GABA)_A$ receptor complex during a voltage clamp experiment. Active (open) $GABA_A$ receptors conduct chloride ions; inward flux is seen as downward deflections in the current trace, which reflect the times the channel is open. Even in the absence of GABA (the endogenous ligand at this receptor), the receptor can open spontaneously (trace labeled *Spontaneous*), but these openings occur more frequently and last longer when GABA is present. (Reproduced from Neelands TR, Fisher JL, Bianchi M, Macdonald RL. Spontaneous and gamma-aminobutyric acid (GABA)-activated GABA(A) receptor channels formed by epsilon subunit-containing isoforms. *Mol Pharmacol.* 1999;55:168-178.)



• **Fig. 1.3** Drug-receptor binding curves illustrating the importance of drug affinity for the receptor. As drug concentration increases, the fraction of receptor bound by drug *(f)* increases until all receptors are bound ($f = 1$). Curves are shown for two drugs with the dissociation constant (K_D) = 1 *(red)* and for $K_D = 5$ *(blue)*. It takes much higher concentrations of drug to occupy the same number of receptors when the K_D is higher (or affinity is lower). When the drug concentration equals K_D, exactly half of the receptors are bound by drug (shown by *circles*).

This model of drug stabilizing a receptor in its active conformation nicely explains the actions of gamma-aminobutyric acid (GABA) on $GABA_A$ receptors (see Fig. 1.2), but it is a very simplified view in several ways: (1) receptors can have more than two states (e.g., voltage-gated sodium ion [Na^+] channel). (2) Different conformational states can have different levels of activity rather than the all-or-none view presented here (e.g., nicotinic acetylcholine receptors). (3) Drugs can bind to more than one state of the receptor or at more than one site.[14–17] However, this model of drug-receptor interactions serves as a foundation for building more sophisticated models. This simplified description is used in the following discussion to derive the basic pharmacologic concepts.

Rearranging the equilibrium expression for drug binding to receptor yields the following expression in which the ratio of the two rate constants is defined as the dissociation constant K_D:

[4]

$$\frac{[R][D]}{[R*D]} \approx \frac{k_2}{k_1} \equiv K_D$$

Note that if K_D is small, then $k_1 \gg k_2$ and the complex of drug and its receptor is favored (as illustrated in Eq. 3). When the converse is true and K_D is large, the drug-receptor complex is not favored. Thus K_D reflects the propensity of the drug-receptor complex to break down. One can alternatively define *affinity* as the inverse of K_D, which reflects the propensity of the drug to form a complex with the receptor:

[5]

$$A \equiv \frac{1}{K_D} = \frac{k_1}{k_2}$$

To illustrate the importance of the dissociation constant K_D, the parameter f (fraction of receptor occupied by drug) is first defined as

[6]

$$f \equiv \frac{[R*D]}{[R]+[R*D]}$$

and then expressed f as a function of drug concentration and the K_D (or affinity) by substituting Eq. 4:

[7]

$$f = \frac{[D]}{[D]+K_D} = \frac{[D]}{[D]+1/A} = \frac{A[D]}{A[D]+1}$$

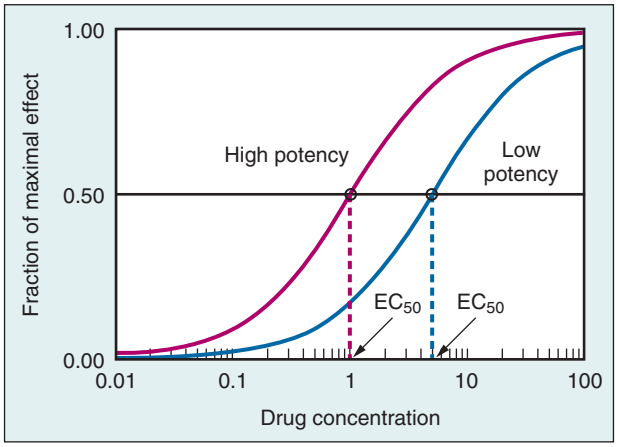
K_D is a fundamental property of the drug-receptor interaction (given constant conditions such as temperature, pH, and so on) but can be different for different drug-receptor pairs. To illustrate the effect of differences in K_D on the formation of drug-receptor complexes, Eq. 7 is plotted for two drugs characterized by different values of K_D (Fig. 1.3).

From Drug Binding to Physiologic Effect

Clark originally proposed that the number of drug-receptor complexes was directly proportional to the physiologic effect of the drug.[8] Although this is not entirely correct, for simplicity, first assume Clark's theory to derive the basic concentration (dose)-effect (response) curve and illustrate potency. Then Clark's assumption will be relaxed to arrive at the notion of efficacy.

If a physiologic response is directly proportional to the fraction of bound receptors, one should be able to derive the concentration-response relationship simply from the binding curve illustrated in Fig. 1.3. Indeed, the familiar sigmoid concentration-effect curve shown in Fig. 1.4 results from plotting the same equation as in Fig. 1.3. The only difference is that drug concentration is plotted on a logarithmic rather than linear scale and the *y*-axis is labeled as "Fraction of maximal effect."

Initially, as drug concentration increases, the increase in effect is rather small. In fact, until a certain concentration threshold is reached, no effect is apparent despite increasing drug concentrations. A further increase in drug concentration causes a steep increase in the effect until maximal effect is attained. This sigmoid relationship characterizes actions of many different drugs acting at different receptors. The circles in the plot denote drug concentrations at which half of the maximal effect is attained. This concentration is termed EC_{50} (effective concentration for 50% effect). Conceptually this is similar to K_D defined earlier. The major difference is that EC_{50} refers to the half maximal *effect, w*hereas K_D refers to half maximal *binding*. The smaller the EC_{50}, the less drug is required to produce the same effect. This is why EC_{50} is commonly used as a measure of drug *potency* or the ability of the drug to elicit a physiologic response.



• **Fig. 1.4** Concentration-effect curves illustrating the influence of potency *(EC_{50})* on curve position for two drugs of the same class. *EC_{50}* = 1 *(red)* and for *EC_{50}* = 5 *(blue)*. *EC_{50}*, Effective concentration for 50% effect.

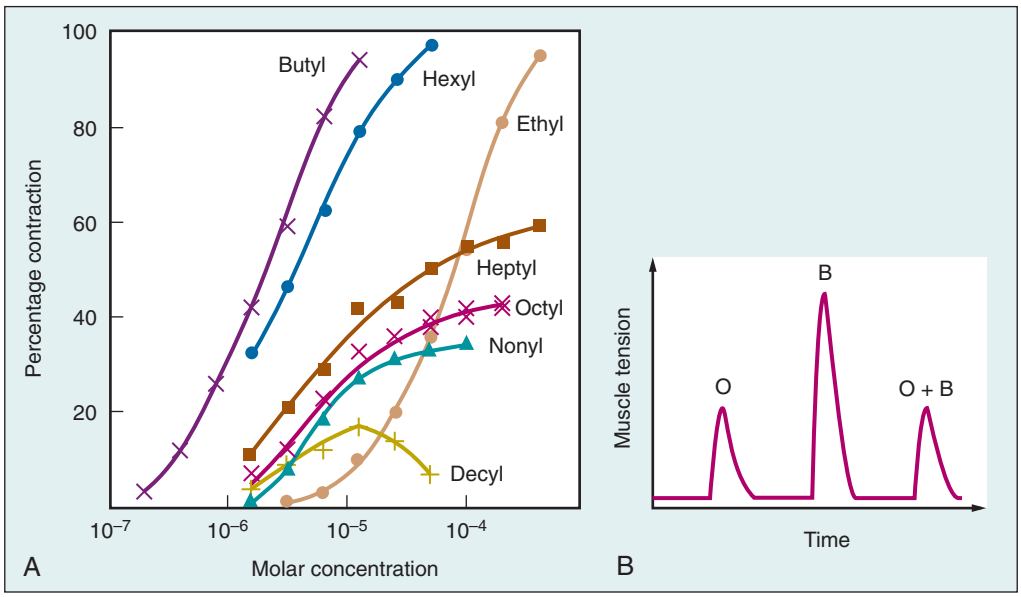
The curve in Fig. 1.4 is derived from an abstract notion of equilibrium between bound and free receptors. It is totally independent of the chemical identity of the drug or the receptor—it reflects the general property of drug-receptor interactions and is fundamental to the understanding of the action of any drug.

Efficacy

The concentration-effect curves in Fig. 1.4 depend on the important assumption that the effect of the drug is proportional to the amount of receptor bound by the drug. This hypothesis makes very strong predictions: (1) given high enough concentration, all drugs will give the same maximal effect; and (2) the slope of the curve should be similar for all drugs acting on the same receptor. Indeed, the only difference between the red and blue curves in Fig. 1.4 is that the blue curve is shifted to the right. However, this is not always true, as shown by Stephenson in 1956 in a landmark study (Fig. 1.5).[10]

While investigating the *pharmacodynamics* of tetramethylammonium (TMA) compounds known to elicit muscle contractions, Stephenson observed that different response curves were not simply shifted versions of each other. Specifically, it appeared that maximal contraction was not always attainable even at the highest concentration of a drug. For instance, even at the highest concentration, octyl-TMA elicited contraction was only 40% of the maximal attainable, whereas 100-fold smaller concentrations of butyl-TMA elicited near maximal contraction (see Fig. 1.5A). This observation alone does not invalidate Clark's theory. It is possible that octyl-TMA has really low affinity for the receptor and is therefore unable to elicit maximal response in the range of experimental concentrations.

The results in Fig. 1.5B definitively rule out this possibility. If the small contraction size elicited by octyl-TMA is due to its low affinity for the receptor, then some receptors will remain unoccupied even at maximal octyl-TMA concentration. If so, additional butyl-TMA should bind these available receptors and make the contraction



• **Fig. 1.5** Examples of differences in agonist potency and efficacy. A, Concentration-effect curves for various tetramethylammonium compounds illustrating that similar molecules can have different potencies (EC_{50s}) and different maximal effects (i.e., partial agonists). B, Muscle contractions elicited by octyl-TMA *(O)* and butyl-TMA *(B)* applied separately or together *(O + B)*. *EC_{50}*, Effective concentration for 50% effect. (Modified with permission from Stephenson RP. Modification of receptor theory. *Br J Pharmacol Chemother.* 1956;11:379–393.)

maximal. Yet, in contrast to this prediction, addition of butyl-TMA did very little to the contraction elicited by octyl-TMA alone. Thus weak affinity of octyl-TMA for the receptor cannot explain submaximal response and Clark's theory therefore must be incomplete.

To explain these observations, Stephenson generalized Clark's theory by proposing that the response R is not directly proportional to the fraction of receptor bound by drug, but instead is some function F of the variable he referred to as stimulus S:

[8]

$$R = F(S)$$

where S is a product of the efficacy (e) and the fraction of the receptors occupied f:

[9]

$$S = ef$$

In the case of muscle contraction, F can be conceptualized as excitation-contraction coupling and efficacy as the ability of the drug-receptor complex to produce excitation. By substituting Eq. 7 into Eq. 9, affinity A, drug concentration D, and efficacy e can be combined in the same equation:

[10]

$$S = e\left(\frac{A*[D]}{A*[D]+1}\right)$$

For conditions where the fraction of the occupied receptors is small, this simplifies to

[11]

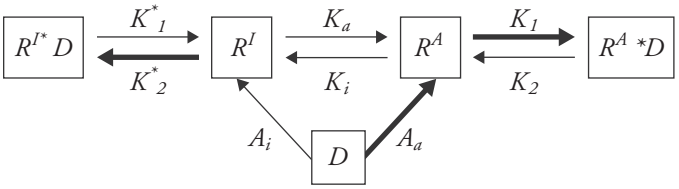
$$S = eAD$$

Accordingly, even when the fraction of the occupied receptors is small, the observed physiologic effect can be quite large if the efficacy is high. Conversely, even if affinity is high but the efficacy is low, the overall effect can be quite low. Therefore the overall drug *potency* for a given system is a function of two variables that characterize drug-receptor interactions: *affinity* and *efficacy*.

Full Agonists, Partial Agonists, and Inverse Agonists

Drugs can be classified based on the features of their concentration-effect relationships. This section focuses on different kinds of agonists and the following section discusses different forms of antagonism. First, features of drug-receptor interactions that make a particular drug an agonist are defined. In schema Eq. 3, it is assumed that drug binds only the active conformation of the receptor (see also Fig. 1.1). In a more general case (schema Eq. 12), drug can bind both active and inactive receptor conformations with different affinities.

[12]



The higher the affinity for the active conformation, the more equilibrium will be driven to the active receptor conformation until essentially all receptors are activated. This is called a *full agonist.* If the affinities for both active and inactive conformations of the receptor are comparable, the drug will be unable to convert a significant fraction of the receptor to the active conformation, even at high concentrations (reviewed for glutamate receptors).[18] This drug is called a *partial agonist.*

This is a microscopic level description of the basis of drug agonism, but in most cases, there is no detailed understanding of the molecular events. It is difficult to measure experimentally the differences in affinity for different conformational states of a receptor. Usually this problem is solved by performing molecular dynamics simulations.[19]

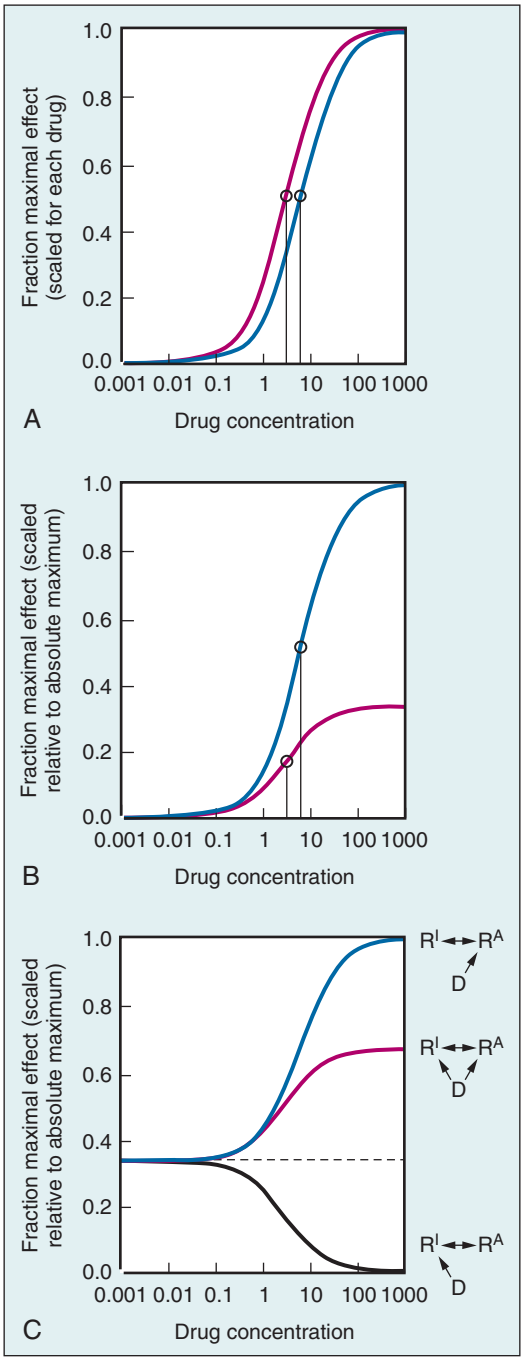
There is, however, a way to discover differences between agonists by characterizing their concentration-effect curves on a macroscopic level. Recall that the overall effect of a drug depends on two factors: affinity and efficacy. According to Eq. 10, efficacy determines the maximal effect attainable at the limit of high drug concentration, and affinity determines the range of drug concentrations at which the steep portion of the concentration-effect curve occurs. Therefore the effect of drug affinity can be isolated by scaling the y-axis of the concentration-response curve to the maximal effect attainable for that drug, and differences in efficacy can be characterized by comparing maximal attainable effects.

Fig. 1.6A shows two drugs that are distinguished by their affinity (higher for the red drug) scaled relative to the maximal effect attainable for each drug. When the effect of each drug is plotted relative to the absolute maximal effect (see Fig. 1.6B), it becomes evident that although the red drug has higher affinity, it has lower efficacy with a maximal response of one-third of that attainable by the blue drug. Therefore the red drug is a *partial agonist,* whereas the blue drug is a *full agonist.* Although the shapes of the plots in Figs. 1.6A and B appear quite different, in fact the relationship between their EC_{50} values stays exactly the same regardless of how the data are plotted.

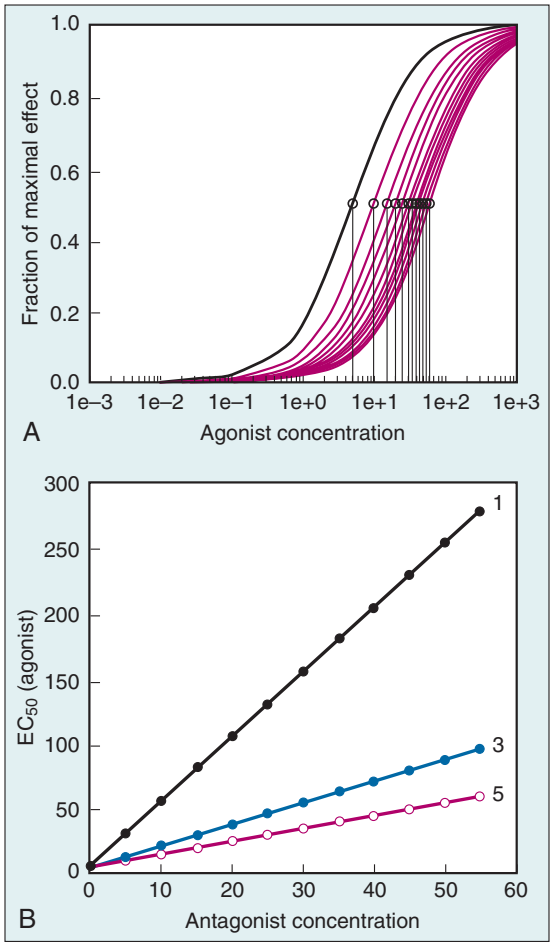
Up until this point we made an implicit assumption that concentration-response curves start at zero. In other words, in the absence of drug there is no effect. In Fig. 1.6C this assumption is relaxed. The plot in Fig. 1.6C shows the behavior of a system exhibiting intrinsic receptor activity, even in the absence of drug. This occurs in systems where even in the absence of drug a significant number of receptors exist in their active conformations. The blue curve shows a full agonist and the red curve shows a partial agonist. When the black drug is added, it appears that the intrinsic activity of the receptor is diminished. This can occur if the drug has a higher affinity for the inactive conformation of the receptor. This drug-receptor interaction is called *inverse agonism;* an inverse agonist is a drug that has a *negative efficacy*. If the inverse agonist was added after adding the full agonist, the overall effect would be diminished, suggesting that the inverse agonist is an antagonist (see later). In fact, the distinction between an antagonist and an inverse agonist can be subtle and is often evident only in genetically modified systems that express constitutively active receptors. For instance, the commonly used β-blockers such as propranolol are in fact inverse agonists at β-adrenergic receptors.[20]

Antagonism

The overall effect of a drug depends on both affinity and efficacy. All agonists have some nonzero value of efficacy and therefore



• **Fig. 1.6** Concentration-effect curves illustrating the concepts of EC_{50}, agonist, partial agonist, and inverse agonist. A, Concentration-effect curves of two drugs. The effect is scaled to the maximal response obtained for each drug. EC_{50} is 3 and 6 for the *red* and *blue* drugs, respectively. B, The same data as A, but the response is scaled to the absolute maximal possible physiologic response. *C,* Concentration-response curve for full agonist *(blue),* partial agonist *(red),* and inverse agonist *(black)* for a receptor with nonnegligible intrinsic activity. Affinity of the drug (D) for the active *(R^A)* and inactive *(R^I)* receptor conformations is indicated by the *single arrows*. *EC_{50},* Effective concentration for 50% effect.



• **Fig. 1.7** Competitive antagonism effect on the EC_{50}. A, Effects of increasing concentrations of a competitive antagonist on the concentration-response of a drug. The *black curve* shows curve in the absence of antagonist. EC_{50} for each curve is shown as a circle. B, Shift in EC_{50} plotted as a function of antagonist concentration derived using the $K_{D(B)}$ values shown. This plot allows calculation of the dissociation constant of the antagonist from the slope (see text). *EC_{50},* Effective concentration for 50% effect; *K_D,* dissociation constant.

produce an observable biologic effect. Conversely, drugs with some affinity for the receptor but no efficacy are defined as *antagonists*. Because antagonists do not produce an effect on their own, their actions can only be observed in the context of modification of the effects of an agonist.

The simplest way to conceptualize actions of an antagonist is to consider competition between an agonist and antagonist for binding to the same receptor. When the antagonist binds, no effect is elicited; when the agonist binds, it elicits an effect dictated by its efficacy. At a given concentration of antagonist, the effect elicited by the agonist will be diminished, but if the relative concentration of the agonist is increased, the same maximum effect will be eventually attained. Therefore the net effect of *competitive antagonism* is a shift in the agonist concentration-effect curve to the right (Fig. 1.7).

This can be expressed mathematically by modifying the previously derived equation for the fraction of receptors bound by agonist as follows:

[13]

$$f = \frac{[A]}{[A] + K_{D(A)}\left(1 + {}^{[B]}\!/\!_{K_{D(B)}}\right)}$$

where A is the agonist, $K_{D(A)}$ is its dissociation constant, B is the antagonist, and $K_{D(B)}$ is its dissociation constant.[21] The *EC_{50}* of the

agonist can now be expressed as a function of the antagonist concentration and its dissociation constant:

$$EC_{50} = EC_{50}^{0}\left(1+{}^{[B]}\!/\!_{K_{D(B)}}\right) \quad [14]$$

If the antagonist concentration is zero then the expression reduces to the EC_{50} of the drug in the absence of antagonist (EC_{50}^{0} in Eq. 14). The expression $\left(1+{}^{[B]}\!/\!_{K_{D(B)}}\right)$, known as the *dose ratio,* indicates the fold increase of the agonist needed to achieve the same response at a given concentration of antagonist. The effect of the dissociation constant of a competitive antagonist on the shift in EC_{50} is shown in Fig. 1.7B. The shift in EC_{50} is proportional to the antagonist concentration, and the proportionality constant (slope) is related to $1/K_{D(B)}$ (the affinity of antagonist for the receptor). The higher the affinity of the antagonist, the less antagonist it takes to shift the concentration-response curve of the agonist.

Another important class of antagonists is *noncompetitive antagonists.* The molecular mechanisms of noncompetitive antagonists are diverse. In the simplest case, irreversible binding of an antagonist takes the receptor out of the available pool to which agonists can bind. If the fraction of these unavailable receptors becomes sufficiently large, the maximal effect of the agonist will be partially reduced, even at very high agonist concentrations. Thus a noncompetitive antagonist makes the concentration-effect curve for a full agonist resemble that of a partial agonist.

Allosteric Drug Interactions

The discussion of antagonists in the previous section rests on an idea that both agonist and antagonist compete for binding to the same receptor site. The notion of what exactly a receptor is has been somewhat abstract, however. As mentioned earlier, most drug receptors are complex biologic macromolecules (example shown in Fig. 1.8), and to discuss allosteric drug interactions—the subject of this section—a few details about receptor structure are clarified.

Multiple Binding Sites on the Same Receptor Protein

Proteins constitute the largest class of receptor molecules. Although the amino acid sequence of proteins is encoded in the genetic code, the final three-dimensional structure of the protein is a result of complex interactions among the many amino acids that make up each subunit, interactions between subunits that make up the receptor, post-translational modifications, the cellular milieu, and so on. Only a small part of the resulting large and complex macromolecule is typically directly involved in binding the agonist. For instance, GABA binds the interface between the α and β subunits of the pentameric $GABA_A$ receptor.[22] The specific portion of a receptor molecule that is directly involved in binding drug is called a *binding site.* Identifying the actual binding site is no simple matter and usually requires a combination of experimental approaches. Indirect evidence for the identity of a binding site could be obtained through recombinant DNA techniques aimed at changing the identity of specific amino acids within the overall receptor-protein sequence by site-directed mutagenesis.[22] Direct evidence for the identity of a binding site can be obtained using x-ray crystallography, NMR spectroscopy, and chemical cross-linking, among other techniques.[23-26]

To determine the effect of changing the identity of a particular amino acid on drug binding, a reliable method for estimating drug binding is needed. Drug effect is not necessarily synonymous with drug binding (see earlier), so the concentration-effect curve cannot be directly used to infer the K_D. When a drug binds its receptor, heat is either absorbed (endothermic reaction) or released (exothermic reaction). These changes in heat can be recorded in solution maintained at constant temperature as a function of increasing drug concentration using a technique called *isothermal titration calorimetry* (ITC). In addition to measuring the binding constant, ITC experiments can also yield measurements of changes in entropy, enthalpy, and Gibbs free energy associated with drug binding, and thus provide a complete thermodynamic profile of the binding reaction that can then be used as a guide for molecular dynamic simulations.[27] Another technique that has gained popularity and was useful in identification of binding sites of anesthetic agents is photolabeling (Fig. 1.9) of drug binding sites using photoreactive drugs.[28] This technique involves an addition of a reactive chemical group such as a diazirine ring to the drug of interest When exposed to ultraviolet light, the diazirine ring forms a reactive carbene that rapidly reacts with amino acid residues in its vicinity, forming a covalent bond. This technique allows for stabilization of the normally transient drug receptor interactions. The binding site can then be identified by mass spectrometry and other structural techniques.[29,30]

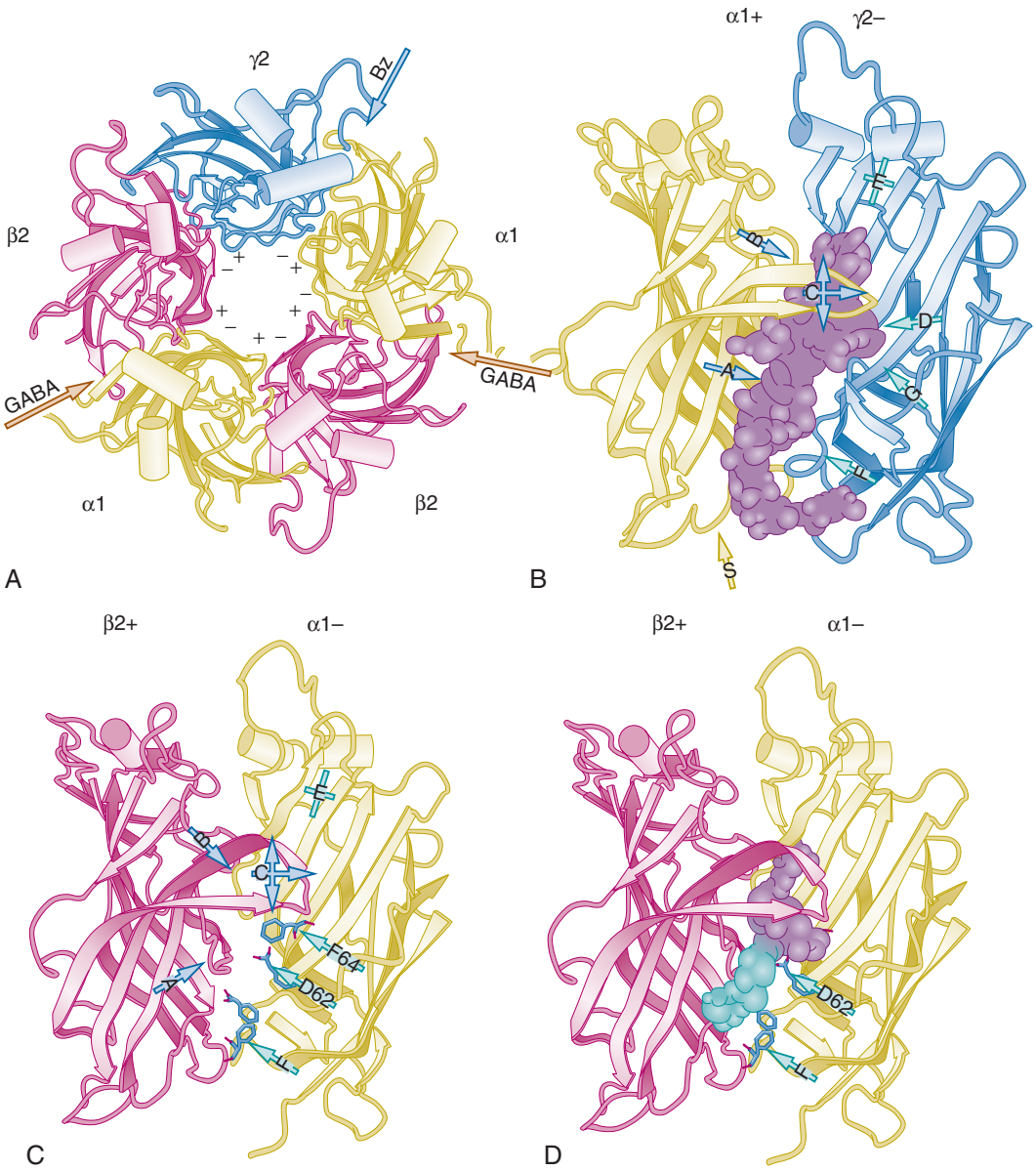
The binding site itself typically consists of a very small fraction of the total amino acid sequence of the protein. Yet binding of drug to the binding site induces a set of complex conformational changes in the overall receptor protein. For instance, binding of GABA to its binding site leads to opening a pore, which allows flux of chloride ions (Cl^-) across the plasma membrane (see Fig. 1.2), a process called *gating*.[31]

Competitive antagonists tend to bind to the same binding site as the agonist (GABA in this case); competition for occupancy of the binding site is sufficient to account for the effects of the antagonist. However, other drugs that bind to the same receptor might do so at a site distinct from that occupied by the agonist. The interaction between drugs binding the same molecule at different sites is referred to as *allosteric* ("other site"). For instance, the noncompetitive $GABA_A$ receptor antagonist picrotoxin most likely binds the receptor within the ion pore.[32]

Allosteric Binding Sites

$GABA_A$ receptors contain a number of distinct binding sites, including those for benzodiazepines, volatile and intravenous anesthetics, and ethanol.[32] Binding of drugs to these allosteric sites can affect GABA affinity, efficacy, and number of spontaneously open ion channels, for example. These kinds of interactions cannot be adequately described as simple agonists and antagonists.

The classic model of allosteric drug interactions was proposed by Ehlert[33] (Fig. 1.10). The allosteric nature of drug interactions allows for many more transformations of the concentration-effect curves elicited by two or more drugs binding the same receptor. To quantify the nature of allosteric interactions, a technique called *response surface modeling* is typically applied. A response surface is a generalization of the concentration-effect curve to more than two dimensions. Experimentally this corresponds to determining the effect of different combinations of two or more drugs acting at the same receptor protein (see Fig. 1.10). This concept will be applied to drug interactions in Chapter 6.

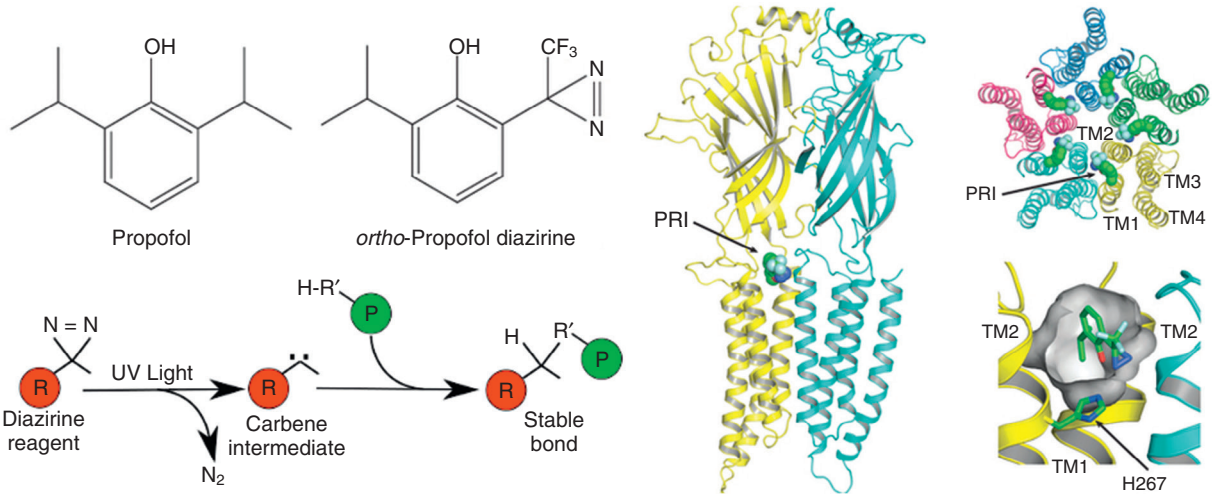


• **Fig. 1.8** Model of the extracellular domains of a pentameric $GABA_A$ receptor. The subtype illustrated consists of two α subunits, two β subunits, and one γ2 subunit. A, View from the extracellular space. GABA binds to the interface between the α and β subunits, benzodiazepines bind to the interface between the α and γ2 subunit. B, Predicted benzodiazepine-binding pocket between the α and γ2 subunit viewed from the side. The binding site loops are labeled *A* to *G*. (C) and (D) The α and β subunit viewed from the side. The volume shown in *green* might be occupied in antagonist-bound states. *Bz,* Benzodiazepines; *GABA,* γ-aminobutyric acid. (Reproduced from Goetz T, Arslan A, Wisden W, et al. GABA(A) receptors: structure and function in the basal ganglia. *Progr Brain Res.* 2007;160:21–41.)

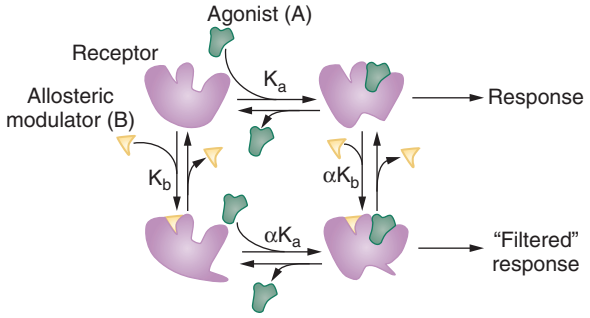
Pharmacogenetics

Because most receptors are proteins whose amino acid sequence is encoded in the DNA, the binding sites can vary significantly between individuals. *Pharmacogenetics* refers to the study of how this genetic variability between individuals contributes to differences in drug effects (see Chapter 4). The effect of genetic variability on the pharmacology $GABA_A$ receptor is illustrated in Fig. 1.11. Because GABA and diazepam (a benzodiazepine) bind different sites on the $GABA_A$ receptor, it is possible to generate mutant receptor molecules that have different responses to one drug (diazepam), while the responses to the other drug (GABA) are preserved. In the wild-type receptor, diazepam acts as positive modulator of GABA, causing a left shift in the GABA concentration-effect curve. Yet after mutating a single amino acid, diazepam acts as a partial agonist.

The dependence of drug effects on the genotype has profound clinical implications. For instance, specific $GABA_A$ receptor α subunit polymorphisms can predict responses to alcohol such as susceptibility to delirium tremens and withdrawal symptoms; these polymorphisms might even predict a propensity for the development of alcohol addiction.[34] Other examples of genetic factors that



• **Fig. 1.9** The left side of the figure illustrates the chemical structure of the propofol analog equipped with a diazirine ring and the chemical reaction that covalently links the diazirine moiety to the receptor in the presence of ultraviolet *(UV)* light. The right side shows the localization of propofol analog *(PR1)* at the interface between $GABA_A$ receptor subunits deduced using this technology. *GABA,* γ-Aminobutyric acid. *H,* hydrogen; *N,* nitrogen; *P,* protein; *R,* arbitrary carbon chain; *TM,* transmembrane helix.



$$\rho = \frac{\alpha[A]/K_A[B]/K_B + [A]/K_A}{\alpha[A]/K_A[B]/K_B + [A]/K_A + [B]/K_B + 1}$$

• **Fig. 1.10** Illustration of allosteric drug-receptor interactions. Agonist *(green)* can bind the receptor *(purple)* with affinity K_a, which leads to a response dictated by the efficacy of the agonist. Alternatively, the receptor can bind an allosteric modulator *(yellow)* with affinity K_b. The receptor-modulator complex can then bind the agonist but not necessarily with the same affinity (thus K_a in this case is multiplied by some modulator-specific constant α). The resulting receptor-agonist-modulator complex can have a different efficacy (expressed as *"Filtered" response*). This complex can then decay by either dissociation of the agonist or the modulator. The overall fraction of receptor bound by the agonist ρ can be expressed in an equation shown at the bottom. (Reproduced from Kenakin T. Allosteric modulators: the new generation of receptor antagonist. *Mol Interv.* 2004;4:222–229.)

contribute to drug responses include genetic variability in enzymes that influence pharmacokinetics (see Chapter 4).[35]

Drug Discovery

Historically, medicines have been derived from plant extracts used without rigorous testing or validation. Most of these medicines were not single compounds but complex mixtures of compounds, only some of which had the desired physiologic actions. Opium, one of the oldest medicines, is a mixture of a number of alkaloids including morphine, which constitutes only ~12% of the total formulation. In the 19th century, major advances in chemistry allowed fractionation of crude plant extracts and isolation of individual compounds, which were then tested to determine which components of the extract were pharmacologically active and had desirable effects. This development was coupled with the purification and determination of the structure of naturally occurring hormones such as norepinephrine.

Structure-Activity Relationship

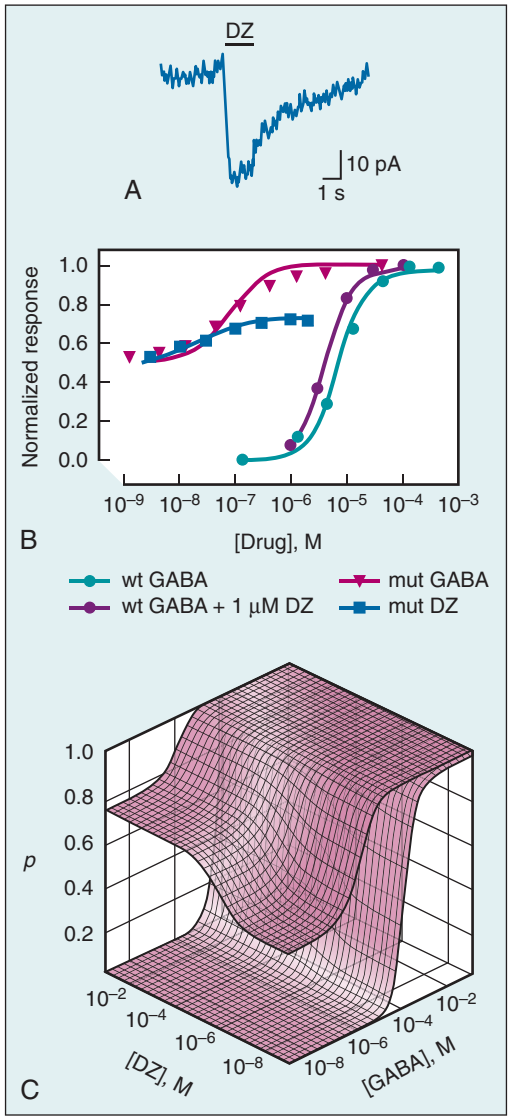
In the early to mid-20th century, many new drugs were synthesized as modifications of physiologically active plant and animal-derived compounds, yielding new drugs with desirable characteristics. The similarity between the structure of tyramine and epinephrine, for instance (Fig. 1.12), suggested the synthesis of many amine compounds that possessed sympathomimetic properties when tested in isolated organ systems such as the trachea and heart. One fundamental insight from this early work was that even small modifications in the chemical structure led to the profound changes in physiologic actions.

Identification of Drug Targets

Although many physiologically active compounds were synthesized during this early era of pharmacology, the mechanisms of action of these drugs remained mysterious as their receptors were not known. A fundamental insight was provided by Ahlquist,[11] who hypothesized that differences in drug effects might not only be due to differences in drug chemical structure but also to differences in the receptors expressed in different tissues. This led to the development of drugs acting in a tissue-specific manner by Black and colleagues.[36] They used a drug previously known as a bronchoconstrictor to develop the first novel, receptor-selective compounds, the β-blockers.[36]

Purification of Receptors

Advances in molecular biology have allowed rapid progress in the identification and molecular characterization of specific receptors



• **Fig. 1.11** Allosteric interaction of GABA and diazepam. A, Response of *spontaneously active mutant* $GABA_A$ receptors to 1 μM diazepam *(DZ)*. B, Concentration-response dependence of activation of wild-type *(wt)* and mutant *(mut)* receptors by GABA and DZ. C, Concentration-response surfaces for GABA and DZ acting at wild-type or α1L263S mutant $GABA_A$ receptors. *GABA,* γ-Aminobutyric acid; *p*, response. (Reproduced from Downing SS, Lee YT, Farb DH, Gibbs TT. Benzodiazepine modulation of partial agonist efficacy and spontaneously active GABA(A) receptors supports an allosteric model of modulation. *Br J Pharmacol.* 2005;145: 894–906.)

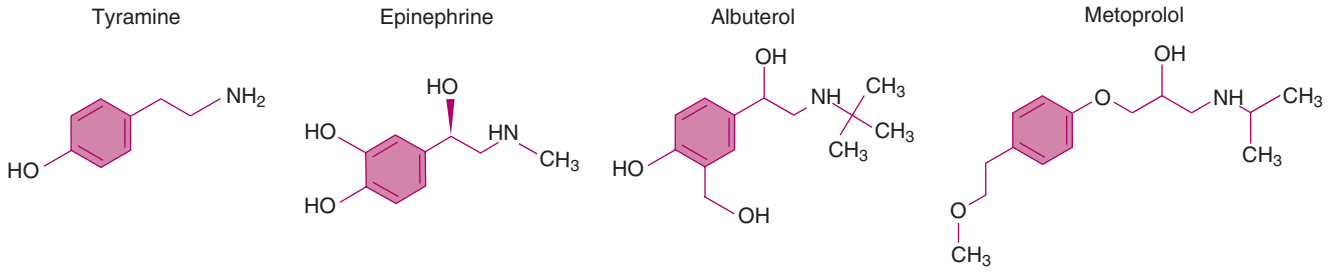
for drugs. In the 1980s, receptors were identified using high-affinity ligands, usually specific antagonists, that were used as bait in affinity chromatography to isolate the low-abundance receptor protein from detergent-solubilized tissue extracts.[37,38] Amino acid sequences of these purified receptors could then be determined, which allowed structural and functional analysis, as well as homology searching.

The advent of molecular cloning of cDNA from the cellular messenger RNA (mRNA) species allowed rapid identification of homologous receptors without tedious receptor purification techniques. In the past 20 years, the proteins encoding the receptors for many therapeutic drugs have been identified and most have been expressed at high levels (overexpressed) in other cell types (heterologous expression) to allow more detailed pharmacologic studies of receptors in isolation from other potentially confounding receptors and signaling molecules. It is now possible to express genes coding for a specific receptor protein in cell culture and simultaneously screen many different compounds for their ability to activate or inhibit the receptor using a variety of optical and other high-throughput drug screening methods.[39]

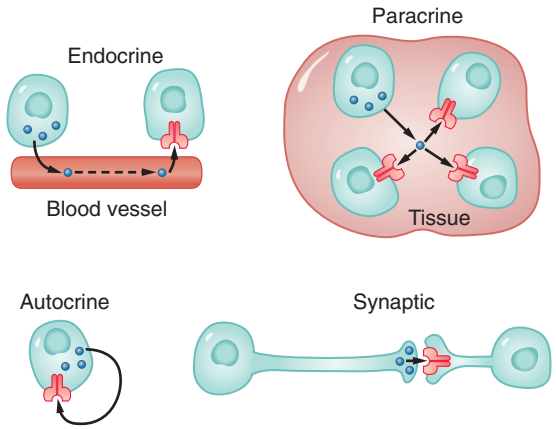
Drug Targets

Most drugs act by facilitating or blocking endogenous signaling molecules involved in intercellular and intracellular signaling, most commonly neurotransmitters or hormones. Most of these extracellular signaling molecules (ligands) are synthesized and released by one cell to affect another by interacting with a cognate receptor (e.g., endocrine signaling, synaptic transmission), although local effects on adjacent cells (paracrine) or the same cells (autocrine) are also common (Fig. 1.13).

Binding sites for hydrophilic extracellular signals typically exist as grooves or pockets on the surface of the extracellular protein domains. Lipophilic compounds (e.g., steroids, retinoids, and thyroxine), in contrast, can traverse membranes to interact with binding sites within the hydrophobic core or intracellular domains of the receptor. NO, HS, and CO are gaseous signaling molecules (gasotransmitters) that can also diffuse across membranes to affect intracellular targets.[40–42] Most transmembrane receptors consist of multiple membrane-spanning segments made up of amphipathic helices that fold to form a complex three-dimensional structure, usually consisting of multiple subunits. In ion channels, these membrane-spanning domains create a gate for ion permeation that is regulated by voltage or ligand binding. In other receptors, the intracellular domain contains protein signaling domains that either directly or indirectly affect signaling pathways. Receptor structures are highly dynamic and can exist in multiple conformations that differ in their activities. Ligands and modulators regulate



• **Fig. 1.12** Similar chemical structures of agonists and antagonists acting on adrenergic receptors. Note the similarity of β agonists such as epinephrine and albuterol with relatively minor modifications needed to generate a β antagonist such as metoprolol.



• **Fig. 1.13** Schematic illustration of endocrine, paracrine, autocrine, and synaptic signaling.

receptor function by selectively binding to specific conformers to alter these conformational equilibria.

Cell Signaling

Signal transduction refers to the process through which receptors act to mediate their physiologic actions (Fig. 1.14). In many cases this process involves molecules that are themselves not involved in binding the original ligand, but act as molecular relays. These molecules are referred to as *second messengers.* Important second messengers include cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), calcium ions, and inositol phosphates. Changes in concentration and subcellular localization of these molecules are coupled to activity of regulatory enzymes and effectors, including ion channels, cyclases, protein kinases, protein phosphatases, and phosphodiesterases. Many second messengers either directly or indirectly regulate protein kinases, which reversibly phosphorylate hydroxylated amino acid residues on key effector molecules in the cell, including receptors, to alter their function and localization.

The interactions between different second messengers form complex molecular signaling networks that allow greater flexibility in how ligand binding affects cellular function and for the coordination between different signals. *Signal amplification* occurs as a result of sequential activation of catalytically active enzymes, each of which can activate multiple downstream targets. *Specificity* is imparted by the receptor itself and its cell- and tissue-specific expression. *Signal integration* occurs as the downstream signaling pathways of different signals interact at multiple levels both positively and negatively (cross talk).[43] Signals can be graded (i.e., analog) or discrete and bistable.[44] *Feedback,* both positive and negative, can occur when downstream components interact with upstream components of the signaling cascade.[45,46] Many signaling pathways are compartmentalized by protein interaction domains on scaffolding proteins that bring together multiple components of the pathway, including receptors and their target effectors to increase their local concentrations.[47] These mechanisms of cell signaling and signal transduction are critical for intercellular communication in multicellular organisms and provide multiple sites susceptible to modulation by exogenous compounds including drugs and toxins.

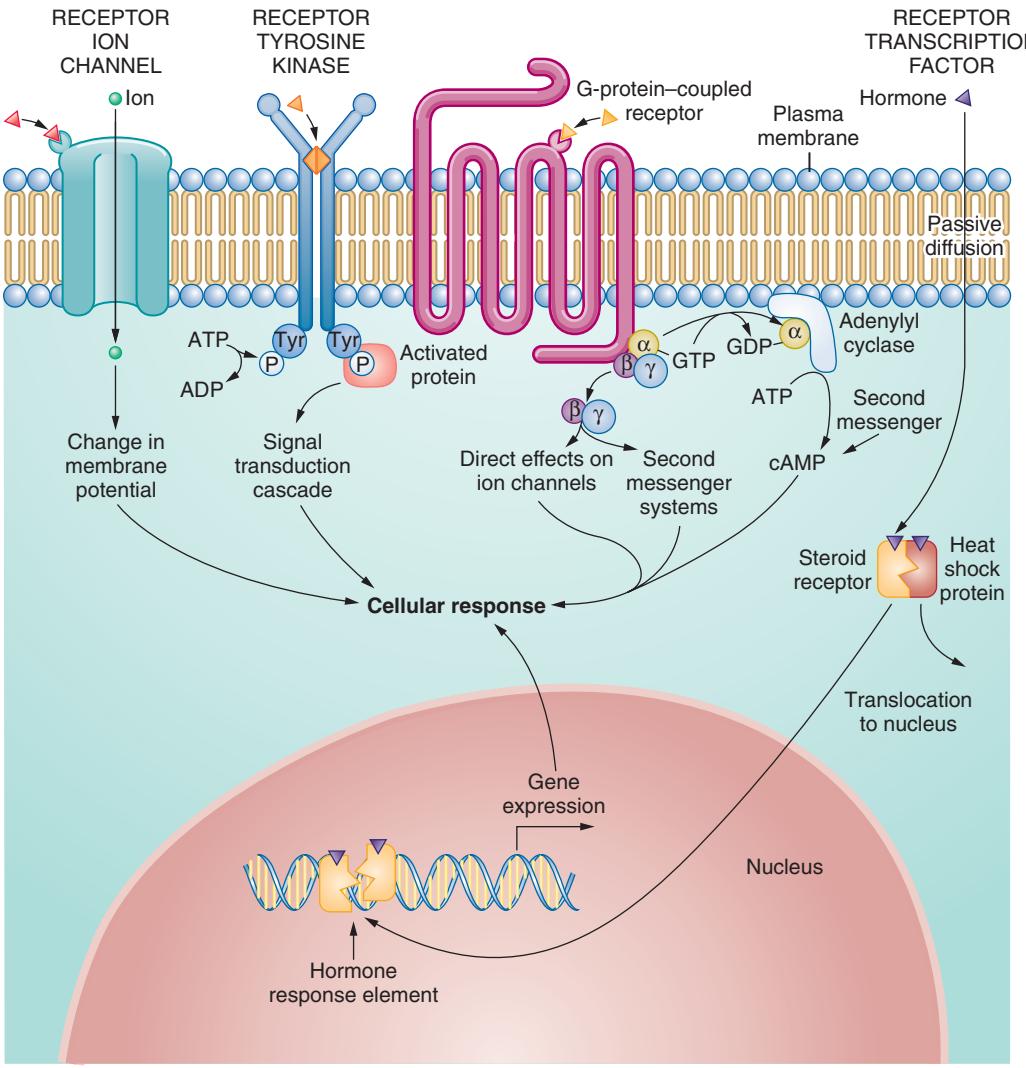
The most common types of drug target proteins involved in signal transduction are G protein-coupled receptors (GPCRs), ligand-gated ion channels (ionotropic receptors), which are major targets of general anesthetics, and voltage-gated ion channels, the major targets of local anesthetics and certain antihypertensive drugs.[16,48–50] There are also a number of enzyme-linked cell surface receptors, a heterogeneous group of receptors usually coupled to intracellular protein kinase or phosphatase activity. These proteins fall into different classes based on their amino acid sequences and biologic activities. The activation of many receptors leads to transient changes in intracellular second messengers.

GPCRs constitute the largest family of cell surface receptor proteins, and indeed comprise the largest family of membrane proteins in the human genome. They mediate the cellular responses to a diverse array of extracellular signals, including hormones and neurotransmitters. GPCRs contain seven transmembrane α helices and bind their ligands in the extracellular space, as demonstrated by the recent three-dimensional structure determined for several members of this class.[51–54] On the cytoplasmic surface, GPCRs transduce their signals into cells by coupling to intracellular heterotrimeric G proteins that are made up of three subunits (α, β, and γ). Although there are many GPCRs, the number of G proteins is much smaller (21 Gα subunits encoded by 16 genes, 6 Gβ subunits encoded by 5 genes, and 12 Gγ subunits in humans). In the inactive form, G proteins bind GDP. When ligand binds the receptor, GDP is exchanged for guanosine triphosphate (GTP), which causes dissociation of the G protein into the α subunit and the βγ dimer, each of which interacts with specific effectors.[55] This process is terminated once GTP is hydrolyzed to GDP (see Fig. 1.14) and the G protein subunits reassociate.

Some G proteins activate their effectors, whereas others inhibit them. Many endogenous signaling molecules exert their effects through multiple subtypes of GPCRs with distinct downstream targets and/or cellular expression. Examples include multiple receptor subtypes for epinephrine, dopamine, serotonin, and endogenous opioids.[25] Natural ligands for a large fraction of the many GPCRs present in the human genome have yet to be identified (orphan receptors) and represent potential future drug targets.[48]

Although the structure of the GPCR determines its ligand recognition, the overall effect is determined by which G protein associates with the receptor and which effectors are coexpressed in the same cell. Some of the well-known effectors of GPCRs are adenylyl cyclases, phospholipases, and various ion channels (Table 1.1). These effector proteins control the concentration of second-messenger molecules such as cAMP and phosphatidylinositol bisphosphate in the case of adenylyl cyclase and phospholipase, respectively. Thus GPCRs are capable of eliciting a diverse range of responses depending on the cellular context in which they are expressed. This feature of G proteins makes them attractive targets for drug development. Furthermore, the effector proteins such as adenylyl cyclases and phosphodiesterases (enzymes that degrade cAMP and cGMP) have themselves been targeted for drug discovery.[56]

In addition to activation of canonical G-protein–mediated signal transduction pathways, GPCR activation leads to feedback pathways that eventually terminate signaling. These feedback pathways fall into two general classes: heterologous and homologous. Although both pathways involve receptor phosphorylation, the former does not require that the GPCR is bound by agonist, while the latter specifically involves agonist-bound GPCRs. Heterologous receptor desensitization involves receptor phosphorylation by second-messenger–dependent kinases (e.g., cAMP-dependent kinase, PKC) that reduces receptor binding to bind G proteins and thus terminates canonical signaling. In contrast, homologous desensitization involves GPCK phosphorylation by G-protein–coupled receptor kinases



• **Fig. 1.14** Major modes of signal transduction and intracellular signaling. Binding of an agonist to a receptor ion channel (e.g., $GABA_A$ receptor or nicotinic acetylcholine receptor) leads to opening of a transmembrane pore that permits movement of ions across the plasma membrane. This leads to a change in membrane potential that results in the physiologic response (e.g., change in the firing characteristics of a neuron or muscle contraction). Binding of a ligand to a receptor tyrosine kinase results in receptor dimerization and phosphorylation of the intracellular kinase domain. The activated (phosphorylated) kinase domain is then specifically recognized by proteins such as Src and phospholipase C that in turn activate a network of downstream effectors. These signal transduction pathways ultimately lead to changes in physiologic functioning of the cell such as glucose utilization and cell growth. Binding of a ligand to a seven-transmembrane domain G-protein–coupled receptor results in the dissociation of the G protein into the membrane α subunit and the soluble βγ dimer. The α subunit then interacts with downstream effectors such as adenylyl cyclase, which converts adenosine triphosphate *(ATP)* into cyclic adenosine monophosphate *(cAMP)* (a second messenger) that then modifies a number of effector proteins. The βγ dimer can also exert direct cellular effects by modulating activity of a number of ion channels, for example. Effects of steroid hormones are mediated by intracellular receptors, which upon binding their ligand dissociate from a heat shock protein and translocate into the nucleus where they serve to modify gene expression by binding to hormone response elements in the promoter regions. *ADP,* Adenosine diphosphate; *GABA,* γ-aminobutyric acid; *GDP,* guanosine diphosphate; *GMP,* guanosine monophosphate; *P,* phophoryl group; *Tyr,* tyrosine.

on the third intracellular loop and carboxyl tail, leading to recruitment of β-arrestins, which targets the receptor for clathrin-mediated endocytosis. This mechanism plays a role in a variety of processes, most notably development of tolerance to opioids (as reviewed in Pierce and Lefkowitz[57]).

Ligand-gated ion channels are involved primarily in fast synaptic transmission between cells (e.g., the nicotinic acetylcholine receptor in neuromuscular transmission). $GABA_A$ receptors are ligand-gated Cl^- channels that open in response to binding their principal agonist, GABA (see Fig. 1.2), the major fast inhibitory

TABLE 1.1 Diversity of G-Protein–Coupled Receptor Signal Transduction Pathways

G-Protein α Subunit[a]	Representative Receptors	Effectors	Effect
$G\alpha_s$	β_1, β_2, β_3—adrenergic, D_1, D_5-dopamine	Adenylyl cyclase, Ca^{2+} channels	Increased cAMP, increased Ca^{2+} influx
$G\alpha_i$	α_2-adrenergic; D_2-dopamine; M_2, M_4 muscarinic; μ, δ,κκ opioid	Adenylyl cyclase, phospholipase A_2, K^+ channels	Decreased cAMP, eicosanoid release, hyperpolarization
$G\alpha_t$	Rhodopsin	cGMP phosphodiesterase	Decreased cGMP (vision)
$G\alpha_q$	M_1, M_3 muscarinic; α_1-adrenergic	Phospholipase Cββ	Increased IP_3, DG, Ca^{2+}
$G\alpha_{12/13}$	Angiotensin II (AT_1), endothelin (ET_A), thromboxane A_2 (TP), and thrombin (PAR_{1-4})	Rho guanine nucleotide exchange factor, others	Rho A activation

Ca^{2+}, Calcium ion; *cAMP,* cyclic adenosine monophosphate; *cGMP,* cyclic guanosine monophosphate; *DG,* diacylglyceron; *IP_3,* inositrol triphosphate.
[a]G-protein α subunits are encoded by 16 genes classified into four families: $G\alpha_s$, $G\alpha_i$ ($G\alpha_i$, $G\alpha_o$, $G\alpha_t$), $G\alpha_q$, and $G\alpha_{12/13}$. *PAR1-4,* protease-activated receptor 1-4. See reference 67 for review.

neurotransmitter in the central nervous system. $GABA_A$ receptors belong to the cys-loop superfamily of ligand-gated ion channels that contains many other neurotransmitter receptors that all share certain structural motifs. Many of the members of this superfamily (Fig. 1.15) have been successfully targeted for drug development.

Another large group of drug targets are voltage-gated ion channels (Fig. 1.16). Like ligand-gated ion channels, these proteins also form pores that allow permeation of ions across the plasma membrane. However, rather than opening in response to ligand binding, pores within these proteins open when transmembrane electrical potential reaches a certain value. The voltage and time dependence of pore opening as well as ion selectivity differs widely between these proteins.[58] Many clinically useful drugs such as local anesthetics and several antiarrhythmic drugs target voltage-gated sodium (Na^+) channels (see Chapter 20).

Another prominent family of proteins that has been successfully targeted for drug discovery includes receptor proteins with enzymatic activity. These receptors typically contain a ligand-binding domain, a single transmembrane domain, and the catalytic domain. Of these, the most prominent are the receptor tyrosine kinases, important targets for novel anticancer drugs. Binding of ligand in the extracellular space activates the tyrosine kinase to add phosphate groups onto tyrosine moieties of other proteins. Some clinically significant signaling pathways that involve receptor tyrosine kinases are receptors for cytokines and insulin.[59] In some cases, both the ligand-binding domain of the receptor and the tyrosine kinase structural domains are a part of the same polypeptide chain, and in other cases these two domains are expressed in different proteins that oligomerize to form a functional receptor.[60] Other receptors with enzymatic activity include tyrosine phosphatases and guanylyl cyclases.[61]

The identity and abundance of proteins, including those that mediate drug actions, are not static. Expression of proteins is dynamically regulated through a network of signaling cascades depending on cell type, developmental stage, and environmental demands, for example. These regulatory cascades converge on proteins, known as *transcription factors,* that control transcription of mRNA. Thus transcription factors play an incredibly important role in controlling the function of the cell and present attractive targets for drug discovery. Various steroid compounds that modulate the endocrine system act on transcription factors to alter gene expression (see Fig. 1.14). Transcription factors consist of homologous domains that control the specificity of ligand binding and regulatory motifs that determine DNA sequences to which these transcription factors bind to modulate gene expression.

Emerging Developments

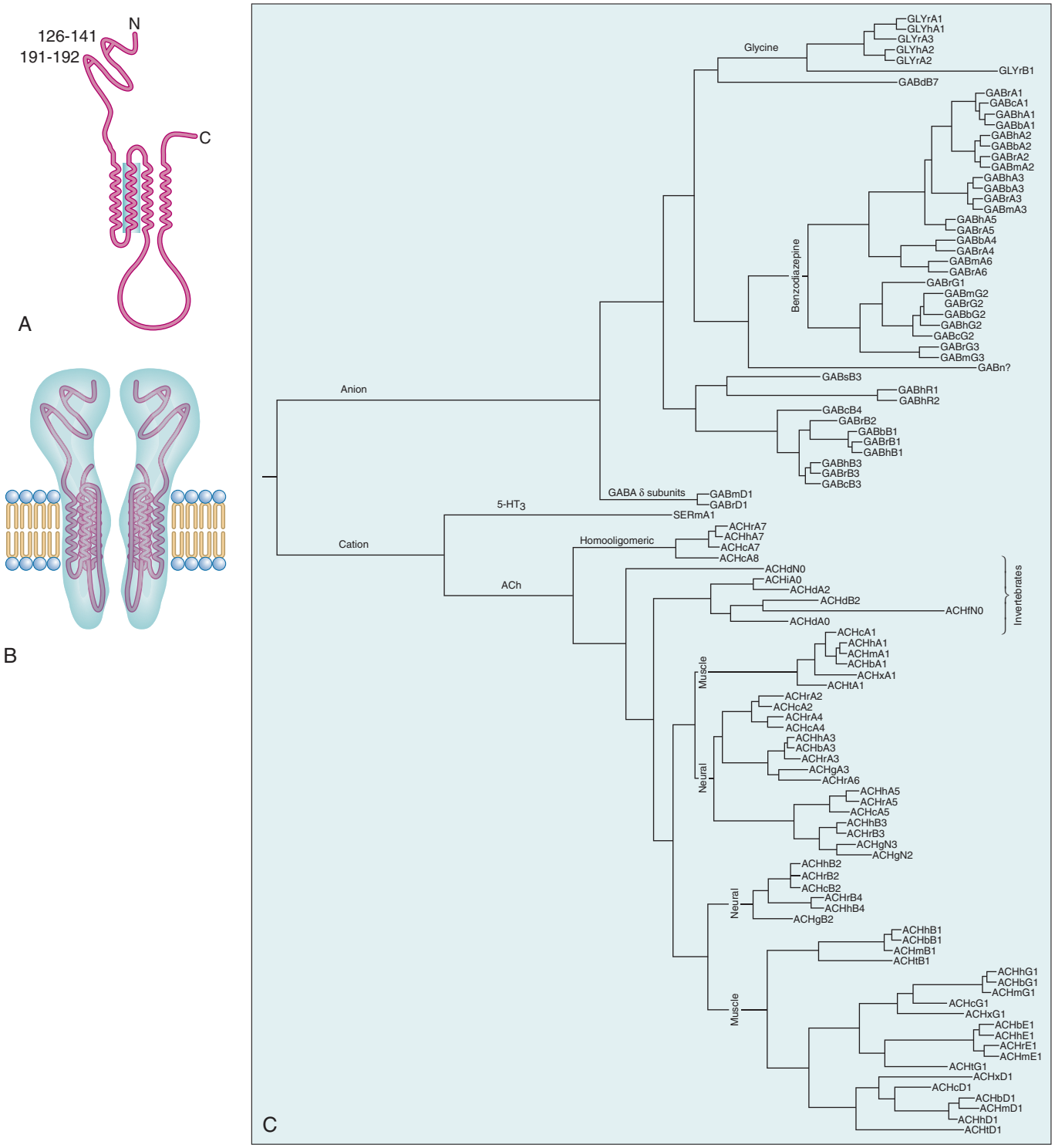
Pharmacophore Modeling

The realization that binding sites of many different proteins are homologous and the observation that chemically similar compounds tend to bind to the same binding site suggest that structure-activity relationships can be formalized. This could in principle significantly reduce the need to characterize experimentally the binding and efficacy of many different compounds and be able to predict which compounds should have the desirable binding characteristics. In practice, however, it is extremely difficult to develop because at the subatomic level, details of all the different forces that govern noncovalent interactions are extremely complex and analytic solutions exist for only the simplest molecules. Currently each potential drug-receptor pair must be numerically simulated, which is computationally expensive and impractical on a large number of drug candidates.

An exciting development in modern drug design—pharmacophore modeling—provides a way to describe qualitatively drug-receptor interactions to provide an albeit imprecise guide for selecting promising drug candidates. Pharmacophore is defined as "an ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biologic target and to trigger (or block) its biologic response."[62] Pharmacophore models combine a large number of observations of active and inactive compounds and attempt to extract statistically significant motifs that predict drug activity (Fig. 1.17). Pharmacophore modeling has been successful in predicting binding characteristics of many candidate drugs.

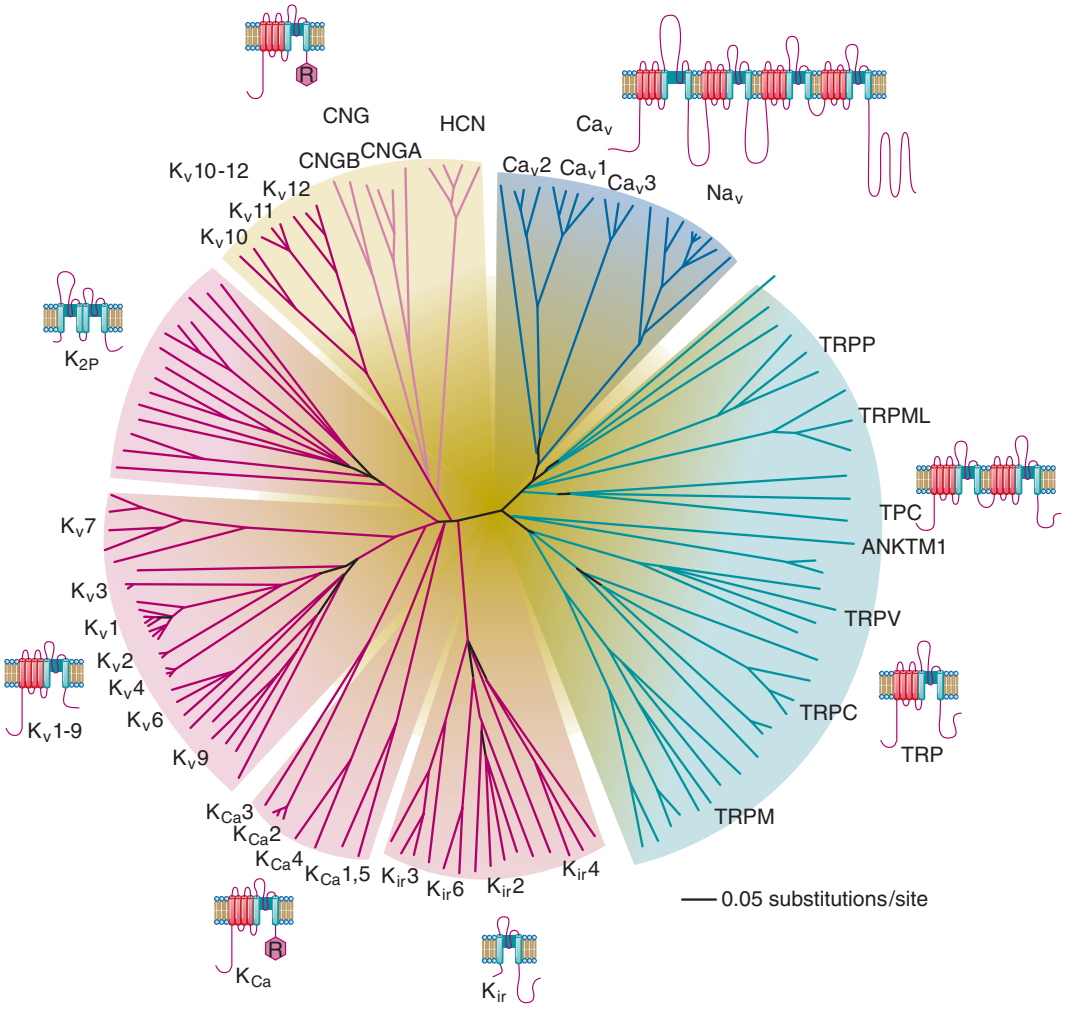
Phenotype-Based Drug Discovery

Using methodologies such as pharmacophore modeling and high-throughput screening, it is now possible to readily synthesize new compounds with high specificity for the desired receptor. This, however, does not guarantee therapeutic efficacy. It has become clear that many of the most prevalent diseases, such as depression and obesity, are mediated by complex changes occurring

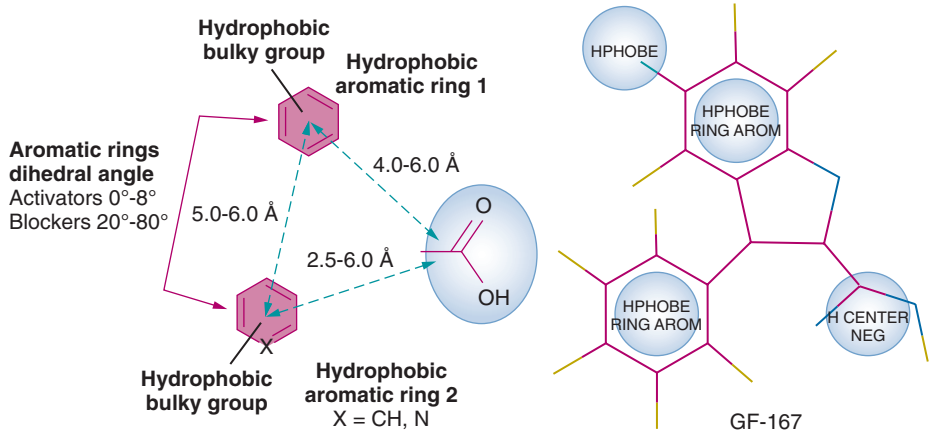


• **Fig. 1.15** Structure and evolutionary relationship of ligand-gated ion channels. A, Proposed structure of a single subunit of a pentameric ligand-gated ion channel. B, Structure of the whole pentamer viewed from the side (in plane). C, Evolutionary relationship between different members of the superfamily based on sequence homology. *GABA,* γ-aminobutyric acid. (Reproduced from Ortells MO, Lunt GG. Evolutionary history of the ligand-gated ion-channel superfamily of receptors. *Trends Neurosci.* 1995;18:121-127.)

simultaneously in many biologic macromolecules. Furthermore, these changes are mediated through networks of molecular interactions involved in signal transduction in a cell type–specific manner. It is exceedingly unlikely therefore that specifically targeting a particular receptor, or second-messenger system, will guide these molecular networks toward "normal" function. Thus paradoxically it is commonly found that some of the most clinically efficacious compounds are not necessarily the most specific on the molecular level. For instance, tricyclic antidepressants act on adrenergic, cholinergic, serotonergic, histaminergic, and dopaminergic systems.



• **Fig. 1.16** Structure and evolutionary relationship between members of the voltage-gated ion channel superfamily. (Reproduced from Yu FH, Yarov-Yarovoy V, Gutman GA, et al. Overview of molecular relationships in the voltage-gated ion channel superfamily. *Pharmacol Rev.* 2005;57:387–395.)



• **Fig. 1.17** Representation of the pharmacophore model illustrating the essential requirements for drug action. For comparison, the stick model and the chemical function descriptors of the master compound GF-167 are shown. (Reproduced from Liantonio A, Picollo A, Carbonara G, et al. Molecular switch for CLC-K Cl^- channel block/activation: optimal pharmacophoric requirements towards high-affinity ligands. *Proc Natl Acad Sci USA.* 2008;105:1369–1373.)

A promising complementary strategy is *phenotype-based* drug discovery. Rather than discovering compounds with the most desirable binding characteristics to a particular receptor, phenotype-based approaches screen compounds based on their ability to produce a desired phenotype in the whole animal. For instance, the cholesterol-lowering medication ezetimibe (Zetia) was identified based on its ability to lower serum cholesterol level in an animal model, although it was not a successful inhibitor of acyl-coenzyme A cholesterol acetyltransferase (the original target for the target-based drug discovery approach).[63]

Novel Antidotes

Anesthesiologists are familiar with the use of antidotes, classically defined as a drug that counteracts the effects of a poison (Tables 1.2 and 1.3). Some classic examples include the anticholinesterases to antagonize neuromuscular blockers, naloxone to antagonize opioids, and protamine to antagonize heparin. The first two agents represent physiologic antidotes that work through receptor antagonism, while the latter represents complex formation to inactive the drug. A number of new antidotes take advantage of complex formation, or sequestration, to reverse the effects of a drug. For example, the newer neuromuscular blocker reversal agents sugammadex and calabadion work by encapsulating the neuromuscular blocker to sequester it from interacting with nicotinic receptors, leading to rapid and complete restoration of neuromuscular function without muscarinic side effects seen with cholinesterase inhibitors.[64] A second novel approach to reversing neuromuscular blockade involves using a chemical antidote is taking advantage of the thiol reactivity of the benzylisoquinolinium blockers to enhance blocker degradation by administering exogenous cysteine as a reversal agent.[65] Reversal of direct acting oral anticoagulants is now achievable with novel antidotes: a humanized monoclonal antibody specific for dabigatran (idarucizumab), and a mutated form of factor Xa that acts as a decoy to neutralize the factor Xa inhibitors rivaroxaban, apixaban, edoxaban, and fundaparinux.[66] A current goal in drug development is to create both specific and universal antidotes to specific drugs or drug classes.

TABLE 1.2 Classical Anesthesia Antidotes

Drug	Antidote
Acetaminophen/paracetamol	Acetylcysteine
Anticholinergic	Physostigmine
Anticholinesterase	Atropine/pralidoxime
Benzodiazepines	Flumazenil
Ca^{2+} Channel blockers	Calcium chloride
Digoxin	Anti-digoxin Fab
Heparin	Protamine sulfate
Malignant hyperthermia	Dantrolene
Neuromuscular Blocker	Anticholinesterase
Opioids	Naloxone
Warfarin	Vitamin K

Ca^{2+}, calcium ion.

TABLE 1.3 Innovative Anesthesia Antidotes

Drug	Antidote
Local anesthetics	Lipid emulsion
Neuromuscular blockers	Encapsulation: sugammadex, *calabadion*
Neuromuscular blockers	Degradation: *cysteine*
DOAC (dabigatran; DTI)	Idarucizumab
DOACs (factor Xa inhibitors)	*Adexanet alfa*
General anesthesia	*Methylphenidate/ketamine*

DOAC, Direct oral anticoagulant; *DTI*, direct thrombin inhibitor.

Key Points

- A drug must first bind a receptor and form a complex to initiate its physiologic effect. The propensity of the drug-receptor complex to form is described by a constant called *affinity*, whereas its propensity to break down is described by the *dissociation constant*.
- Most drug receptors are proteins in the plasma membrane that are involved in cell signaling, such as G-protein–coupled receptors and ion channels.
- Drug binding is not equivalent to *drug effect*. The propensity of the drug-receptor complex to elicit *a physiologic* effect is governed by a characteristic constant called *efficacy*.
- Together, affinity and efficacy give rise to drug *potency*, typically measured as effective concentration for 50% of maximal effect (EC_{50}).
- Depending on their relative efficacies, drugs are characterized as *full, partial,* or *inverse agonists.* Drugs with receptor affinity but no efficacy are referred to as *antagonists*.
- Drugs often bind receptors at multiple distinct binding sites, which can influence receptor actions in complex ways. These interactions are called *allosteric*.
- *Signal transduction* is the process by which receptors transduce signals from extracellular messengers via *second messengers* to regular cellular functions.
- The ability of a drug to bind a particular binding site depends on interactions determined by the chemical structure of the drug and the structure of the binding site. The compatibility between a chemical compound and a binding site can be expressed in a *pharmacophore* model.

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2

Pharmacokinetic and Pharmacodynamic Principles for Intravenous Anesthetics

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CHAPTER OUTLINE

Historical Perspective

Unique Aspects of Anesthetic Pharmacology
- Anesthesiology Compared With Other Disciplines
- A Surfing Analogy as a Simple Conceptual Framework

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- General Schema
- Pharmacokinetics
- Pharmacodynamics
- The Biophase
- Drug Interactions

Pharmacologic Modeling
- PK-PD Models as Versions of Pharmacologic Reality
- PK-PD Model Building Methods
- Limitations in Building & Applying PK-PD Models
  - *Early Model Misspecification*
  - *Stereochemistry*
  - *Active Metabolites*
  - *Variability*

Pharmacologic Simulation
- Unimportance of Individual PK-PD Model Parameters
- Importance of PK-PD Model Simulation

PK-PD Model Simulation and Anesthesia Posology
- Bolus Front-End and Back-End Kinetics
- Infusion Front-End Kinetics
- Infusion Back-End Kinetics
- Influence of Dose on Bolus Onset and Offset of Effect
- Influence of Loading Dose on Infusion Front-End and Back-End Kinetics
- Influence of Special Populations
- Influence of a Second Drug on Effect

PK-PD Models and Technology
- Target-Controlled Infusion

Emerging Developments
- PK-PD Advisory Displays
- Propofol Measurement in Expired Gas
- Allometric Scaling in Pharmacokinetics

The science broadly referred to as clinical pharmacology is the foundation on which anesthesiologists base their therapeutic decisions, including the rational selection of anesthetics and the formulation of safe and effective dosage regimens. Focusing exclusively on intravenous anesthetics, this chapter reviews the fundamental theory and practical application of clinical pharmacology in anesthesia, including pharmacokinetics, pharmacodynamics, the "biophase" concept, compartmental models, and pharmacologic simulation. Although clinical pharmacology is grounded in complex mathematics, the chapter avoids excessive reliance on equations by emphasizing a conceptual understanding of the quantitative ideas, and highlights the intuitive understanding that comes from computer simulation of pharmacologic models. Understanding what a pharmacologic model is and how such a model is built and applied is therefore an important focus of the chapter.

The ultimate goal of the chapter is to provide the clinician with a solid understanding of the fundamental concepts of clinical pharmacology, thereby enabling practical clinical application of these concepts, primarily through the use of pharmacologic simulation. From a pharmacology perspective, there is perhaps nothing more relevant to day-to-day decision making in anesthesiology than the theories explained here. These concepts are the scientific foundation to answer a very important clinical question: "What are the right drug and the optimal dose for my patient?"

Historical Perspective

From the earliest days of modern anesthesia, anesthesiologists sought to understand the dose-response relationship. Using dose escalation study methods, clinician-scientists quantified the magnitude and duration of anesthetic effect over a spectrum of doses, thereby identifying a dosage range that would produce anesthesia without excessive toxicity. For many decades, modern anesthesia practice relied on such dose-response studies as the basis for rational drug administration schemes.

With advances in analytical chemistry and the widespread availability of computing technology, new approaches to understanding drug behavior emerged. By measuring blood anesthetic concentrations over time using techniques such as radioimmunoassay or gas chromatography, it became possible to characterize the relationship between drug dose and the time course of drug levels in the bloodstream, a field of study called pharmacokinetics (often

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Abstract

This chapter presents a review of modern pharmacokinetic and pharmacodynamic concepts that comprise the scientific foundation of rational drug selection and administration of intravenous anesthetics.

Keywords

intravenous anesthetics
pharmacokinetics
pharmacodynamics
drug interactions
clinical pharmacology
pharmacologic simulation

abbreviated as PKs[a]). A natural extension of this new discipline of pharmacokinetics was the characterization of the relationship between the concentration of the drug and the magnitude of effect, a branch of pharmacology called pharmacodynamics (abbreviated as PDs[b]). Coherent linkage of these two pharmacologic disciplines, pharmacokinetics and pharmacodynamics, necessitated creation of the biophase concept wherein plasma drug concentrations from PK studies are translated into apparent "effect site" concentrations, which are then related to drug effects measured in PD studies.

The underlying theory of pharmacokinetics was largely developed in therapeutic areas unrelated to anesthesiology.[1–3] However, because the clinical pharmacology of anesthesia is so unique[4,5] (e.g., the necessity to predict onset and offset of drug effect very accurately), some PK concepts have been developed by anesthesia investigators for specific application in anesthesia.[6–8] Moreover, because of the ease with which profound anesthetic effects can be noninvasively measured in real time (e.g., the peripheral nerve stimulator for neuromuscular blockers, the electroencephalogram [EEG] for hypnotics, among others), many important theoretical advances in pharmacodynamics applicable to other fields of medicine have originated from the study of anesthetics. An especially notable example is the conception of the biophase or effect site concept.[9]

Compared with old-fashioned dose-response methods, a major advantage of these more sophisticated PK-PD studies is that the analysis results in a quantitative model of drug behavior. Using nonlinear regression techniques, equations are fit to raw PK and PD data, yielding a set of PK-PD parameters estimates (i.e., distribution volumes, clearances, potencies) that constitute a quantitative model.[10] Unlike dose-response studies of the past, these quantitative PK-PD models can be applied to more diverse and clinically relevant circumstances through computer simulation.[11]

The application of modern PK-PD concepts into anesthesia practice has blossomed in unanticipated ways. Automated administration of intravenous anesthetics according to a PK model, a technology known as target-controlled infusion (TCI), is now commonplace.[12] The use of real-time PK-PD simulation to guide anesthetic administration, wherein a PK-PD prediction module is placed alongside a traditional physiologic monitor, is also an emerging technology with promising potential.[13]

Unique Aspects of Anesthetic Pharmacology

Anesthesiology Compared With Other Disciplines

The pharmacology of anesthesia is unique compared with other disciplines within medicine (Table 2.1). Perhaps the most obvious difference relates to the safety of anesthetic drugs. Many drugs within the anesthesia formulary produce profound physiologic alterations (e.g., unresponsiveness, paralysis, ventilatory and hemodynamic depression) and have a very low therapeutic index. There are few therapeutic areas in medicine where 2 to 3 times the typical therapeutic dose is often associated with severe adverse or even lethal effects (see Chapter 7). It is perhaps for this reason more than any other that the specialty of anesthesiology evolved. The consequences of "under" or "over" dosing anesthetics can be catastrophic.

[a]When used as an adjective in this chapter, "pharmacokinetic" is abbreviated as "PK."

[b]When used as an adjective in this chapter, "pharmacodynamic" is abbreviated as "PD."

TABLE 2.1 Unique Aspects of Anesthesia Clinical Pharmacology Related to Safety and Efficiency

Safety Issues
• Very low therapeutic index drugs
• Severe consequences to "under" or "over" dosing
• Necessity to adjust the level of drug effect frequently
Efficiency Issues
• Necessity to produce onset of drug effect quickly
• Necessity to produce offset of drug effect quickly

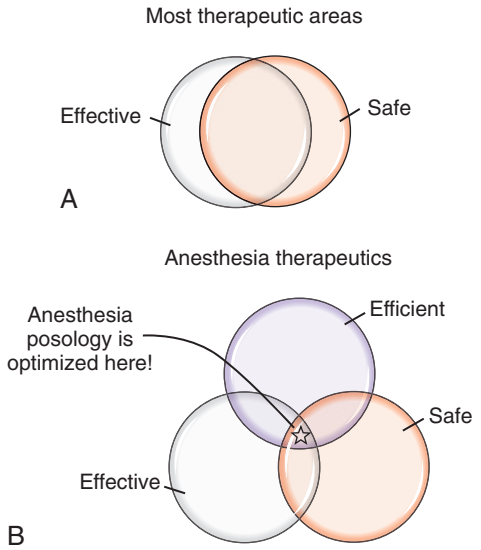
Another important difference between anesthesiology and other therapeutic areas relates to efficiency. Most settings in clinical medicine do not require immediate onset and rapid offset of pharmacologic effect. When an internist prescribes an antihypertensive, for example, the fact that a few days may be required for establishment of a steady-state therapeutic effect is of little consequence. Similarly, when terminating therapy, the necessity to wait a few days to achieve complete dissipation of drug effect is usually of no clinical importance.

Anesthesiologists, in contrast, must respond to the dynamic needs of patients under anesthesia during which the optimal degree of central nervous system depression can vary widely and frequently, requiring continuous adjustment of drug concentrations. In addition, the anesthesiologist must respond to the practical realities of modern medical practice in terms of operating room efficiency and the outpatient revolution; the anesthesiologist must rapidly anesthetize the patient and then quickly reanimate him or her when the surgeons have finished their work, enabling the patient to transition quickly through the recovery process in preparation for going home. Thus optimal anesthesia posology exists at the nexus of at least three domains: safety, effectiveness, and efficiency. Most other therapeutic areas in medical practice are not constrained by this efficiency imperative (Fig. 2.1).

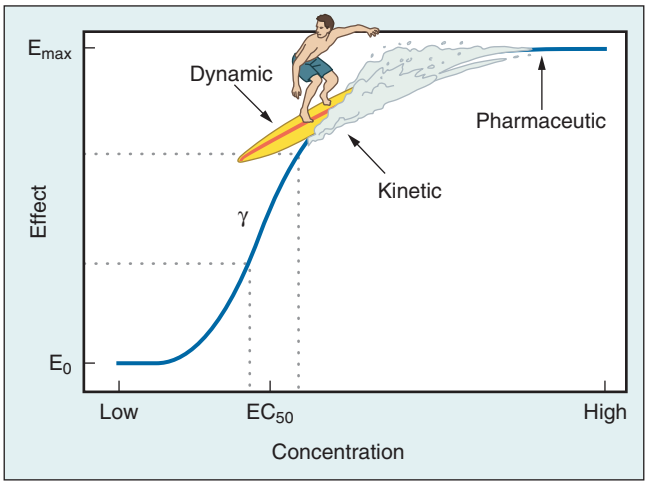
In summary, the profound physiologic alterations of the anesthetized state (and their reversal) must be produced on demand to ensure the rapid achievement and maintenance of the anesthetic state intraoperatively with return of responsiveness, spontaneous ventilation, and other vital functions at the appropriate time. To achieve this degree of pharmacologic control, anesthesiologists in the modern era increasingly rely on the application of advanced PK-PD concepts and technology to formulate and implement rational dosing schemes.[14,15] In addition, anesthesiologists take advantage of drugs that were specifically developed to address the unique concerns of anesthesia pharmacology (i.e., drugs with rapid onset and predictable offset of effect).[4]

A Surfing Analogy as a Simple Conceptual Framework

A surfing analogy is helpful in simply conceptualizing how PK-PD principles can be applied to the problem of rational drug administration in anesthesia.[16] The anesthesiologist typically targets the upper portion of the steep part of the concentration-effect relationship; that is, the concentration that produces considerable drug effect but from which drug effect will recover quickly once drug administration is terminated. This can be visualized as a surfer riding near the crest of a wave as in Fig. 2.2. Targeting ("surfing") the steep portion of the concentration-effect relationship makes it



• **Fig. 2.1** Venn diagrams comparing the posology of most therapeutic areas with anesthesia therapeutics. In most therapeutic areas (A), there is considerable overlap between safe doses and effective doses. In contrast, in anesthesia practice the overlap between safe doses and effective doses is much smaller (B). In addition, anesthesiologists must also adjust the dosage to achieve practical efficiency (see text for full explanation). (Adapted with permission from Kuck K, Egan TD. Getting the dose right: anaesthetic drug delivery and the posological sweet spot. *Br J Anaesth*. 2017 1;119(5):862-864.)



• **Fig. 2.2** A surfing analogy as a graphical explanation of how anesthesiologists use a combination of three approaches (i.e., pharmacokinetic, pharmacodynamic, and pharmaceutic) to administer anesthetics to maintain the anesthetic effect while making rapid recovery possible. See the accompanying text for a detailed explanation. E_0, Effect at zero drug concentration; E_{max}, maximal drug effect; EC_{50}, concentration that produces 50% of maximal drug effect; γ, steepness of the curve. (Reproduced with permission from Egan TD, Shafer SL. Target-controlled infusions for intravenous anesthetics: surfing USA not! *Anesthesiology*. 2003;99:1039–1041.)

possible to achieve large reductions in effect with relatively small decreases in concentration.

In clinical pharmacology terms, there are essentially three approaches to targeting this area of the concentration-effect relationship. Perhaps the most straightforward among them is the PD approach, wherein a drug effect measure is used as a feedback signal to guide drug administration irrespective of the drug concentration achieved. Propofol titrated to a specific processed EEG target or a neuromuscular blocker administered to maintain a specific degree of twitch depression as measured by a peripheral nerve stimulator are examples of this PD approach.

Another common approach in targeting the steep portion of the concentration-effect relationship is the PK approach. Drawing on knowledge about the concentration-effect relationship (i.e., therapeutic windows), the PK approach targets drug concentrations that are typically appropriate for a given anesthetic application. The use of an agent specific vaporizer to deliver some fraction or multiple of an inhaled agent's minimum alveolar concentration (MAC), and the use of a TCI device to infuse propofol to a specified concentration (e.g., the Diprifusor, AstraZeneca, Cambridge, England; and others) are sophisticated examples of this approach. Of course, even in situations when an advanced delivery technology is not used, standard dosage regimens for drugs in anesthesia are devised to achieve concentrations that are within the therapeutic window based on the drug's pharmacokinetics.

A third approach to targeting the steep portion of the concentration-effect relationship can be referred to as the "forgiving drug" or "pharmaceutic" approach. The pharmaceutic approach takes advantage of the responsive pharmacokinetic profiles of modern anesthetic agents. With this approach, within the constraints of acceptable adverse effects such as hemodynamic depression, it is unnecessary to hit the target with as much precision and accuracy as with the other approaches. Because short-acting agent concentrations can be manipulated up or down rapidly, adjustments can be made quickly as suggested by PD feedback. If the empirical dosage scheme is obviously too high or too low, the anesthetist can achieve a more appropriate level of drug effect in short order. Short-acting agents essentially make it unnecessary to hit the target perfectly.

As a practical matter, of course, anesthetists combine all three approaches (i.e., the PD, PK, and pharmaceutic approaches). Typically, pharmacokinetically responsive agents are administered by advanced, target-controlled delivery devices according to PD feedback. Adjusting the propofol TCI target based on feedback from a processed EEG brain function monitor is an example of this combined approach to anesthesia drug delivery. The pharmacologic science underpinning this three-pronged approach to rational drug selection and administration for intravenous anesthesia is the focus of this chapter.

Clinical Pharmacology

Posology

Although defining exactly what comprises the field of "clinical pharmacology" is challenging,[17] it consists of numerous branches, including pharmacokinetics, pharmacodynamics, toxicology, drug interactions, and clinical drug development. Defined in general terms, clinical pharmacology is the branch of pharmacology concerned with the safe and effective use of drugs. Articulated in a more practical way, the ultimate goal of clinical pharmacology is the translation of the relevant pharmacologic science into rational drug selection and dosing strategies.

Posology, although a little used term, is the science of drug dosage and is thus also a branch of clinical pharmacology (or perhaps a synonym). Combining the Greek words *posos* (how much) and *logos* (science), posology can be thought of more simply as "dosology." In the posology of anesthesia, the fundamental question "What is the optimal dose for my patient?" has numerous, clinically important permutations as shown in Table 2.2. All of these questions

have obvious clinical relevance in the day-to-day practice of anesthesia.

The accurate and precise prediction of the time course and magnitude of drug effect is the primary pharmacology-related task of anesthesia. Given the unique challenges of anesthesia pharmacology, one could argue that pharmacokinetics and pharmacodynamics are perhaps more relevant in anesthesia than in any other therapeutic area of medicine. Indeed, despite the conspicuous unpopularity of these mathematically oriented fields among anesthesia practitioners, perhaps without conscious acknowledgment, anesthesiologists are real-time clinical pharmacologists applying PK-PD principles to the optimization of anesthetic posology (and the myriad posologic questions suggested by Table 2.2).

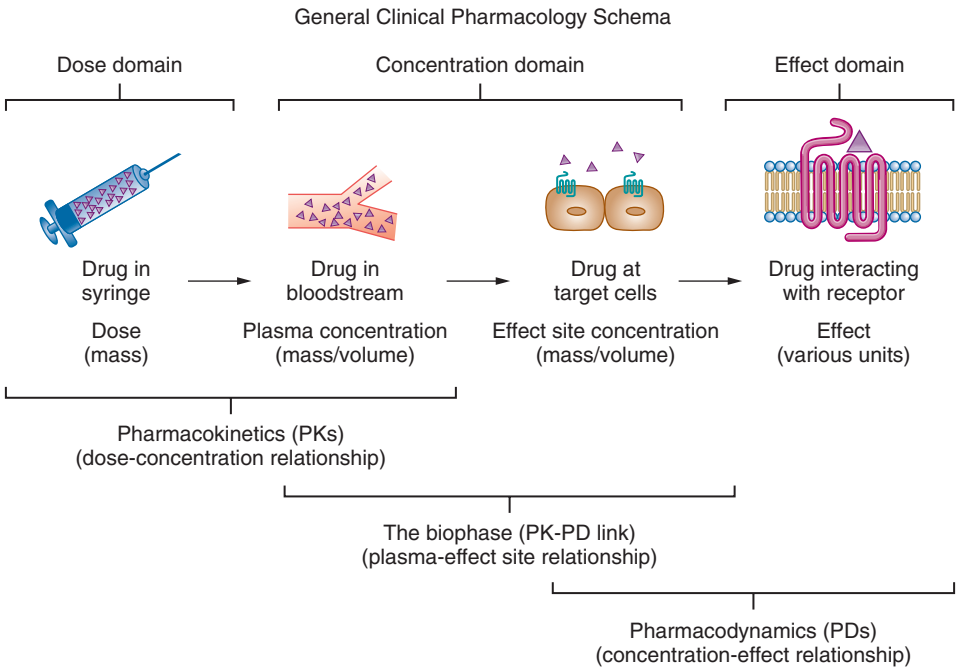
TABLE 2.2 Selected Clinically Important Questions in the Posology of Anesthesia

- What is an appropriate initial dose?
- How soon will the intended effect begin?
- When will the effect peak?
- How long will the effect last?
- Should the drug be given by bolus or infusion or both?
- When will repeat bolus doses or infusion rate changes be necessary?
- When should drug administration stop to promote timely emergence?
- What are the typical therapeutic target concentrations?
- What are the expected consequences of underdosing or overdosing?
- Will tolerance develop?
- What factors might alter the dosage requirement (e.g., demographic, pathologic, genomic)?
- What is the expected amount of variability in drug response?
- How will drug interactions influence outcome?

General Schema

A general schema summarizing a framework for understanding clinical pharmacology is presented in Fig. 2.3. The topic can be considered clinically from three domains: the dosage, concentration, and effect domains. Similarly, the underlying science can be divided into three areas of study: pharmacokinetics, the biophase, and pharmacodynamics. Before advances in clinical pharmacology the clinician could consider only the adequacy of intravenous anesthetic therapy in terms of dosage or effect (i.e., without the aid of a computer model, predicted concentrations in the plasma and effect site were not available and thus the concentration domain was unknowable). Likewise, before the development of modern pharmacologic modeling theory, the three distinct disciplines of clinical pharmacology (i.e., pharmacokinetics, the biophase, and pharmacodynamics) were naively lumped together in the study of the dose-response relationship.

From the practitioner's standpoint, the adequacy of therapy can be considered in any of the three clinical domains. Is the dosage adequate? Are the predicted concentrations adequate? Is the intended effect adequate? From the scientist's perspective, the answers to these clinically oriented questions are grounded in the principles of pharmacokinetics, pharmacodynamics, and the biophase. For some drugs (now mostly older drugs), because a suitable PK model does not exist, consideration of the concentration domain cannot contribute to therapeutic decisions. Similarly, because for some drugs the measurement of drug effect in real time is difficult (e.g., opioids in unresponsive, mechanically ventilated patients), consideration of the effect domain plays a lesser role in guiding therapy.



• **Fig. 2.3** A general schema of clinical pharmacology divided into dose, concentration, and effect domains. The science underpinning the field can be divided into the disciplines of pharmacokinetics, pharmacobiophasics, and pharmacodynamics. See the accompanying text for a detailed explanation. The *purple triangles* represent drug molecules. *PDs,* pharmacodynamics; *PKs,* pharmacokinetics.

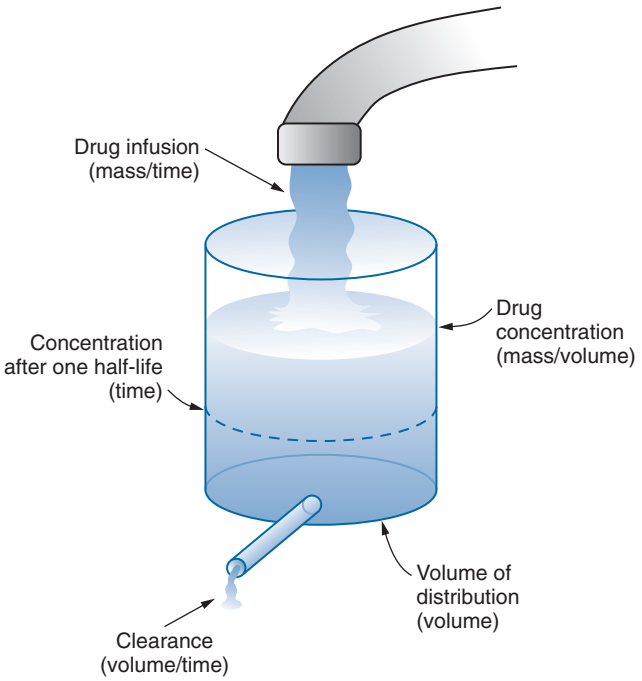
Consider the fate of drug molecules as summarized in Fig. 2.3. The anesthesiologist administers the desired dose intravenously using a handheld syringe or pump (the dose domain). The drug is then distributed via the circulation to body tissues and eventually eliminated through biotransformation and/or excretion according to the drug's pharmacokinetics. The predicted plasma (or blood) concentration versus time profile can be the basis of therapeutic decisions regarding subsequent doses (the concentration domain), although the plasma concentration is sometimes misleading because it might not be in equilibrium with the site of action. Meanwhile, some very small fraction of the administered drug is distributed from the blood to the target cells in the effect site or biophase according to the drug's biophase behavior. The predicted concentration in the effect site (also the concentration domain) is a more reliable indicator of the adequacy of therapy than is the blood concentration because the target receptors are always in equilibrium with this concentration. Finally, the drug molecules in the biophase interact with the relevant receptors, producing the intended effect (the effect domain). For drugs with easily measurable effects, the dose and concentration domain are obviously less relevant to successful therapy because drug effect is the ultimate goal of therapy; when there is a reliable, real-time effect measurement, the drug can be administered to the targeted level of effect irrespective of what the dose or predicted concentration may be.

Pharmacokinetics

Pharmacokinetics is typically defined in introductory pharmacology courses as "what the body does to the drug." A much better and clinically useful definition is the study of the relationship between the dose of a drug and the resulting concentrations in the body over time (the dose-concentration relationship; see Fig. 2.3). In simple terms, pharmacokinetics is the drug's disposition in the body.

Commonly considered PK parameters include distribution volumes, clearances, and half-lives; other, less intuitively meaningful PK parameters such as microrate constants are mathematical transformations of these more common parameters.[18] A simple hydraulic model representation of these fundamental parameters for a one-compartment model is presented in Fig. 2.4. The pharmacokinetics of most anesthetic drugs are described by more complex models with two or three compartments (see also "PK-PD Model Building Methods" in later text). When conceptualized in terms of an hydraulic model, of course, multicompartment models consist of additional containers (i.e., volumes) connected to the central volume by pipes of varying sizes.

Distribution volumes, expressed in units of volume such as liters or liters per kilogram, are "apparent" in that they are estimated based on the volume of water into which the drug appears to have distributed; they do not represent any actual volume or anatomic space within the body. Clearance parameters, expressed in units of flow such as liters per minute or liters per kilogram per minute, simply quantify the volume of plasma from which the drug is completely cleared per unit of time. For drugs with a very high hepatic extraction ratio (i.e., the liver biotransforms almost all the drug delivered to it), the central clearance is nearly equal to hepatic blood flow (e.g., about 1 L/min). Half-lives, perhaps the most commonly known PK parameter, are expressed in units of time and represent the time required for the concentration to decrease by 50% after drug administration has ceased. Half-life varies directly with volume of distribution and inversely with clearance; these relationships make intuitive sense given that a larger volume will take longer to clear and that a higher clearance will obviously speed the decline of drug levels.

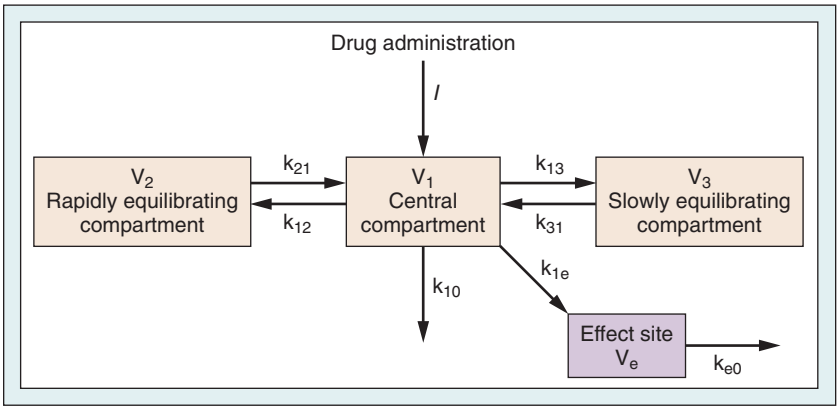


• **Fig. 2.4** A hydraulic representation of a one-compartment pharmacokinetic (PK) model simply illustrating various PK parameters. Water running from the faucet into the container represents an infusion of drug. The size of the container represents the volume into which the drug will distribute (i.e., the volume of distribution). The height of the water level is the drug concentration. The water flowing out of the pipe at the bottom of the container represents drug elimination (i.e., clearance). The half-life of the drug after the infusion is stopped is also shown.

Pharmacodynamics

Pharmacodynamics is typically defined as "what the drug does to the body." A better definition is the study of the relationship between the concentration of the drug in the body and its effects (i.e., the concentration-effect relationship; see Fig. 2.3). In straightforward terms, pharmacodynamics is a description of drug effects, both therapeutic and adverse.

Particularly important PD parameters include potency and the steepness of the concentration-effect relationship (see "PK-PD Model Building Methods" in later text). Expressed in units of mass per volume (e.g., micrograms per milliliter; nanograms per milliliter), potency is usually estimated as the concentration required to produce 50% of maximal effect, often abbreviated as the C_{50} (sometimes called the EC_{50}, the effective concentration producing 50% of maximal effect; see Fig. 2.2). Obviously, the lower the EC_{50}, the more potent is the drug. The EC_{50} is important in determining the range of target concentrations that will be necessary for effective therapy (i.e., the therapeutic window). The steepness of the concentration-effect relationship is typically quantified by a parameter called *"gamma,"* a unitless number that reflects the verticality of the concentration-effect relationship. A highly vertical concentration-effect relationship (i.e., large gamma) means that small changes in drug concentration are associated with large changes in drug effect; some groups of drugs (e.g., opioids) have steeper concentration-effect relationships than others.[19]



• **Fig. 2.5** A schematic representation of a three-compartment model with an effect compartment attached to the central compartment to account for the equilibration delay between concentration in the central compartment and drug effect. *I*, Drug input; k_{12}, k_{13}, and so on, rate constants characterizing drug movement between compartments and out of the system; k_{e0}, rate constant for drug elimination out of the effect compartment; V_1, V_2, and so on, compartment volumes. See the accompanying text for a detailed explanation.

The Biophase

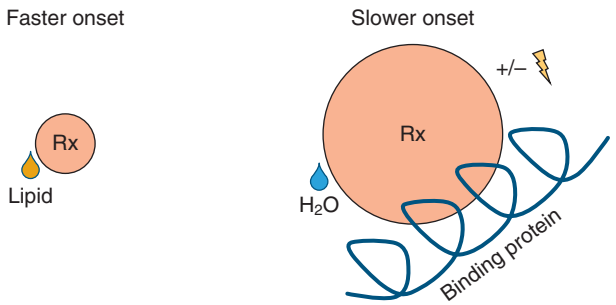
The biophase concept is a nuance of clinical pharmacology that is perhaps not as widely covered in pharmacology courses because its clinical application is most relevant to just a few acute care disciplines like anesthesiology. "Pharmacobiophasics," a neologism not in common usage (coined by author TDE), is the study of drug behavior in the biophase. The biophase is the site of drug action, often referred to as the *effect site* (e.g., target cells and receptors within the brain, the neuromuscular junction, the spinal cord).

The biophase concept is essential to clinical anesthetic pharmacology because during non–steady-state conditions (i.e., after a bolus injection or an infusion rate change) the concentration of drug in the blood does not correlate well with drug effect. After a bolus injection, compartmental models predict that peak plasma drug concentration occurs immediately (i.e., a key "well stirred" model assumption), and yet peak drug effect does not occur immediately. This is because most drugs do not exert their effect in the blood; rather, they must be delivered to the site of action (i.e., the biophase) before they can elicit the desired therapeutic effect. Thus predictions regarding the magnitude of drug effect based on plasma concentrations can be misleading, particularly when plasma drug concentrations are rapidly changing such as after a bolus injection.

As originally proposed by investigators working with d-tubocurarine and pancuronium,[9,20,21] the biophase (effect site) concept has revolutionized the ability to predict the time to maximal drug effect during non–steady-state conditions. As shown in Fig. 2.5, incorporating a theoretical "effect compartment" into a standard compartmental PK model enables characterization of the plasma-biophase equilibration process. It is the central compartment concentration (i.e., the concentration in the arterial blood) that drives the concentration in the effect site.

The key pharmacobiophasics parameter, expressed in units of inverse time, is a rate constant called k_{e0} (see "PK-PD Model Building Methods" in later text).[9,20,22] The k_{e0} characterizes the rate of equilibration between plasma and effect site concentrations. When k_{e0} is known for a drug, it is possible to predict the time course of "apparent" effect site concentrations based on the time course of plasma concentration. These effect site concentrations correlate directly with drug effect. Thus the biophase can be viewed as the link between drug disposition in the blood (pharmacokinetics) and drug effect at the site of action (pharmacodynamics).

The time required to achieve peak effect site concentration after bolus administration is a function of the drug's physicochemical properties in vivo. Small, lipid-soluble, un-ionized, unbound molecules (i.e., drugs with a high "diffusible fraction") reach peak effect site concentration more rapidly than larger, less lipid-soluble, charged, highly protein-bound drugs (Fig. 2.6). For drugs that achieve a peak effect site concentration more slowly, the onset of therapeutic effect can be hastened with higher doses (see Fig. 2.16).



• **Fig. 2.6** A schematic representation of the physicochemical properties that hasten or slow the achievement of peak effect site concentration. Small, lipid-soluble, un-ionized, unbound molecules reach peak effect site concentration more rapidly. Molecular weight, the octanol-water partition coefficient, pKa, and the percent protein bound are the parameters that quantify these physicochemical properties. *Rx* indicates a drug molecule. The lipid droplet indicates high lipid solubility. The *H_2O* droplet represents high water solubility. The *+/– lightning bolt* indicates a charged molecule. The *ribbon-like structure* represents a protein binding molecule such as albumin.

Drug Interactions

In anesthesiology, unlike most medical disciplines, PD drug interactions are frequently produced by design. Anesthesiologists take advantage of the PD synergy that results when two drugs with different mechanisms of action but similar therapeutic effects are combined.[23] These synergistic combinations can be advantageous because the therapeutic goals of the anesthetic can often be achieved with less toxicity and faster recovery than when individual drugs are used alone in higher doses. In fact, except for specific, limited clinical circumstances in which a volatile agent or propofol alone is an acceptable approach (e.g., a brief procedure in a pediatric patient such as tympanostomy tubes or radiation therapy), modern-day anesthesia involves at least a two-drug combination consisting of an analgesic (typically an opioid) and an hypnotic (e.g., an inhaled agent or propofol).[24] Therefore from a strictly pharmacologic perspective, anesthesiology can be thought of as the practice of PD synergism using central nervous system depressants.

Because anesthetics are rarely administered alone, understanding the interactions between drugs is critical to their safe and effective use.[25,26] Although PK interactions (i.e., where one drug alters the concentration of another) are sometimes observed in select clinical circumstances,[27] PD interactions are an important part of nearly every anesthetic. This topic is of such importance in anesthesia pharmacology that an entire chapter is devoted to it (see Chapter 6); a limited discussion is included here.

The study of drug interactions in anesthesiology has traditionally been approached using the "isobologram" method.[28,29] An isobologram is a curve defining the concentrations of two drugs that, when given together, produce the same effect (the isobole is an "iso" or "equal" effect curve). Perhaps the most common example of an isobole in anesthesiology is a plot showing the reduction in the MAC of an inhaled agent produced by an opioid.[30,31] The main limitation of an isobologram is that the curve applies to only one level of drug effect. This is a problem in anesthesiology because during anesthesia patients experience a spectrum of drug effect ranging from minimal sedation to profound central nervous system depression.

Response surface methods address this shortcoming of the isobologram. The response surface approach creates a three-dimensional plot of the two drug concentrations (e.g., propofol and fentanyl) versus drug effect (e.g., sedation), quantitatively describing the PD interaction of the two drugs (see Chapter 6). The response surface method is an advance because it describes the drug interaction over the entire range of drug effect and thereby enables simulation from one clinical state to another. This is critical in anesthesia pharmacology because anesthesiologists must take the patient from the awake to the anesthetized state, and then back to the awake state again on demand.[4,16] Response surface methods yield a set of parameters that indicate whether the interaction is additive, synergistic, or antagonistic.

Pharmacologic Modeling

PK-PD Models as Versions of Pharmacologic Reality

Scientific models seek to represent empirical objects, biologic phenomena, or physical processes in a coherent and logical way. Models are a way of thinking about and understanding the natural world; models are essentially a simplified version of reality intended to provide scientific insight.

By providing a framework for understanding the natural world, models can also be a means of creating new knowledge. Knowledge from models comes in many forms, each with certain advantages and limitations. In biomedical science, for example, models of physiologic processes conducted in test tube experiments provide in vitro knowledge wherein confounding variables can be carefully controlled. Experiments conducted in animal models of disease provide in vivo insight that reflects biologic reality at the whole animal level. Since the advent of computational scientific methods, models of natural phenomena are often represented as a mathematical system (an equation or set of equations); these mathematical models provide in silico understanding, meaning that experiments that might be practically impossible or too expensive in actual subjects can be conducted by computer simulation.

PK-PD models are examples of this kind of mathematical model applied to clinical pharmacology.[32] Various equations are used to represent the pharmacologic processes of interest.[2] Although a PK-PD model is a gross oversimplification of reality (e.g., the body is not a set of three containers connected by pipes as suggested in Fig. 2.5), considerable insight into drug behavior has come from the application of PK-PD models to important questions in anesthesia pharmacology. When applying PK-PD models through simulation, rather than conducting the experiment in a test tube (in vitro) or in an experimental animal (in vivo), the experiment is conducted in the computer (in silico) on a virtual subject or subjects.

It is axiomatic that the true utility of a pharmacologic model is a function of its performance in the real world. Clinically useful models adequately describe past observations and satisfactorily predict future observations. Among scientists involved in all kinds of modeling, it is often quipped that "all models are wrong, but some models are useful!"[33] There is no question that PK-PD models, despite their limitations, are very useful in refining the posology of anesthesia practice.[14,15]

PK-PD Model Building Methods

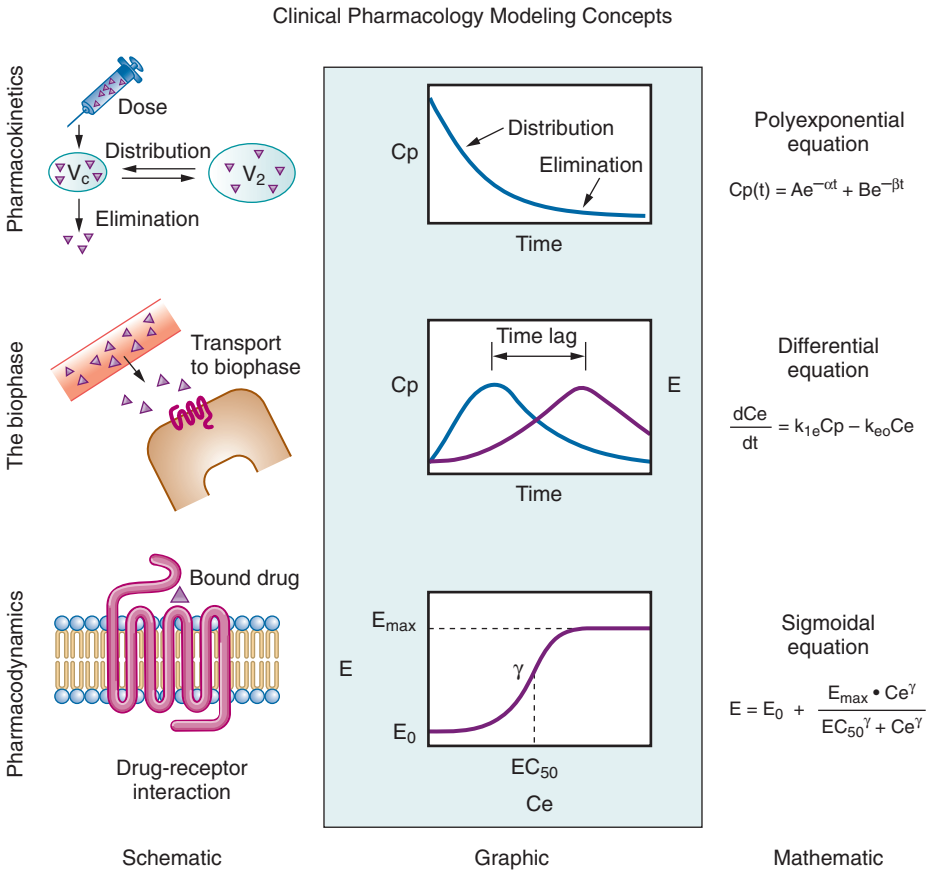
A summary of the PK-PD model building process is outlined in Fig. 2.7. The process, of course, begins with the gathering of the raw data in appropriately designed experiments.[34,35] Elements of a well-designed PK-PD modeling experiment for an intravenous anesthetic include careful attention to the administered dose by infusion[15]; frequent, prolonged sampling of arterial blood for concentration measurement[36,37];use of a quality-assured, validated drug assay; and administration of sufficient drug to elicit maximal or near-maximal effect (but not too rapidly).[20] Without quality raw data it is impossible to characterize the pharmacologic system using modeling techniques.

Because the mathematics involved in PK-PD modeling can be complex, it is perhaps best for the clinician to consider the modeling methods from other perspectives.[38] As shown in Fig. 2.7, approaching the modeling process from schematic and graphic perspectives makes the mathematics less intimidating for non-mathematicians. Ultimately the mathematical equations involved are simply quantitative expressions of the ideas and concepts represented by the schematic diagrams and plots.

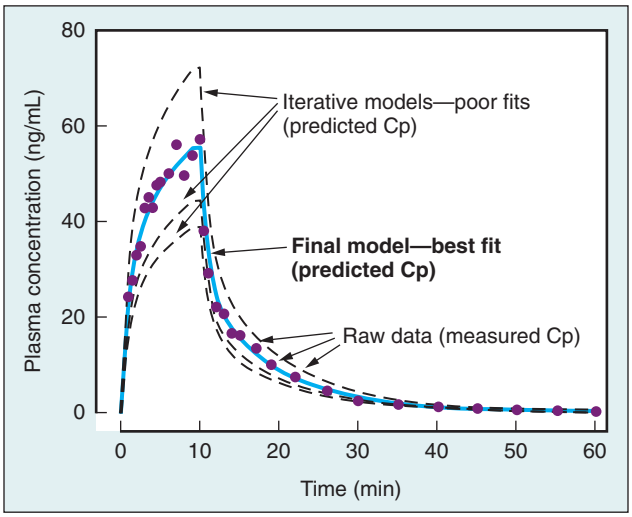
Schematically, basic PK processes are well represented by a compartmental model (see upper panel of Fig. 2.7). After injection into the central compartment, a drug is either distributed to other compartments or is eliminated from the central compartment altogether. Graphing these PK processes reveals the distinct distribution and elimination phases typically observed in plasma concentration decay curves. Curves of this general shape can be represented by polyexponential equations of the form shown in upper panel of Fig. 2.7.[39]

Fig. 2.8 summarizes how raw PK data from a single subject might be modeled in a typical PK model building experiment. Using nonlinear regression techniques, a polyexponential equation is fit to the raw concentration versus time data.[40] This is an iterative process in which the nonlinear regression software alters the parameters of the equation repeatedly until the "best model" is obtained, thereby estimating the PK parameters of the model (i.e., distribution volumes, clearances, microrate constants).[41] The best model is one that fits the data well (e.g., minimizes the difference between the measured concentration and the concentration predicted by the model).[42] The PK model enables prediction of the time course of drug concentrations in blood or plasma.

Biophase behavior and pharmacodynamics can be modeled in generally the same way. When the biophase is considered schematically, the delay between peak plasma concentration and peak drug effect is a function of the time required for drug delivery to the site of action (middle panel of Fig. 2.7).[10] This delay (or hysteresis



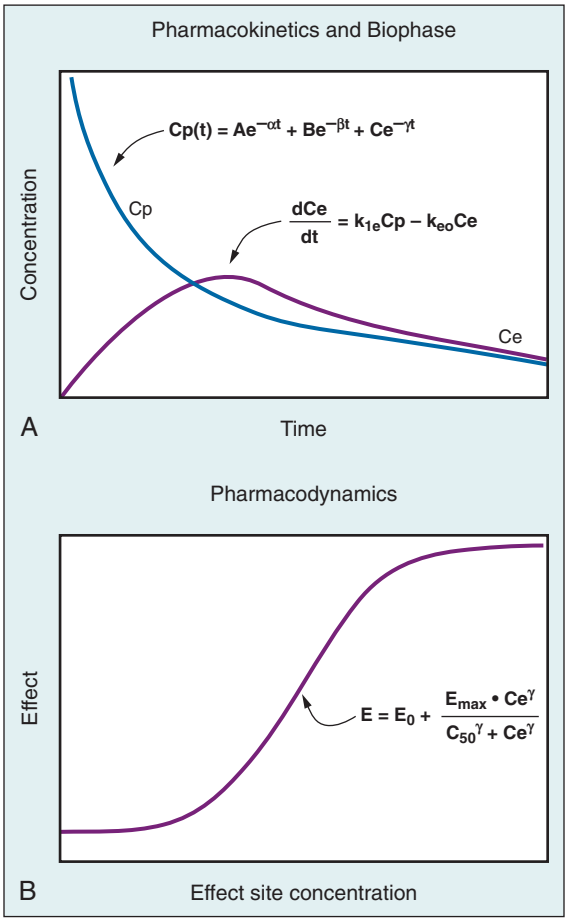
• **Fig. 2.7** A summary of clinical pharmacology modeling concepts for the disciplines of pharmacokinetics, the biophase, and pharmacodynamics. The modeling foundation for each area is presented schematically, graphically, and mathematically. The purple triangles represent a drug. See the accompanying text for a detailed explanation, including discussion of the equations. *Ce,* effect site concentration; *Cp*, plasma concentration; *E,* effect; E_0, effect at zero drug concentration; E_{max}, maximal drug effect; EC_{50}, concentration that produces 50% of maximal drug effect; γ, steepness of the curve.



• **Fig. 2.8** An example of fitting a model (a polyexponential equation in this case) to raw pharmacokinetic (PK) data from a single experimental subject. The measured plasma concentrations (i.e., the raw data) are represented by the *pink circles.* Preliminary models (i.e., poor fits) generated during the iterative, nonlinear regression process are shown as *dotted lines.* The final model (i.e., best fit) is shown as a *thick, blue line.* The thick, blue line thus represents the predicted concentrations according to the PK model. See the accompanying text for a detailed explanation.

in engineering terms) is represented by a simple plot showing a time lag between peak plasma concentration and peak effect, and can be characterized by a simple differential equation of the general form shown. Using nonlinear regression and other techniques, the biophase modeling process estimates the key biophase model parameter called k_{e0} (see previous text).[9,22] The biophase model enables prediction of effect site concentrations.

These effect site concentration predictions are essential for the PD modeling process. Considered schematically, the PD system is represented by a drug molecule interacting with a target receptor (bottom panel of Fig. 2.7). This drug-receptor interaction is represented graphically by a sigmoidal curve. In the absence of drug, the level of biologic effect is at baseline (E_0). As drug concentration in the effect site (predicted from the biophase model) increases, eventually some drug effect is produced. As the steep portion of the concentration-effect relationship is approached, more pronounced degrees of drug effect are observed. Further increases in drug concentration produce greater and greater effect, eventually reaching the biologic maximum (E_{max}). This sigmoidal curve is represented by equations of the general form shown in the bottom panel of Fig. 2.7. Using nonlinear regression techniques such as those illustrated in Fig. 2.8, the PD modeling process fits the sigmoidal equation to the raw PD data, thereby estimating the parameters of the equation. Combined with the PK and biophase model, the PD modeling process enables prediction of the time course of drug effect.



• **Fig. 2.9** Basic equations for modeling drug plasma concentration *(Cp)*, effect site concentration *(Ce)*, and effect. These equations (or various transformations of these equations) are the mathematical basis for pharmacokinetic-pharmacodynamic modeling. The equations represent curves of the appropriate shape to characterize the raw data. See text for complete explanation. *Ce,* effect site concentration; *Cp*, plasma concentration; E_0, effect at zero drug concentration; E_{max}, maximal drug effect; C_{50}, concentration that produces 50% of maximal drug effect;

In summary, PK-PD model building is an exercise in fitting appropriate equations to experimental data using nonlinear regression modeling software and other related techniques.[41] As summarized in Fig. 2.9, the mathematical equations simply represent the general shape of the relationships being modeled. A polyexponential equation is typically used to characterize the plasma concentration decay curve. A differential equation is the basis for modeling the delay between equilibration of plasma and effect site concentration. A sigmoidal equation is used to characterize the concentration-effect relationship. Fitting the equations to the raw data results in a set of PK-PD parameter estimates that constitute the quantitative model.[18] These parameters can then be used to conduct PK-PD simulations to explore the clinical implications of the models. It is important to emphasize that the iterative, nonlinear regression process yields only parameter "estimates;" the true values of the parameters are unknowable.[a]

It is of course possible to fit these equations to an individual subject's data and also to a group of subjects' data. Because a main thrust of PK-PD modeling is to characterize drug behavior in the population for which it is intended, a primary focus of modeling is to build a model that represents the entire population (not just an individual).[35] Special techniques such as "mixed-effects" modeling (e.g., the NONMEM program and others)[43,44] have been developed and refined to estimate typical PK-PD parameter values for an entire population (and also the intersubject variability of the parameters).[45] Sophisticated methods to quantify the influence of "covariate" effects (e.g., age, body weight, metabolic organ failure, among others) on the PK-PD system have also been described.[46]

Limitations in Building & Applying PK-PD Models

As simplified versions of reality, PK-PD models fail to account for certain biologic complexities. In selected situations, these complexities make it difficult or impossible to apply PK-PD models in a useful way. Thus intelligent construction and application of PK-PD models requires awareness of their limitations.

Early Model Misspecification

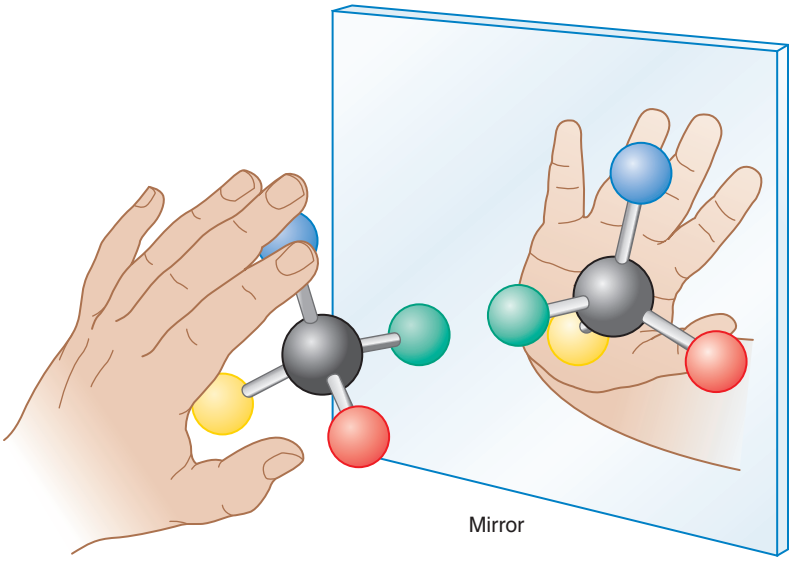
A major shortcoming of the standard compartmental PK model is a function of model misspecification during the early period after drug injection.[47] Standard compartmental models assume the central volume is well stirred and that peak plasma concentration occurs immediately after injection, an assumption that is obviously invalid. Similarly, standard compartmental models assume that plasma concentration declines monotonically after it reaches a peak; although perhaps less obvious, this assumption is also false.[48] Careful study of the early period after drug injection confirms that standard compartmental models sometimes do not reliably predict drug disposition in the first few minutes after injection.[47] Model misspecification is important because anesthetics are often intended to exert their most profound effects very soon after a bolus is administered.[49]

The reasons underpinning this model misspecification in the period shortly after bolus injection are numerous and include the influence of cardiac output on drug distribution, the appearance of a "recirculatory," second concentration peak (after the first circulation time), and pulmonary uptake of drug, among others.[48,50,51] These limitations of compartmental models can be addressed with more complex physiologic and recirculatory models,[52–55] although standard compartmental models are more commonly applied clinically despite their sometimes poor performance. These more physiologically based PK modeling approaches have identified factors that influence anesthesia induction doses, such as age, cardiac output, and concomitant use of drugs that alter cardiac function.[50,56,57]

Stereochemistry

Chirality in molecular structure introduces substantial complexity in characterizing drug behavior with PK-PD models if the chiral drug is studied as a racemate.[58] Taken from the Greek word *chier* (meaning hand), "chiral" is the term used to designate a molecule that has a center (or centers) of three-dimensional asymmetry. The appropriateness of the term's Greek origin is clear when considering that a pair of human hands are perhaps the most common example of chirality (Fig. 2.10). Although they are mirror images of each other, a pair of hands cannot be superimposed. Similarly, chirality in molecular structure results in a set of mirror image molecular twins (i.e., the two enantiomers of a racemic mixture) that cannot be superimposed. This kind of molecular handedness in biologic

[a]In this chapter, "parameter estimates" will sometimes be referred to as just "parameters."



• **Fig. 2.10** The concept of molecular chirality compared to the anatomic asymmetry of a pair of human hands. Like a pair of hands, chiral molecules are identical, mirror images of one another, but they cannot be superimposed. The molecular asymmetry of chirality is a function of the tetrahedral bonding characteristics of the carbon atom (carbon is represented in *black;* the *other colors* represent any four different groups of atoms). The two molecules shown are considered enantiomers; when combined, they constitute a racemic mixture. Chirality has important pharmacologic implications in terms of pharmacokinetic-pharmacodynamic behavior.

systems is ubiquitous in nature and is almost always a function of the unique, tetrahedral bonding characteristics of the carbon atom.[59]

Drug chirality is significant because the molecular interactions that are the mechanistic foundation of drug action and disposition occur in three dimensions and therefore can be altered by stereochemical asymmetry (see Chapter 1).[60] Thus, pharmacologically, not all enantiomers are created equal! The implications of chirality span the entire PK-PD spectrum. Enantiomers can exhibit differences in absorption and bioavailability, distribution and clearance, potency, and toxicology. When a pharmacologic process discriminates in a relative fashion between enantiomers (e.g., one enantiomer being metabolized more rapidly than the other), it is termed *stereoselective.* If the discrimination is absolute (e.g., one enantiomer being completely incapable of producing drug effect), the process is termed *stereospecific.*

The implications of chirality on PK-PD modeling are obvious. A PK-PD model of a racemic mixture is really a model of two drugs with presumably different PK and PD behavior and thus must be interpreted with caution. This "racemate" complexity applies to a surprisingly diverse array of anesthetic drugs, including thiopental, methohexital, ketamine, isoflurane, desflurane, mepivacaine, bupivacaine, ibuprofen, ketorolac, and methadone, among others.[61] It is for this reason that novel drug development in anesthesia over the past decade has avoided racemic mixtures (there is considerable pressure from regulatory bodies like the United States Food and Drug Administration to do so).[62,63] Single enantiomer formulations such as (S)-ketamine, ropivacaine, cisatracurium, and levobupivacaine are all cases in point; single enantiomer formulations often have some clinical advantage in terms of their PK and/or PD behavior, reflecting the PK-PD differences between enantiomers.[61]

Active Metabolites

When a drug has an active metabolite, applying a PK-PD model of the parent compound to predict overall drug effect is obviously problematic. Not only will the metabolite contribute to drug effect, but the metabolite will also have a different rate of concentration decay (i.e., different pharmacokinetics). The PK-PD model of the parent drug does not account for this complexity and thus the model must be applied with awareness of this shortcoming.[64] Therapeutic drug monitoring of parent drugs with active metabolites has long been known to be fraught with similar problems.[65]

This active metabolite issue applies to a number of anesthetic drugs, including diazepam, midazolam, codeine, morphine, and ketamine, among others. Particular interest in recent years has been focused on morphine's active metabolite, morphine-6-glucuronide (M6G). Because M6G accumulates in patients with altered renal clearance mechanisms (unlike the parent drug),[66,67] prolonged administration of morphine in patients with kidney failure can be complicated by severe ventilatory depression.[68] PK-PD models for morphine that also include the concentration time course and effect of the M6G metabolite provide a scientific explanation for these clinical observations.[69]

Variability

Another major shortcoming in applying PK-PD models clinically is that standard simulations using PK-PD model parameters do not typically include an expression of variability in the PK-PD predictions. As a result, from a statistical perspective, these standard simulations are being applied deterministically rather than probabilistically. Given the well-described and considerable variability in drug behavior in terms of both PK and PD relationships[70] (and that PK-PD model parameters are only estimates), this shortcoming of standard PK-PD model simulation is an important one. Applying advanced statistical methods such as Monte Carlo simulation to standard PK-PD analysis is a means of addressing this problem by providing the clinician with a sense of the expected variability in drug behavior.[71]

Pharmacologic Simulation

Unimportance of Individual PK-PD Model Parameters

In contrast to well-entrenched conventional wisdom, single PK-PD model parameter estimates considered in isolation are not very helpful in drawing clinically useful conclusions. PK-PD studies in the anesthesia literature traditionally include a table of values for PK-PD parameters such as in the left column of Table 2.3. In

the early days of PK-PD modeling, it was commonplace for investigators to make clinical inference by comparing a particular parameter value for one drug with the corresponding parameter of another drug. For example, certain clinical conclusions might have been drawn depending on how the half-lives or clearances for a pair of drugs compared.

The problem with this simplistic approach is that it fails to account for the complexity of the typical PK model. A standard three-compartment model as shown in Fig. 2.5, for example, has six fundamental parameters (i.e., three clearances and three distribution volumes); these fundamental parameters can be converted to a variety of other parameters (e.g., half-lives, microrate constants).[18] These multiple parameters interact in a complex way over time in determining the predicted drug concentration.[6,72] Thus comparing a single PK parameter value of one drug with that of another drug is of limited value and provides very little clinically relevant intuitive understanding.

TABLE 2.3 Selected Traditional Pharmacokinetic-Pharmacodynamic Model Parameters Versus Practical Model Predictions[a]

Traditional Parameters (From the Model)	Practical Model Predictions (From Model Simulation)
Pharmacokinetic	**Front-End and Back-End Bolus Behavior**
Distribution volumes	Time to peak effect after a bolus injection?
Clearances	Time to offset of effect after a bolus injection?
Half-lives	
Pharmacobiophasics	**Front-End and Back-End Infusion Behavior**
k_{e0}	Time to steady state after beginning an infusion?
Pharmacodynamic	Time to offset of effect after stopping an infusion?
E_0	**Dosage Domain Issues**
E_{max}	Dosage necessary to achieve a specified target concentration?
EC_{50}	Dosage reduction necessary when combining synergistic drugs?
Gamma (γ)	**Concentration Domain Issue**
	Concentration necessary to achieve specified effect?

E_0, Effect at zero drug concentration; *EC_{50}*, concentration that produces 50% of maximal drug effect; *E_{max}*, maximal drug effect; *gamma (γ)*, steepness of the curve; *k_{e0}*, rate constant for drug elimination out of the effect compartment.

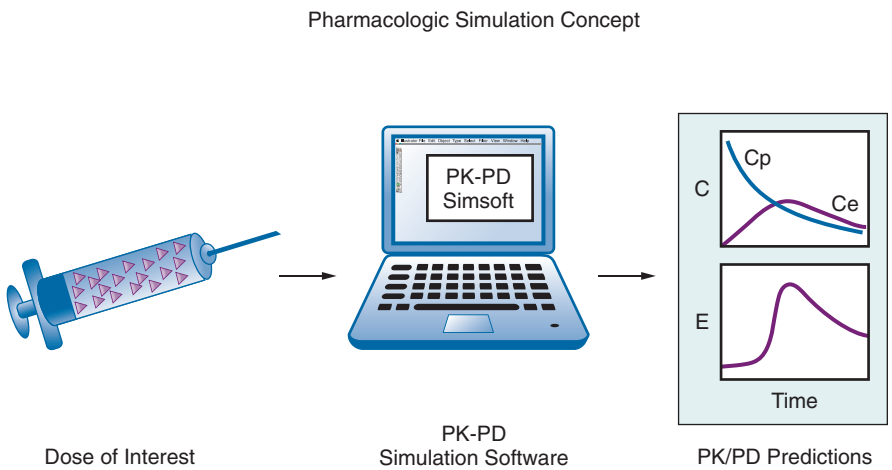
[a]Single PK-PD parameters considered in isolation are not clinically useful; predictions from model simulations are very useful (see text for complete explanation).

Importance of PK-PD Model Simulation

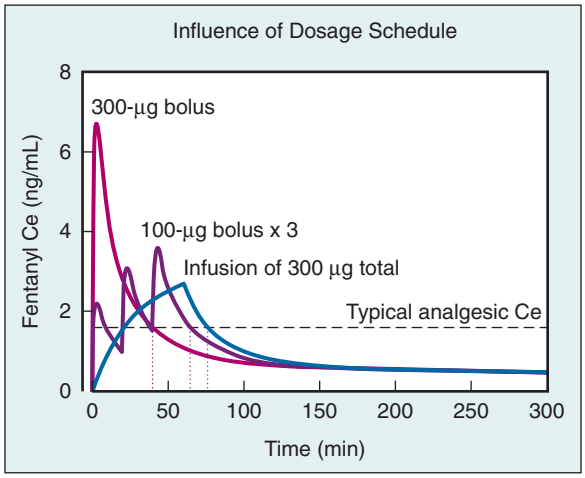
Understanding the clinical implications of a table of PK-PD parameters is best accomplished through in silico application of the associated model by computer simulation.[73] Through simulation, the practically oriented clinical questions shown on the right column of Table 2.3 (among many other questions) can be explored and answered. In contrast to a table of parameter values, PK-PD model simulation provides straightforward, clinically oriented information that the practitioner can apply in actual practice.[38]

The PK-PD model simulation process is summarized in Fig. 2.11. Using PK-PD model simulation software, the user inputs a dosing scheme of interest. The simulation software predicts the time course and magnitude of drug concentration and effect according to the model. An infinite number of such simulations can be performed in silico to gain insight into anesthesia posology. When presented graphically, the results of PK-PD simulations provide a picture of the time course of drug concentration and effect. Most commonly, drug effect site concentrations are simulated. Combined with knowledge about the concentration-effect relationship (i.e., pharmacodynamics), clinical insight into optimal dosing is gained.[74]

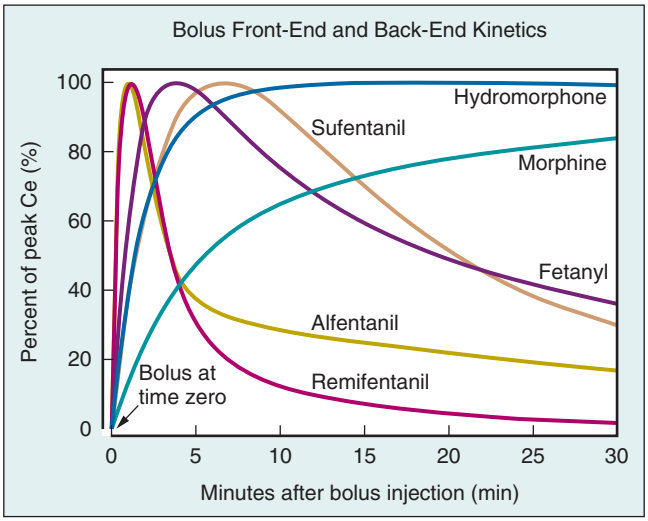
The simulation in Fig. 2.12 illustrates the power of PK-PD simulation in terms of intuitively understanding the implications of various dosing schemes. The simulation depicts the very different time courses of drug concentration in the biophase when identical total doses of fentanyl (i.e., 300 µg) are administered in three different ways. By providing a simple picture of how a specified dosing scheme translates into effect site concentrations over time (and how the resulting concentration versus time profile compares to therapeutic windows), PK-PD simulation constitutes a powerful tool to study and optimize anesthesia posology.



• **Fig. 2.11** A simple representation of the concept of a pharmacokinetic-pharmacodynamic (PK-PD) model simulation. Using PK-PD model simulation software (called "PK-PD Simsoft" in this figure just for illustration purposes; PK-PD Simsoft is not an actual product), the user inputs a dosing scheme of interest. The simulation software predicts plasma concentrations *(Cp)*, effect site concentrations *(Ce)*, and effect *(E)* according to the parameters of the PK-PD model. In this diagram, PK-PD Simsoft is a fictitious simulation software product. See the accompanying text for a detailed explanation.



• **Fig. 2.12** A pharmacokinetic simulation of predicted fentanyl effect site concentrations *(Ce)* resulting from three different regimens to administer 300 µg of fentanyl (a single 300-µg bolus, three 100-µg boluses every 20 minutes, an infusion of 300 µg at a constant rate over 1 hour). The *horizontal dotted line* indicates a typical analgesic fentanyl level. The *colored vertical dotted lines* represent the time at which the fentanyl concentration falls permanently below the typical analgesic level. See the accompanying text for a detailed explanation. The simulations were conducted with pharmacokinetic-pharmacodynamic parameter estimates from the literature.[107]



• **Fig. 2.13** A simulation exploring bolus injection front and back-end pharmacokinetic behavior for a variety of commonly used opioids. For comparison purposes, the effect site concentrations *(Ce)* are normalized to the percentage of the peak. See the accompanying text for a detailed explanation. The simulations were conducted with pharmacokinetic-pharmacodynamic parameter estimates from the literature.[69,107–113]

PK-PD Model Simulation and Anesthesia Posology

Exploring anesthesia posology through PK-PD simulation equips the practitioner with the knowledge necessary to formulate rational drug selection and administration schemes. Although the possibilities are endless in terms of the number and variety of PK-PD simulations that can be performed, a limited set of straightforward simulations form the foundation on which the answers to many routine anesthesia posology questions are based.

Among this fundamental set of simulations, perhaps the most important are those that address the front-end and back-end PK behavior of intravenous anesthetics. Because drug behavior is substantially different for bolus injections compared with infusions,[7] the two conditions must be considered separately. Other fundamental simulations include the influence of dose on the onset and offset of effect after bolus injection, the influence of dose on the front and back-end kinetics of infusions, the influence of special populations on drug behavior, and the influence of a second drug on PD effect.

Bolus Front-End and Back-End Kinetics

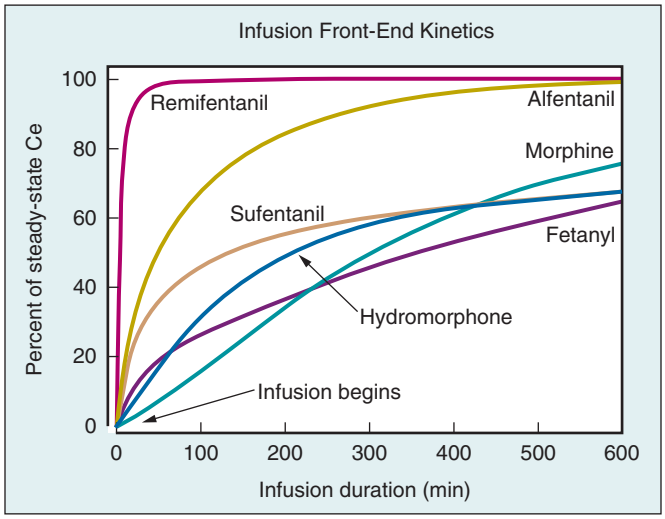
As noted in Table 2.2, important posologic questions regarding bolus injections include "How long will it take to reach peak effect and how long will it take for the effect to dissipate?" The simulations plotted in Fig. 2.13 explore these questions for a number of commonly used opioids. After bolus injection, remifentanil and alfentanil predicted effect site concentrations reach a peak quickly and then decline significantly before any of the other opioids have even begun to peak. This rapid achievement of peak effect site concentrations for these two highly lipid-soluble fentanyl congeners is likely a function of their high "diffusible fractions" (i.e., the proportion that is un-ionized and unbound — see Fig. 2.6). Interestingly, morphine's front-end kinetics are notably different. Morphine does not approach a substantial fraction of the ultimate peak until 20 to 30 minutes have elapsed.

The simulations depicted in Fig. 2.13 have obvious clinical implications. When a brief pulse of opioid effect followed by a quick offset is desirable (such as a brief period of intense analgesia before injection of local anesthetic during a regional block), remifentanil or alfentanil would be rational choices. In contrast, when the clinical situation calls for a slower onset followed by a more sustained period of opioid effect, one of the other opioids may be more appropriate. Given the lockout period of a typical patient-controlled analgesia (PCA) dosing regimen, it is surprising that morphine has been the mainstay of PCA therapy; fentanyl's latency to peak effect of 4 to 5 minutes is much more favorable for PCA, particularly in terms of avoiding a "dose stacking" problem wherein the patient requests additional doses before the prior doses have reached their peak effect.

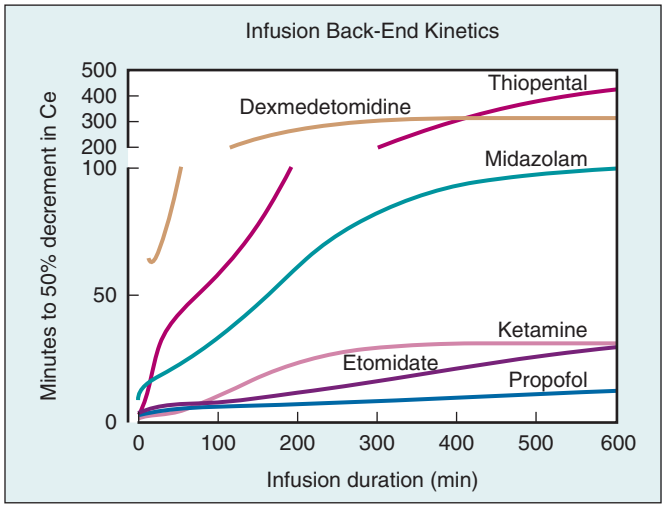
Infusion Front-End Kinetics

The relevant questions concerning the posology of anesthetic infusions are similar to those for bolus injections (see Table 2.2). The simulations plotted in Fig. 2.14 explore the front-end kinetic behavior of a number of opioids when administered by infusion. With the exception of remifentanil, no opioid comes anywhere near the ultimate steady-state level even after many hours of infusion. Remifentanil is the only opioid in common use that can be expected to reach steady state during the time course of typical anesthetic.

Several clinically important points are evident from inspection of the simulations presented in Fig. 2.14. Most obviously, although remifentanil is a notable exception, the practitioner must be aware that when an opioid infusion is ongoing, the concentrations will continue to rise for the duration of any conceivable anesthetic (this general rule applies less fully to alfentanil). An extension of



• **Fig. 2.14** Simulations exploring infusion front-end pharmacokinetic behavior for a variety of commonly used opioids. For comparison purposes, effect site concentrations *(Ce)* are normalized to a percentage of the eventual steady-state concentration. See the accompanying text for a detailed explanation. The simulations were conducted with pharmacokinetic-pharmacodynamic parameter estimates from the literature.[69,107–113]



• **Fig. 2.15** Simulations exploring the infusion back-end pharmacokinetic behavior for a variety of commonly used sedative-hypnotics. This simulation is usually referred to as the *context-sensitive half-time* (the context being the duration of a continuous, steady-state infusion) or the 50% decrement time (for effect site concentrations). The upper portion of the vertical axis is shown on a more compressed scale than the lower portion. See the accompanying text for a detailed explanation. The simulations were conducted with pharmacokinetic-pharmacodynamic parameter estimates from the literature.[114–120] *Ce,* Effect site concentration.

this observation is that if the level of opioid effect part way through a long anesthetic is appropriate, it would be necessary to decrease the infusion rate somewhat to maintain the existing therapeutic concentration (without the infusion rate decrease, the concentration will continue to rise).

That remifentanil reaches a steady state quickly is at least partially responsible for its popularity as part of a total intravenous anesthetic (TIVA) technique. However, even for remifentanil, it is best to precede an infusion with a bolus injection as a "loading dose" to speed achievement of a steady-state drug level (see later text). Because they take so long to reach steady state, the loading dose concept is even more important when using the other opioids in Fig. 2.14.

Infusion Back-End Kinetics

The simulations presented graphically in Fig. 2.15 summarize the back-end kinetic behavior for a number of commonly used intravenous sedative-hypnotics when administered by infusion. In terms of anesthesia posology, these simulations are valuable in explaining how various sedative-hypnotics exhibit different recovery profiles depending on the duration of the infusion. The simulation also helps guide therapeutic decision making in terms of the best time to turn off a continuous infusion to promote a timely emergence from anesthesia.

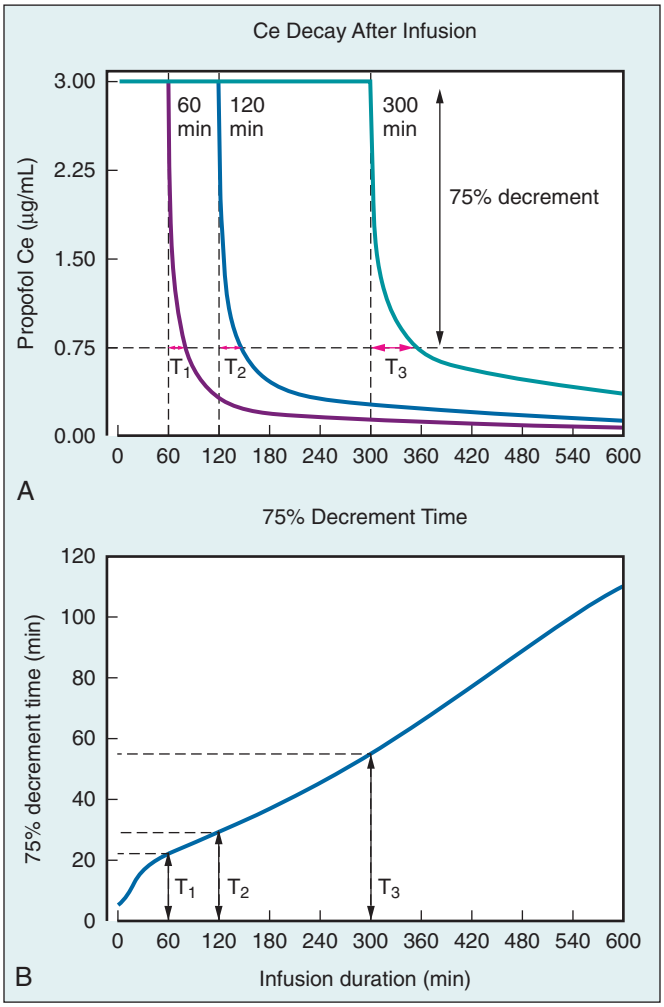
The simulations in Fig. 2.15 predict the time necessary to achieve a 50% decrease in drug concentration after termination of a variable length continuous infusion to a steady-state drug level. Using concepts originally developed for opioids,[7] these simulations are an attempt to provide *context-sensitive half times* (CSHTs).[6] In this case the context is the duration of a continuous infusion. The CSHT has also been referred to as the 50% decrement time (although the decrement time concept usually refers to simulations of effect site concentrations, not plasma).[8] These simulations illustrate how PK parameters interact in a complex way that can only readily be understood through model simulation.[7,72] The CSHT simulations also illustrate the utter irrelevance of using terminal half-lives to predict drug offset behavior for intravenous anesthetics described by three compartment models.[72]

Interpreted from a clinical perspective, CSHT simulations are very instructive. For example, they provide an explanation for why propofol has been so widely embraced as an intravenous anesthetic for TIVA; propofol has a relatively short, time-independent CSHT that is well suited for longer infusions. The CSHT simulations also explain at least one reason why thiopental and midazolam never emerged as popular anesthetics for infusion (and why "barbiturate coma" was sometimes complicated by extremely long recovery times). Another interesting clinical correlation from the CSHT simulations is that when infusion duration is very brief (i.e., <15 to 20 minutes), many of the sedative-hypnotics exhibit similar back-end kinetic behavior.

It is important to emphasize that the shapes of these back-end kinetic curves vary depending on the percentage decrease in concentration simulated; this is why the term *decrement time* was coined (e.g., the 20%, 50%, or 80% decrement times).[8] For most TIVA cases involving propofol, the relevant concentration decrease to promote recovery is closer to 75% rather than 50% (i.e., the biophase concentration must decline from a therapeutic target of approximately 3–4 μg/mL to 0.5–1 μg/mL for the patient to regain responsiveness). The simulations in Fig. 2.16 illustrate this important nuance. For propofol, as for most drugs, the time required for recovery lengthens as the duration of infusion lengthens; the drug input history is clinically important.

Influence of Dose on Bolus Onset and Offset of Effect

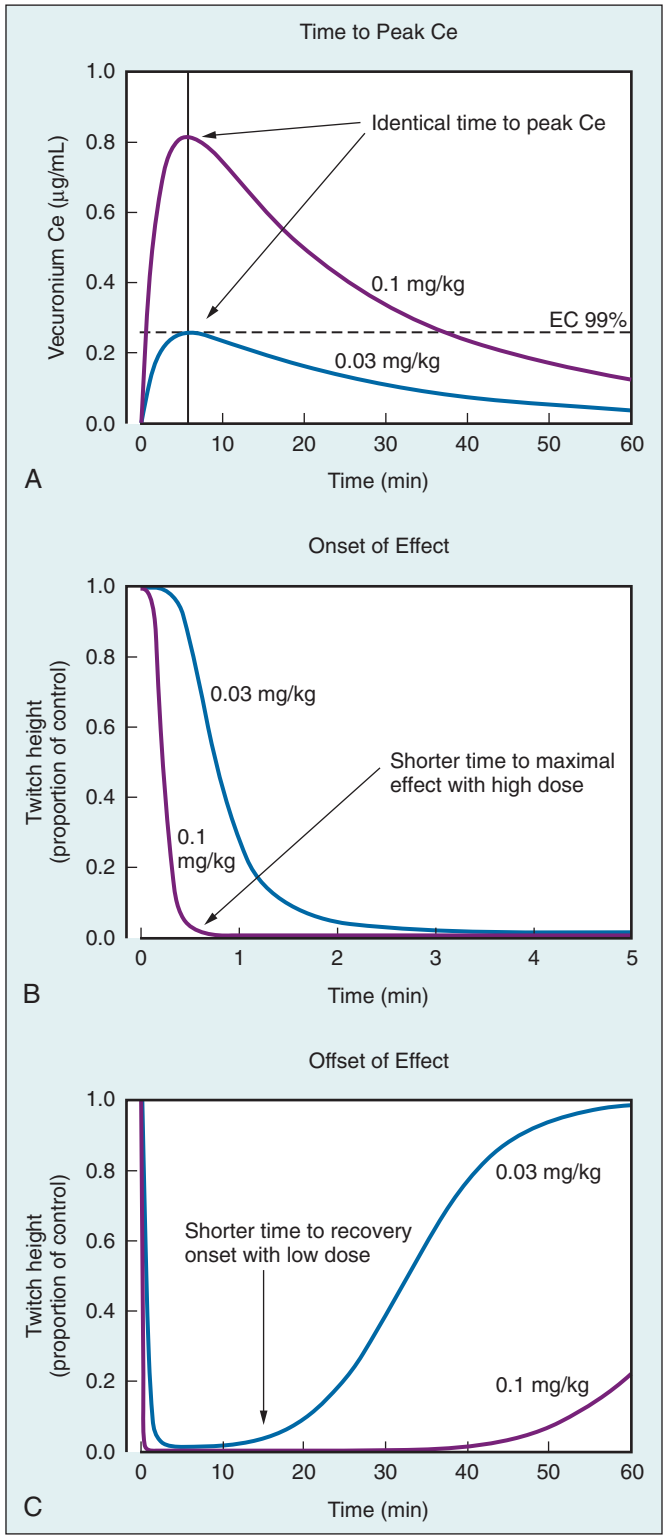
The simulations presented graphically in Fig. 2.17 summarize the influence of dose on the onset and offset of drug effect using the



• **Fig. 2.16** A pair of simulations exploring propofol's infusion back-end kinetic behavior. The upper panel simulates the effect site concentration decay curves after continuous, steady-state infusions of propofol targeted to 3 µg/mL for infusions lasting 60, 120, and 300 minutes. The lower panel illustrates how the infusions simulated in the upper panel map to a 75% decrement time simulation for propofol. T_1, T_2, and T_3 are the 75% decrement times for the 60-, 120-, and 300-minute infusions respectively. See the accompanying text for a detailed explanation. The simulations were conducted with pharmacokinetic-pharmacodynamic parameter estimates from the literature.[119] *Ce,* Effect site concentration.

neuromuscular blocking drug vecuronium as a prototype. The simple posologic question addressed by this simulation is "How much does a larger dose speed the onset of maximal drug effect and what is the PK "penalty" in terms of prolonging the duration of drug effect?"

Inspection of Fig. 2.17 reveals a pattern well known to clinicians. The larger "intubating" dose of vecuronium does indeed speed the onset of maximal drug effect, but it comes at the cost of prolonging the duration of muscle relaxation. A larger dose does not change the biophase behavior of the drug; predicted peak effect site concentrations occur at the same time for both the smaller and larger doses as shown in the upper panel of Fig. 2.17. The reason that maximal drug effect occurs more quickly with the larger dose is simply that the biophase concentration required for pronounced drug effect is achieved earlier (i.e., before the peak biophase concentration occurs). The rapid onset of drug effect associated



• **Fig. 2.17** A trio of simulations exploring the influence of bolus dosage on the onset and offset of neuromuscular blockade induced by vecuronium. Two doses, one larger (0.1 mg/kg, shown in *purple*) and the other smaller (0.03 mg/kg, shown in *blue*) are simulated. The upper panel (A) shows the time course of predicted effect site concentrations. The middle panel (B) plots the onset of the pharmacodynamic effect in the first few minutes in terms of the muscle "twitch" height compared with control. The lower panel (C) graphs the drug offset behavior during the first 60 minutes. See the accompanying text for a detailed explanation. The simulations were conducted with pharmacokinetic-pharmacodynamic parameter estimates from the literature.[121] *Ce,* Effect site concentration; EC_{99}, the effective concentration for 99% of maximal drug effect.

with the larger dose shown in the middle panel of Fig. 2.17 results in the prolonged recovery plotted in the lower panel.

The clinical implications of this simulation are obvious. The clinician must balance the competing clinical imperatives of rapid onset against rapid recovery of neuromuscular blockade. Depending on the duration of the scheduled procedure and other factors (e.g., full stomach considerations, need for postoperative mechanical ventilation, among others), the rapid onset of neuromuscular blockade might be more important than the potential disadvantages of a longer period of muscle relaxation, justifying the selection of a larger initial dose of drug. The advent of shorter-acting muscle relaxants and sugammadex has rendered this issue less relevant than in days past, but of course the general concepts involved apply to all intravenous anesthetic classes (not just neuromuscular blockers).

In summary, the time to peak drug effect is a function of not only plasma-biophase concentration equilibration but also pharmacokinetics and potency.[15] If a supramaximal dose is administered, peak clinical effect may be observed before peak effect site concentration is achieved simply because the concentration necessary to produce maximal effect is attained before the effect site concentration peaks (this situation represents an "overshoot" of typical target concentrations; the overshoot can be produced by design to hasten the onset of significant drug effect).

Influence of Loading Dose on Infusion Front-End and Back-End Kinetics

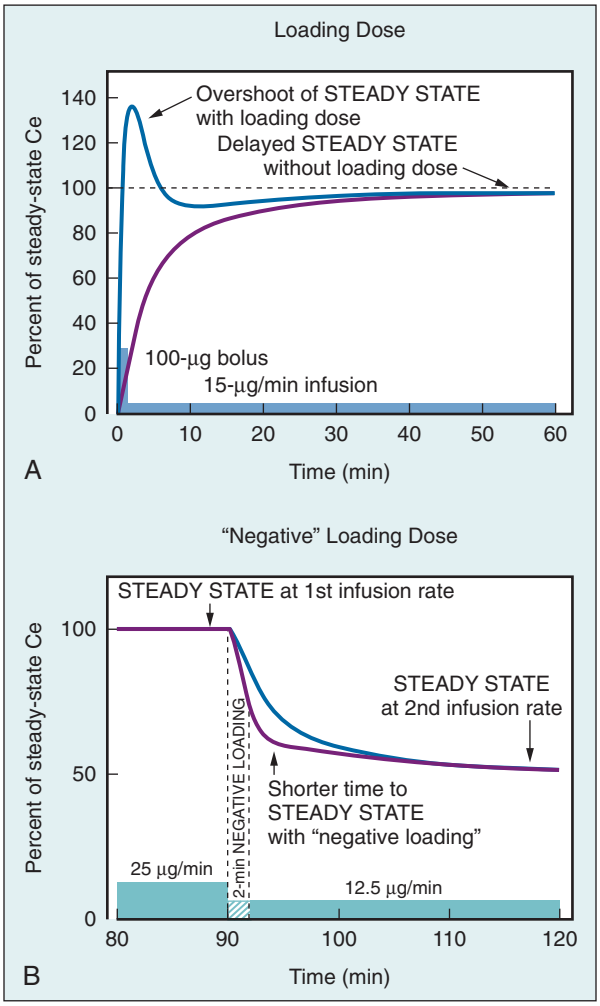
The simulations presented graphically in Fig. 2.18 illustrate the concept of "loading" doses. A bolus injection loading dose before starting an infusion shortens the time to achievement of concentrations nearer the ultimate steady state. Similarly, while the term is not firmly established, a "negative" loading dose (i.e., briefly stopping an ongoing infusion before reducing the infusion rate) can also be used to hasten establishment of the new steady-state drug concentration associated with the reduced infusion rate.

The simulations in Fig. 2.18 illustrate the effectiveness of the loading dose concept. Even for a pharmacokinetically responsive drug like remifentanil, the loading dose (and negative loading dose) technique is very effective in hastening achievement of steady-state drug concentrations. Without the loading dose (and negative loading dose), the eventual steady-state concentrations are achieved significantly later when considered in the context of the operating room where minute-by-minute adjustments of the level of drug effect are often necessary.

The clinical implications of this loading dose concept are even more important when applied to most other drugs in intravenous anesthesia. As illustrated in the simulations shown in Fig. 2.14, for drugs with less favorable PK-PD profiles in terms of the time required to achieve steady-state concentrations (e.g., fentanyl, propofol, among many others), the loading dose concept is even more important. It must be emphasized that the utility of the negative loading dose may be catastrophically overshadowed if the user neglects to resume the infusion after the brief stoppage.

Influence of Special Populations

A very common posologic issue in everyday anesthesia practice relates to the formulation of rational dosing strategies in special populations. Certain demographic factors (e.g., age, gender), anthropometric measurements (e.g., body weight, height, body mass index), and disease states (e.g., kidney or hepatic failure,

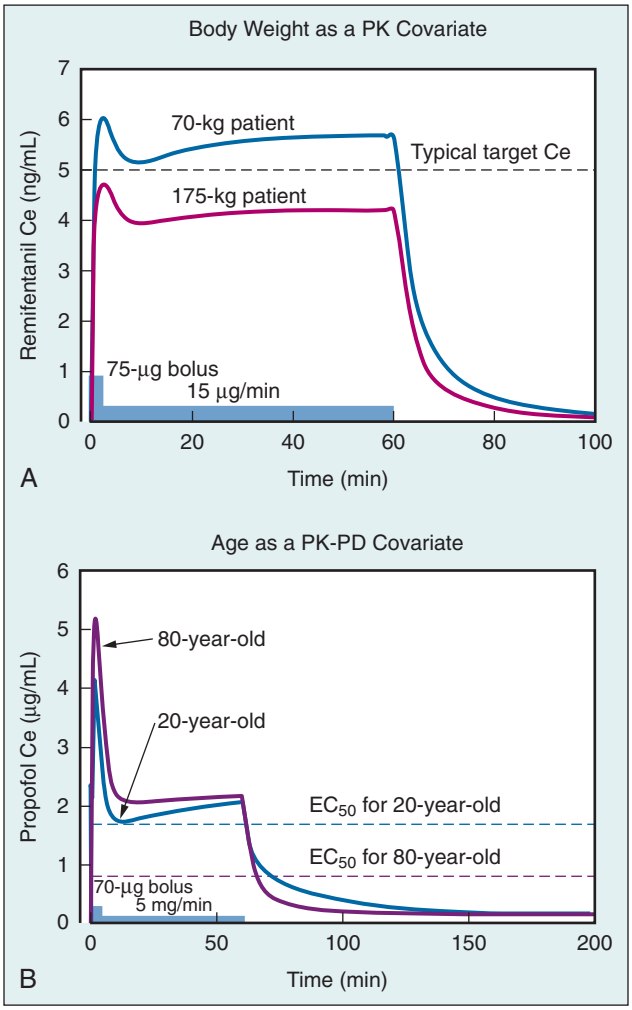


• **Fig. 2.18** A pair of simulations exploring the influence of loading doses on the time to reach steady-state effect site concentrations using remifentanil infusions as an example. The standard loading dose concept, in which a bolus injection is given before starting a continuous infusion, is illustrated in the upper panel (A). The notion of a "negative" loading dose, in which the drug infusion is briefly stopped before the existing infusion rate is decreased, is shown in the lower panel (B). See the accompanying text for a detailed explanation. The simulations were conducted with pharmacokinetic-pharmacodynamic parameter estimates from the literature.[109] *Ce,* Effect site concentration.

hemorrhagic shock) can influence the PK-PD behavior of certain drugs. The doses required in some special populations can be dramatically different compared with the normal patient.

PK-PD modeling techniques can be used to characterize quantitatively how drug behavior is altered in a special population of interest. After building a standard PK-PD model, the influence of the special population factor of interest (e.g., age, body weight, kidney failure), referred to as a *covariate,* can be examined by exploring how the covariate relates to the individual PK-PD model parameters. The covariate can be included in the model to see if it improves model performance. For example, body weight can be related to a distribution volume, or age can be related to drug potency (EC_{50}), and so on.

The simulations presented graphically in Fig. 2.19 illustrate the important impact that covariate effects can have on PK-PD behavior and thus on rational dosing strategy. According to the upper panel



• **Fig. 2.19** A pair of simulations exploring the influence of covariate effects on drug behavior. The upper panel (A) plots the predicted effect site concentrations *(Ce)* of remifentanil when identical doses (i.e., not scaled by weight) are administered to lean and obese adults. The lower panel (B) plots the predicted effect site concentrations (Ce) of propofol when identical doses are administered to older and younger patients. See the accompanying text for a detailed explanation. The simulations were conducted with pharmacokinetic-pharmacodynamic parameter estimates from the literature.[122,123] *Ce,* Effect site concentration; EC_{50}, effective concentration for 50% of maximal drug effect; *PD,* pharmacodynamic; *PK,* pharmacokinetic.

of Fig. 2.19, significantly obese patients require more remifentanil to achieve the same effect site concentration as leaner patients (but not as much as would be suggested by total body weight). Similarly, as depicted in the lower panel of Fig. 2.19, older patients require less propofol to achieve identical effect site concentrations compared with younger patients; in this case, this dosage reduction is a function of both PK and PD factors.

The exploration of covariate effects on PK-PD behavior is perhaps one of the most important aspects of current clinical pharmacology research in anesthesia. Studies examining covariate effects in the form of demographic factors, anthropometric measurements, and disease states now constitute a large part of the anesthesia clinical pharmacology literature. Knowing what factors significantly alter the dosage requirement (and how to implement that knowledge quantitatively) is important in enabling the clinician to personalize therapy for each individual patient.

Influence of a Second Drug on Effect

Because modern anesthesia is a multidrug process, understanding how anesthetics interact quantitatively is critical to formulation of optimal dosing strategies. In particular, accounting for the PD synergy of opioids and hypnotics (both intravenous and inhaled) when used in combination is among the most important posologic issues in anesthesia given the prominent role these combinations play in most every anesthetic.

The simulations presented graphically in Fig. 2.20 illustrate the PD synergy observed when propofol and remifentanil are combined for provision of TIVA. The upper panel (C) plots the expected PD effect in terms of the probability of loss of responsiveness. Remifentanil alone at the concentrations predicted from the routine dosing regimen produces zero probability of losing responsiveness. But when the remifentanil is added to the propofol regimen, substantial synergy is evident and the likelihood of loss or responsiveness is increased dramatically. This degree of PD synergy is typical of virtually all hypnotic-opioid combinations (i.e., both intravenous and inhaled).

The clinical implications of this PD synergy are enormous. In practical terms, the synergistic interaction decreases the dosage necessary for both drug classes. The main advantage associated with reduced dosage is faster recovery. Viewed in terms of PD theory, the synergistic combinations steepen the concentration-effect relationship and make a faster recovery possible because drug levels need decrease only moderately to promote emergence from anesthesia (see Fig. 2.2).

PK-PD Models and Technology

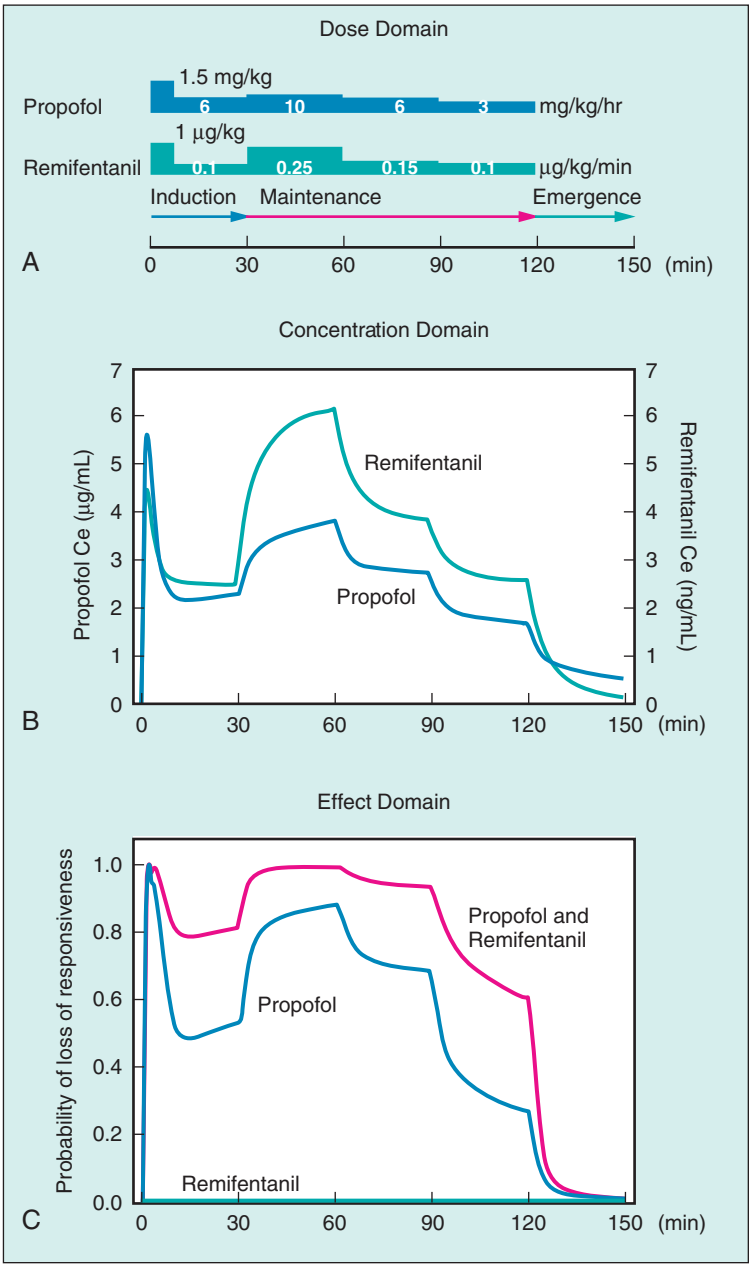
Target-Controlled Infusion

Until recently, the most sophisticated delivery system for intravenous anesthetics was the "calculator pump." Combining advances in pharmacologic modeling with modern infusion pump technology has culminated in the development of more sophisticated methods of intravenous drug delivery.[75] By coding a PK model into a computer program and linking it to an electronic pump modified to accept computerized commands, delivery according to a drug's specific PK profile can be achieved.

This concept was first applied to propofol[76]; commercial embodiments of the concept are now available for many commonly used intravenous anesthetics. The user of these target controlled infusion (TCI) systems designates a target concentration to achieve rather than specifying an infusion rate as with a traditional calculator pump. The TCI system then calculates the necessary infusion rates to achieve the targeted concentration as shown schematically in Fig. 2.21.[12]

Borrowing from inhalation anesthesia concepts, TCI pumps make progress toward the concept of a "vaporizer" for intravenous drugs because they address the fundamental limitation associated with delivering drugs directly into the circulation.[75] Constant rate infusions result in continuous drug uptake. TCI systems, in contrast, gradually decrease the rate of infusion based on the drug's PK behavior.

Known in its general form as the bolus, elimination, and transfer method (i.e., "BET" method),[77] the dosing scheme implemented by a TCI pump accounts for the initial concentration after a bolus dose and the subsequent drug distribution and clearance while an

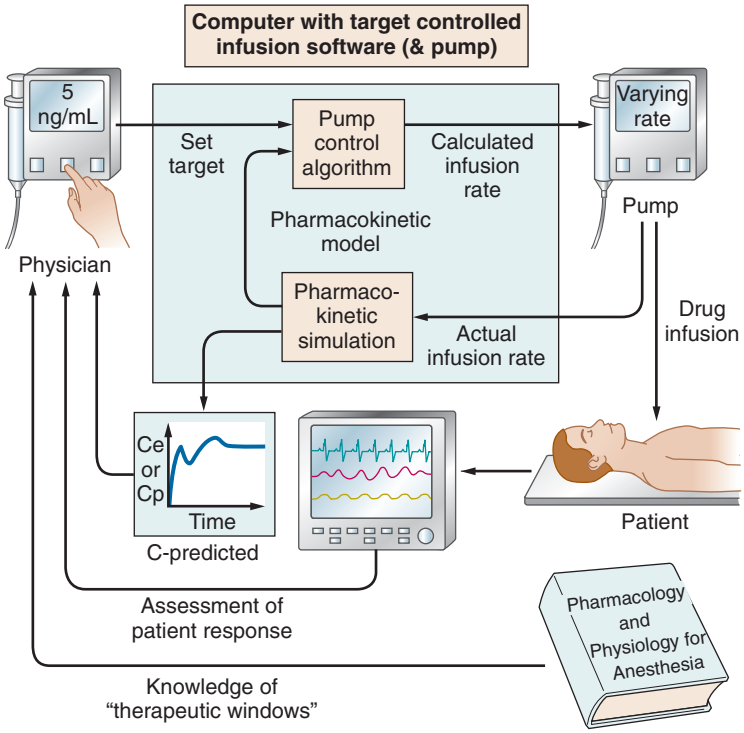


• **Fig. 2.20** Simulations exploring the influence of a second drug using propofol and remifentanil as prototypes. The dose (A), concentration (B), and effect (C) domains are presented for an entire anesthetic from induction to emergence. The effect predictions in the upper panel (C) are based on a response surface pharmacodynamic (PD) drug interaction model. Substantial PD synergy is evident when the opioid is added to the sedative. See the accompanying text for a detailed explanation. The simulations were conducted with pharmacokinetic-pharmacodynamic parameter estimates from the literature.[26,90,119,123] *Ce,* Effect site concentration.

infusion is ongoing. TCI dosing algorithms are essentially functional translations of basic PK equations into operating instructions for the infusion pump.[78] Recognizing the importance of the biophase concept, modern TCI pump algorithms have enabled targeting of effect site concentrations.[79–81]

Delivery of drug via a TCI system requires a different knowledge base of the physician. Rather than setting an infusion rate based on clinical experience and literature recommendations, the physician using a TCI system designates a target concentration and the system determines the infusion rates necessary to achieve that concentration over time. The TCI system changes the infusion rates at frequent intervals, sometimes as often as every 10 seconds. Successful use of a TCI pump thus requires knowledge of the therapeutic concentrations appropriate for the specific clinical application.[12] The clinician interfaces with the calculator pump in the dosage domain, whereas TCI systems require input in the concentration domain (Fig. 2.3). Successful use of TCI requires knowledge of PK models, the biophase concept, PD models, and the concept of covariate effects for special populations.

Computer-controlled drug delivery in the operating room is now a well-established technique internationally. Although it has not been possible to show an obvious improvement in outcome associated with the technology,[82] its popularity around the world attests to a high level of user satisfaction among clinicians. Sadly, although TCI systems are widely used in North America for research purposes, the systems are not yet commercially available for routine clinical use in the United States (unlike much of the rest of the world), in part because of perceived regulatory barriers.[16] Current research in the area is focused on perfecting drug models used by the TCI systems, such as expanding the models to include important covariate effects such as body weight, and "personalizing" population models with individualized feedback.[83,84]



• **Fig. 2.21** A schematic representation of a target-controlled infusion system for anesthetic drugs. According to knowledge of therapeutic windows, patient response, and the current prediction of drug concentration (C-predicted), the physician sets the anesthetic drug concentration target. Using a pharmacokinetic model for the drug, the computer calculates the appropriate infusion rates over time to achieve and maintain the target concentration and directs the infusion pump to administer the appropriate amount of drug. The pump reports to the computer the amount of drug administered to the patient so that the computer's pharmacokinetic simulation of the current drug concentration can be updated and confirmed (see text for details). *Ce,* Effect site concentration; *Cp,* plasma concentration. (Adapted with permission from Egan TD. Target-controlled drug delivery: progress toward an intravenous "vaporizer" and automated anesthetic administration. *Anesthesiology.* 2003;99:1214–1219.)

Emerging Developments

PK-PD Advisory Displays

Research is now being conducted to bring anesthetic pharmacology models to the operating room through automated acquisition of the drug administration scheme and real-time display of the predicted pharmacokinetics and pharmacodynamics.[13] Based on high-resolution PK-PD models, including a model of the synergistic PD interaction between sedatives (i.e., propofol and inhaled anesthetics) and opioids,[26,85] this technology automatically acquires (from pumps and the anesthesia machine) the drug doses administered by the clinician and then presents the drug dosing history (bolus doses, infusion rates, and expired concentrations), the predicted drug concentrations in the effect site (past, present and future), and the predicted drug effects, including sedation, analgesia, and neuromuscular blockade.

These "advisory" display systems potentially represent an advance compared with "passive" TCI systems in that they include not only PK predictions regarding drug concentrations but also PD predictions regarding the likelihood of certain anesthetic effects. Response surfaces constitute the fundamental basis of these display systems; that is, the information displayed is based on response surface, PD drug interaction models. Existing prototypes of these display systems actually depict two-dimensional, three-dimensional, or topographic views of response surfaces.[86,87]

These display systems can perhaps best be understood as clinical pharmacology information technology at the point of care. In terms of the unmet need that such systems are intended to address, the basic notion is that a great deal of information regarding the behavior of anesthetic drugs exists in the form of PK, PD, and response surface drug interaction models. The information contained within the multitude of pharmacologic models is complex and is by definition mathematically oriented; much of it appears in scientific journals that are not intended for the clinician. The information initially appears in original research publications and then is interpreted and integrated into textbooks, monographs, and reviews. In total, this massive volume of mathematically based information is so large and intimidating that it is very difficult for the clinician to digest and incorporate into daily practice. These pharmacology display systems are meant to bring this sophisticated body of clinical pharmacology information from scientific journals to the bedside by displaying the information in a readily understandable format in real time.[86–88] That clinicians cannot solve complex polyexponential equations in their heads "on the fly" to guide rational drug administration is a basic assumption of these advisory systems.

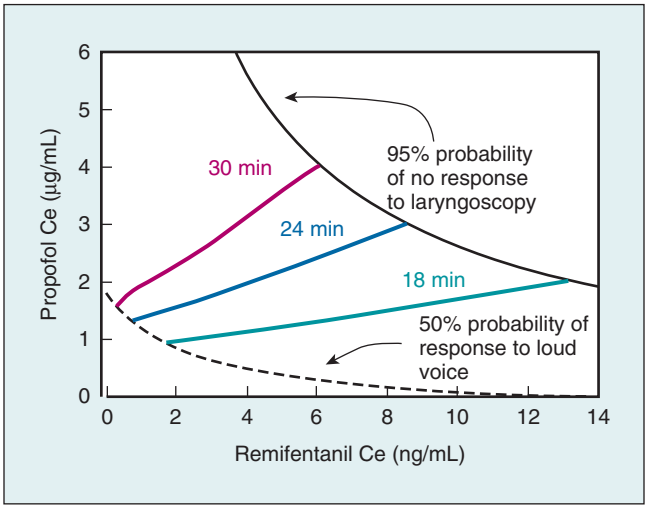
There are at least two advisory displays systems currently in development.[a,86,87] Although quite different in terms of how the information is portrayed, the two systems share in common the tabular and graphical display of predicted drug concentrations and predicted drug effect, including a prediction of the synergism between hypnotics and opioids. The systems include prediction modules that allow the clinician to simulate various dosage regimens in real time and thereby rationally choose the optimal drug administration scheme to address the dynamic nature of anesthesia and surgery. For example, as illustrated in Fig. 2.22, based on information presented by the advisory systems, it is possible to navigate to positions on the drug interaction response surface that optimize the speed of recovery, among other outcomes of interest.

This concept of "navigating" a PD drug interaction response surface is a novel way of conceptualizing how best to adjust drug dosing during an anesthetic.[88] The response surface is navigated in the sense that various points on the surface "map" are targeted at different times to achieve the goals of the anesthetic (e.g., immobility, hemodynamic control, rapid emergence, good analgesia

[a]Dr. Egan has a financial conflict (potential royalties) related to the Navigator system marketed by General Electric Healthcare, Chicago, Illinois.

upon emergence). Rather than simply thinking about hypnotics and opioids in isolation, the response surface approach enables an in-depth, clinically relevant understanding of the significant synergy that results when sedatives and opioids are administered together.

Fig. 2.23 presents a graphical example of the concept of navigating the response surface using propofol and remifentanil as prototypes. The simulation illustrates how the clinician moves to different parts of the surface during different phases of the anesthetic to match drug effect to the prevailing surgical conditions. The notion of integrating PD drug interaction models with PK models to select optimal drug combinations through simulation has been the focus of considerable investigation in recent years. Optimal concentration targets for propofol and remifentanil in combination for the provision of TIVA have been proposed.[25,26,89,90] Similar in silico approaches have also been used to identify the optimal combination of opioids and volatile anesthetics using sevoflurane and remifentanil as prototypes.[85,91] Based on the PK-PD models available for other opioids and volatile agents, it appears feasible to develop optimal concentration targets (and dosage schemes) for nearly any combination of the various opioids and inhalation agents.[92]

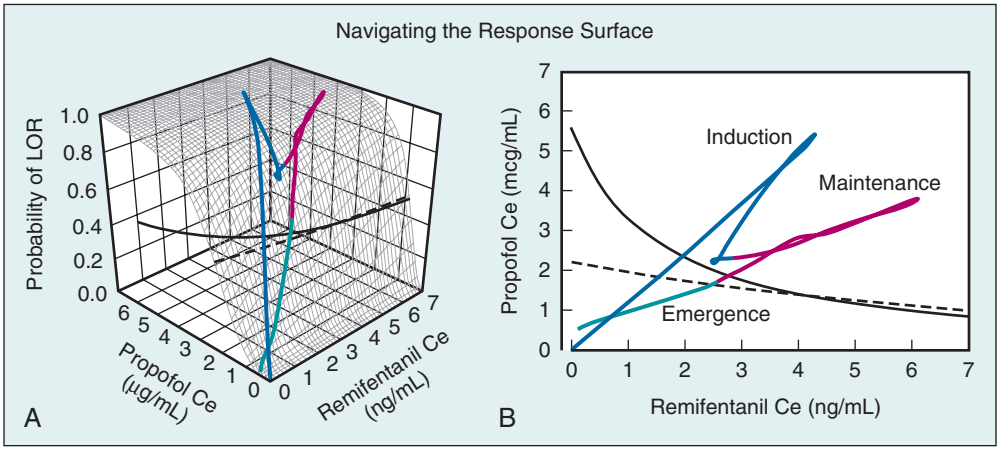


• **Fig. 2.22** A simulation exploring the recovery times associated with different combinations of propofol and remifentanil for a 10-hour intravenous anesthetic. The plot is a topographic view of a pharmacodynamic drug interaction response surface for propfol and remifentanil. The isoboles represent the combinations of the two drugs that produce a 95% probability of no response to laryngoscopy (*solid line*) and a 50% probability of response to "name spoken loudly and repeatedly" (*dotted line*). The three colored lines between the isoboles show the time required to move from "deep anesthesia" to "awake" after stopping 10-hour infusions. See the accompanying text for a detailed explanation. The simulations were conducted with pharmacokinetic-pharmacodynamic parameter estimates from the literature.[26,90,119,123] *Ce,* Effect site concentration.

The ability to simulate various "navigation" decisions immediately before they are implemented (i.e., to explore the clinical consequences of a proposed change in therapy) is a key advance that these display systems potentially bring to clinical care. Pharmacology display systems can be likened to the "heads-up" display systems frequently used as a navigational aid to pilots in commercial and military aircraft. Applying the aviation analogy to anesthesia, display systems can potentially provide increased "situational awareness," "waypoints" to fly toward, and a smooth "glide path" to landing.

Of course, there are obvious challenges to be overcome before these display systems can be adopted into clinical practice. Their utility in terms of improved clinical outcomes (e.g., faster recovery, improved analgesia on emergence) and/or user acceptance (e.g., decreased physician workload) must be satisfactorily demonstrated in clinical testing. Preliminary evidence suggests that the models displayed by these systems perform reasonably well,[85,90] but much work remains to be done. An additional barrier to implementation of these advisory systems is the typical clinician's level of understanding regarding these complex models. Education and training will likely be necessary for the clinician to embrace the technology.

Although it is too early to predict what role clinical pharmacology display technology might play in future anesthesia practice, the concept is certainly an exciting area with some potential to bring more sophisticated clinical pharmacology knowledge to the point of care. In the future real-time display of predicted pharmacokinetics and pharmacodynamics of anesthetic drugs might be found alongside traditional physiologic vital sign monitors.[11,86] Of course, the pharmacokinetic component of these systems has already been widely implemented in the form of passive TCI systems. More



• **Fig. 2.23** A simulation exploring the concept of navigating the pharmacodynamic drug interaction response surface. This simulation presents the same information as in Fig. 2.20 except that the data are plotted on a three-dimensional response surface *(left panel)* and a two-dimensional topographic view of the response surface *(right panel).* The three phases of the anesthetic are shown as *colored lines*. See the accompanying text for a detailed explanation. *Ce,* Effect site concentration; *LOR,* loss of responsiveness.

recently PK-PD simulation programs (i.e., "apps") specifically designed for implementation on smartphones are now readily available and may become increasingly visible near anesthesia workstations.

Propofol Measurement in Expired Gas

The ability to measure in real time the concentration of volatile anesthetics in the expired gas of anesthetized patients has been viewed as a significant advantage of the inhalation anesthesia approach because it enables drug administration in the concentration domain (see Fig. 2.3). Recent work by several laboratories has shown that it might be feasible to develop a device that measures the concentration of propofol in expired gas.[93]

The feasibility of the concept was first demonstrated using a variation of mass spectrometry known as proton transfer reaction mass spectrometry that can detect propofol in minute amounts (parts per billion by volume) in the expired breath of anesthetized patients.[94] More recently several groups have further refined the technology using similar techniques.[95,96] Preliminary results suggest that the overall concept and technique are indeed promising and could have far-reaching implications in anesthesia research and practice.[93] For example, real-time measurement of propofol concentration could replace the need for taking arterial blood samples during research studies in which the concentration of propofol must be controlled. Similarly, the online measured propofol concentration could replace or refine the use of TCI systems to deliver propofol. Finally, it is conceivable that real-time propofol measurement could be used as the control variable for the closed-loop, automated infusion of propofol.

Of course, there are many obstacles to be overcome before the technology moves into mainstream clinical practice. For example, the propofol versus time waveform obtained with the current technology is not ideal because it can be difficult to identify the end-tidal portion of the waveform. In addition, there is a significant delay between peak propofol concentration as determined by PK simulation (after a bolus injection) and the detection of peak propofol concentration in expired gas using the current technology.[97,98] Most importantly, the technical complexity (e.g., difficulties with miniaturization, among others) and expense of the mass spectrometry–based approaches likely represents a considerable barrier to commercialization. Recent work with an alternative technique, ion mobility spectrometry, could potentially overcome some of these barriers.[99]

Allometric Scaling in Pharmacokinetics

Recently the concept of allometric scaling has received considerable attention in the PK analysis of anesthetic drugs.[100] Allometry, at least in part, is the study of how changes in body size influence physiologic behavior. In general, the absolute metabolic rate of animals increases with body size. However, the relationship between body size and metabolic rate in not linear. It has long been recognized that an animal species' metabolic rate scales to its mass to the ¾ power; this well-validated observation is known as Kleiber's law.[101,102]

Assuming that drug clearance is somehow proportionally related to metabolic capacity, in pharmacokinetic analysis allometric concepts have traditionally been used as an approach to scale small animal–based (e.g., rats) PK information to humans in the process of drug development (i.e., "interspecies" allometry). More recently, however, this idea has been extended to "within species" scaling of drug clearance to humans of varying body weights. One obvious advantage of this approach is that total body weight can be used instead of other body size parameters, such as lean body mass, which require complex calculation. Such allometric scaling approaches have been successfully applied to pharmacokinetic models for propofol that characterize the influence of obesity on the drug's disposition.[103,104]

However, critics of the allometric scaling approach for human intraspecies pharmacokinetic analysis (e.g., to characterize the influence of obesity on a drug's disposition) point out that the scientific foundation supporting the practice is not well established and potentially flawed. Such critics contend that the rigorous science underpinning allometry was not developed for the relatively small range of body weights represented within a single species and that allometric scaling should only be used if the approach clearly improves the PK model performance.[105] Thus the proper role of within species allometric scaling in modern PK analysis is currently a matter of considerable controversy and debate.

Key Points

- Compared with other therapeutic areas, the pharmacology of anesthesia is unique because of the low therapeutic indices of anesthetic agents (a safety issue), and because the anesthesiologist must predict the temporal profile of drug effect with great accuracy and precision (an efficiency issue).
- Clinical pharmacology is the branch of pharmacology concerned with the safe and effective use of drugs and includes pharmacokinetics and pharmacodynamics. Grounded in the principles of clinical pharmacology, posology is the science of drug dosage ("dosology"). The ultimate goal of clinical pharmacology is to provide the scientific foundation for rational posology (i.e., what is the right dose for my patient?).
- Pharmacokinetics, simply described as "what the body does to the drug," is the study of the relationship between drug dose and drug concentrations produced over time (i.e., the dose-concentration relationship).
- Pharmacodynamics, simply described as "what the drug does to the body," is the study of the relationship between drug concentrations and drug effects (i.e., the concentration-effect relationship).
- The biophase is the theoretical site of drug action or effect site (e.g., target cells and receptors within the brain, neuromuscular junction, spinal cord). It is important to consider predicted drug concentrations in the biophase (and not just the plasma) because most drugs do not exert their effect in the bloodstream and thus plasma concentrations usually do not correlate well with drug effects, especially during non–steady-state conditions (such as after a bolus injection or an infusion rate change).
- Because anesthetics are rarely administered alone (i.e., modern anesthesia usually involves at least a two-drug combination consisting of a hypnotic and an analgesic), the study of drug interactions is an important part of clinical pharmacology. Most

anesthetics commonly used in combination, such as remifentanil and propofol, interact in a synergistic way so that much less of each drug is required (compared with doses necessary when the drugs are used alone).

- Pharmacokinetic-pharmacodynamic models are simplified versions of pharmacologic reality. These models are mathematical expressions of the relationship between drug dose and concentration (pharmacokinetics) and drug concentration and effect (pharmacodynamics).
- Pharmacokinetic-pharmacodynamic models are built by fitting appropriately shaped equations to actual experimental data using nonlinear regression techniques. Although pharmacologic model building is a mathematical exercise, the models can be readily understood by considering them schematically and graphically.
- The clinical implications of pharmacokinetic-pharmacodynamic models can be easily grasped and conveyed through the use of computer simulation. A proposed dosing scheme can be input into a pharmacokinetic-pharmacodynamic model, producing a "picture" of the predicted drug levels and drug effects. These computer simulations (i.e., in silico experiments) are intuitively understandable and are readily applied to clinical situations.
- A limited set of straightforward simulations form the foundation on which the answers to many routine anesthesia posology questions are based. These fundamental simulations explore bolus front-end and back-end kinetics, infusion front-end kinetics, infusion back-end kinetics (i.e., the context-sensitive half-time), the influence of loading doses, special populations, and a second drug.
- Target-controlled infusion (TCI) devices represent an important advance in drug delivery technology. By coding a pharmacokinetic model into a computer program and linking it to an electronic pump, drug delivery according to the drug's specific pharmacokinetic profile can be achieved. The TCI user designates a plasma or effect site concentration rather than an infusion rate; the TCI system then computes the appropriate infusion rates based on the kinetic model.
- Response surface models are a sophisticated method to characterize pharmacodynamic drug interactions. When integrated with pharmacokinetic information, response surface models can be used to identify target concentrations that optimize certain outcomes of interest such as the speed of recovery. The concept of navigating a pharmacodynamic drug interaction response surface is a novel way of conceptualizing how best to adjust drug dosages during an anesthetic.

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Shafer SL, Varvel JR. Pharmacokinetics, pharmacodynamics, and rational opioid selection. *Anesthesiology*. 1991;74:53–63. Using the fentanyl congeners as examples, this landmark paper first described the simulation techniques that would ultimately come to be known as the context sensitive half-time and the 20% to 80% decrement times. The simulation study also demonstrated the important differences in bolus versus infusion kinetic behavior. (Ref. 7).

Hughes MA, Glass PS, Jacobs JR. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *Anesthesiology*. 1992;76:334–341. This important paper provided the name (i.e., the context-sensitive half-time) for the new simulation technique originally put forward by Shafer and Varvel. The simulation study first extended the concept to the sedative-hypnotics. (Ref. 6).

Sheiner BL, Beal SL. Evaluation of methods for estimating population pharmacokinetic parameters. II. Biexponential model and experimental pharmacokinetic data. *J Pharmacokinet Biopharm*. 1981;9:635–651. This landmark paper was one of the first examples of the use of NONMEM, a mixed-effects pharmacologic modeling software package that eventually emerged as a standard in population pharmacologic modeling. (Ref. 44).

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Kern SE, Xie G, White JL, et al. A response surface analysis of propofol-remifentanil pharmacodynamic interaction in volunteers. *Anesthesiology*. 2004;100:1373–1381. This modeling study was an early description of a pharmacodynamic response surface interaction model for propofol and remifentanil that could be used for total intravenous anesthesia dose optimization through simulation. (Ref. 26).

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Shafer SL, Varvel JR, Aziz N, et al. Pharmacokinetics of fentanyl administered by computer-controlled infusion pump. *Anesthesiology*. 1990;73:1091–1102. This paper was one of the first descriptions of the use of target-controlled infusion technology in anesthesia. (Ref. 106).

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3

Pharmacokinetics of Inhaled Anesthetics

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CHAPTER OUTLINE

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Historical Perspective

The discovery of drugs with anesthetic properties was a landmark event in the history of pharmacology, medicine, and even civilization, in that it made otherwise painful surgical treatments of disease possible. Without a means of providing anesthesia, it was impossible for the modern discipline of surgery to develop. Before the discovery of anesthetic drugs, surgical intervention was limited to simple operations that could be completed quickly.

The first anesthetics were administered by inhalation before the evolution of techniques for intravenous drug administration, and anesthetics remain the most important class of inhaled drugs (barring oxygen, of course). Diethyl ether was first used clinically as a general anesthetic by Long in 1842, and was independently developed by Morton in 1846. Morton's public demonstration of the anesthetic properties of ether at the Massachusetts General Hospital on October 16, 1846, is one of the most important moments in the history of medicine and is now commemorated as Ether Day in Boston and World Anaesthesia Day throughout the world; Long's contribution is also honored as National Doctor's Day in the United States, marking the day that he administered the first ether anesthetic for surgery (March 30, 1842).

Ether remains in clinical use in developing countries given its low cost and relatively high therapeutic index, but its high volatility and explosivity limit its general use. Nitrous oxide was first used for dental analgesia by Wells in 1844, and in 1847 Simpson introduced chloroform (trichloromethane) as a nonexplosive alternative to ether. The first century of anesthesia was dominated by these drugs, of which only nitrous oxide is still widely used.[1]

Since its early origins the practice of anesthesia has been driven by the development of techniques to facilitate the safe delivery of inhaled anesthetics, and these concepts remain important. Administration of drugs by inhalation has a number of unique and important attributes primarily owing to special pharmacokinetic and chemical properties that guide the safe and effective use of inhaled anesthetics.

Classes of Inhaled Anesthetics

General anesthetics include a range of structurally diverse inhaled and injectable compounds that are defined by their ability to induce a reversible comatose state characterized by unconsciousness, amnesia, and immobility. The inhaled anesthetic drugs belong to three broad classes: ethers, alkanes, and gases (Fig. 3.1). (The latter classification is somewhat arbitrary as all inhaled anesthetics are delivered as gases, but gaseous anesthetics are those that normally exist as gases at standard temperature and pressure: nitrous oxide, cyclopropane, noble gases). The ethers and alkanes are volatile liquids (i.e., they have a vapor pressure that is less than atmospheric pressure at room temperature; see later text) and are delivered as

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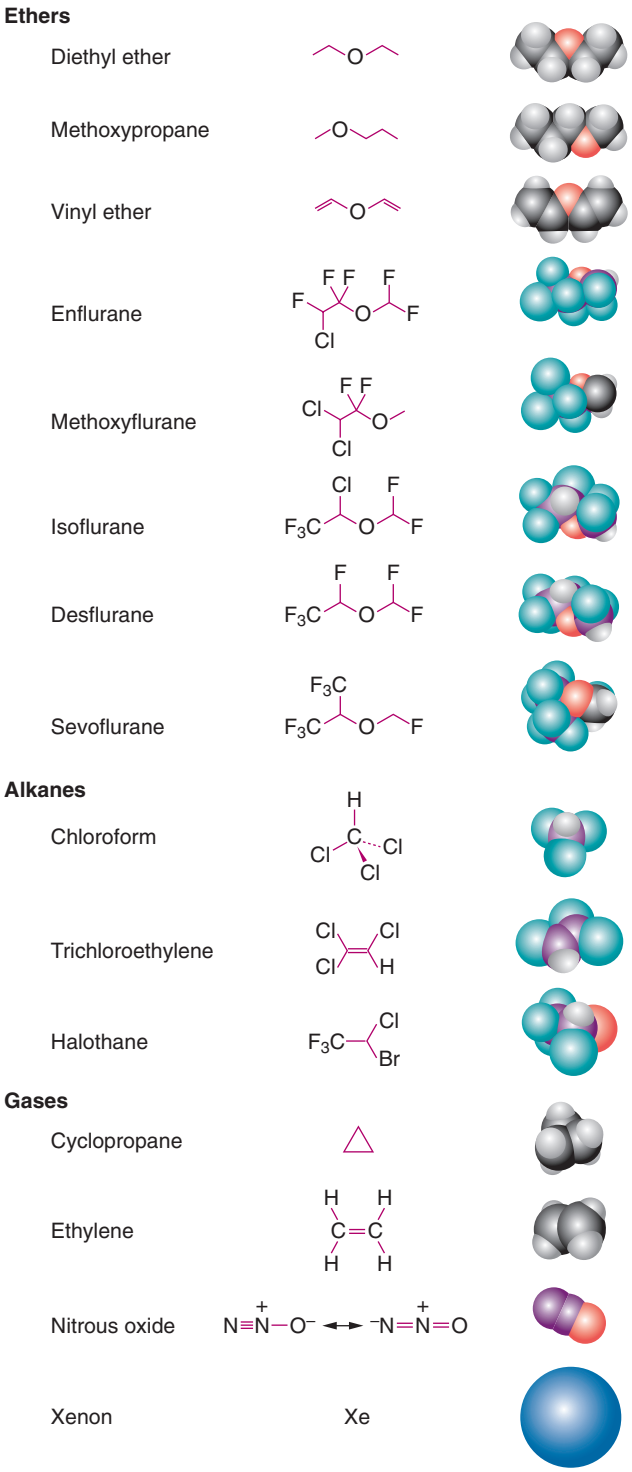
Abstract

Inhaled anesthetics, beginning with diethyl ether, were first introduced into clinical practice in the 1840s. Since then a wide variety of inhaled agents, including ethers, alkanes, nitrous oxide, cyclopropane, and xenon, have been used to induce unconsciousness, amnesia, and immobility. The pharmacokinetics of these drugs depends on their physical properties. The rate of inhaled anesthetic uptake and elimination from the alveoli is driven largely by blood solubility; both are faster with less soluble agents. The effects of inhaled anesthetics depend on the anesthetic concentration at their effect sites, which parallels the alveolar anesthetic concentration and not the total amount of absorbed anesthetic. The potency of different agents can be compared using the minimum alveolar concentration of anesthetic required to prevent movement in 50% of subjects in response to a standardized surgical stimulus. Physiologic factors that govern inhaled anesthetic uptake and elimination include alveolar ventilation and cardiac output. Extrinsic factors that affect inhaled anesthetic uptake and elimination, by determining changes in the alveolar concentration, include minute ventilation, fresh gas flow, and inspired concentration. Inhaled anesthetic tissue distribution depends on relative perfusion, the gradient between arterial and venous anesthetic concentration, and intertissue distribution. Inhaled anesthetics differ dramatically in their degree of metabolism, mostly by the cytochrome P450 system; the volatile anesthetics in use today are minimally metabolized. Emerging developments in inhaled anesthetics include alternative delivery methods and anesthetic applications outside of the operating room.

Keywords

minimum alveolar concentration
partition ratio
FA:FI ratio
concentration effect
second gas effect
low flow anesthesia



• **Fig. 3.1** Inhaled anesthetic agents by class, with chemical structure and space-filling model drawn to scale.

vapors (the gas phase in equilibrium with the liquid phase at a given temperature; a condensable gas). The modern era of volatile anesthetics—those halogenated with fluorine—began with the synthesis of halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) by Suckling in 1951, which was successfully introduced as an anesthetic in clinical trials in 1956. Subsequent attempts to minimize the adverse effects of halothane (particularly the propensity to develop hepatitis, rare but often fatal, or ventricular arrhythmias) led to the development in the 1960s by Terrell and others of a series of halogenated methyl ethyl ethers, including methoxyflurane (2,2-dichloro-1,1-difluoro-1-methoxyethane), enflurane (2-chloro-1-[difluoromethoxy]-1,1,2-trifluoro-ethane), isoflurane (2-chloro-2-[difluoromethoxy]-1,1,1-trifluoro-ethane), and subsequently in the 1990s, desflurane (2-[difluoromethoxy]-1,1,1,2-tetrafluoro-ethane) and sevoflurane (1,1,1,3,3,3-hexafluoro-2-[fluoromethoxy] propane).[1]

Physical Properties

Inhaled drugs differ from intravenous drugs in that their delivery depends on uptake into the blood by the lungs, followed by delivery to their effect sites in the central nervous system in the case of anesthetics. The delivery of inhaled drugs to the lungs depends on the physical properties of the drugs themselves, in particular their solubility in blood and their vapor pressure (Table 3.1).[61]

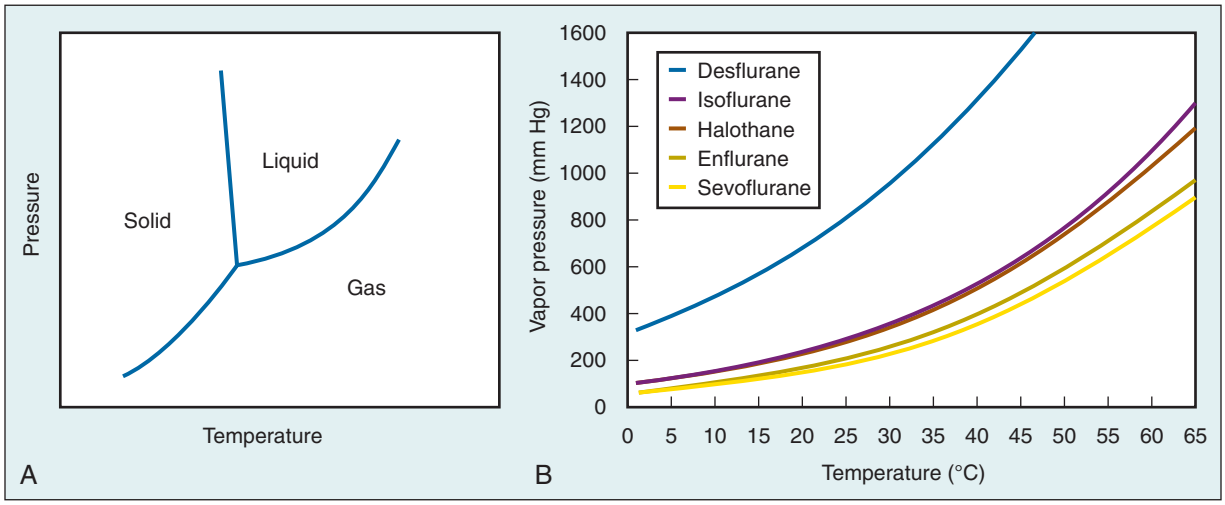
Vapor pressure is the partial pressure of a vapor in thermodynamic equilibrium with a liquid—that is, the partial pressure at which the rate of liquid evaporation into the gaseous phase equals the rate of gaseous condensation into liquid. Vapor pressure varies nonlinearly with temperature according to the Clausius-Clapeyron relationship (Fig. 3.2). The boiling point is the temperature at which the vapor pressure equals ambient atmospheric pressure. Substances that have high vapor pressures at room temperature (e.g., many of the inhaled anesthetics) are volatile. Partial pressure is the portion of the total pressure of a gaseous mixture supplied by a particular gas; for an ideal gas, this is the mole fraction of the mixture multiplied times the total pressure of the gas. Inhaled anesthetic partial pressures are commonly expressed as volume percent (vol%), which is the percent of the total volume contributed by a particular gas, or for an ideal gas, the mole percent. At standard temperature and pressure, the volume percent times total pressure equals the partial pressure, but importantly, partial pressure changes with temperature.

The *solubility* of a gas is the amount of gas that can be dissolved homogenously into a solvent at equilibrium; it is a function of the partial pressure of the gas above the liquid solvent and the ambient temperature. Solubility depends on the solvent—for example, polar substances tend to be more soluble in polar solvents. According to Henry's law, for a given solvent at a given temperature the amount of gas dissolved in solution is directly proportional to the partial pressure of the gas. Relative solubilities can be described according to the partition ratio (also known as the partition coefficient), which is defined as the ratio at equilibrium of the concentration of the dissolved gas in one solvent to the concentration of the dissolved gas in the other solvent (or in the gaseous phase). At equilibrium the partial pressure of the dissolved gas in the two solvents is equal, even though the concentrations are not (Fig. 3.3). The concentration of a gas in a liquid is derived by multiplying the gas partial pressure times its solubility expressed as its solvent:gas partition ratio (at standard temperature and pressure). For inhaled anesthetics, the blood:gas partition ratio is critically important to alveolar uptake. More soluble agents, such as ether or halothane, have high blood gas partition ratios and take longer to reach an equilibrium between inhaled and exhaled partial pressure owing to their greater uptake into blood and tissues. Conversely, less soluble agents, such as nitrous oxide and desflurane, dissolve in lower quantities and approach equilibrium more rapidly (see later text). Following Henry's law, the solubility of gases such as inhaled anesthetics in aqueous liquids increases at lower temperatures. Various tissues also have tissue-specific partition ratios

TABLE 3.1 Properties of Inhaled Anesthetics

Agent	Boiling Point (°C) at 1 Atm	Vapor Pressure (mm Hg) at 20°C	MAC For 40-Yr-Old in O_2 (%)	Blood:Gas Partition Ratio at 37°C	Oil:Gas Partition Ratio at 37°C
Halothane	50.2	243	0.75	2.4	224
Enflurane	56.5	172	1.7	1.8	97
Isoflurane	48.5	240	1.2	1.4	98
Sevoflurane	58.5	160	2	0.65	47
Desflurane	22.8	669	6	0.45	19
Nitrous oxide	–88.5	39,000	104	0.47	1.4
Xenon	–108.1	—	60–70	0.14	1.9

(Modified from Eger EI 2nd, Eisenkraft JB, Weiskopf RB. Metabolism of potent inhaled anesthetics. In: Eger EI 2nd, Eisenkraft JB, Weiskopf RB, eds. *The Pharmacology of Inhaled Anesthetics.* Chicago: Healthcare Press; 2003:167–176.)

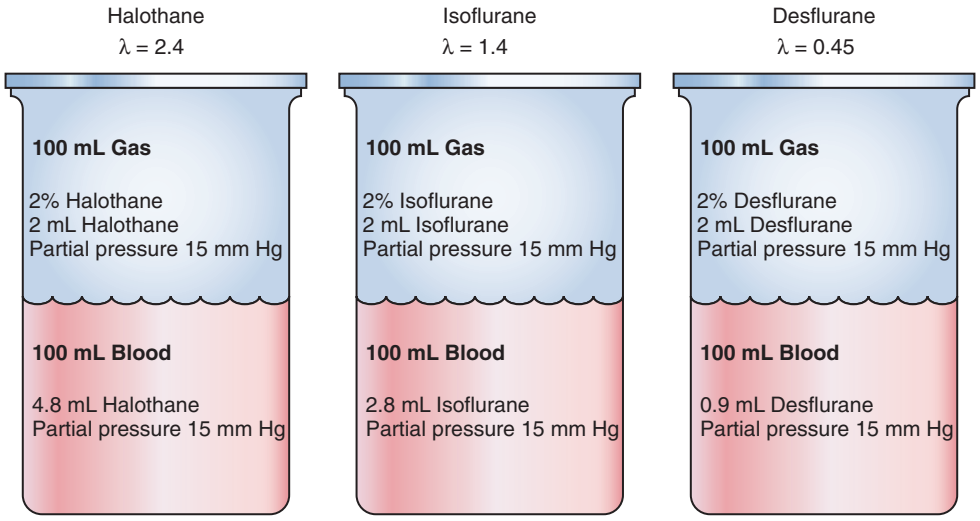


• **Fig. 3.2** Pressure and temperature relationships. A, A qualitative state diagram for water. The vapor pressure is the pressure at which the liquid and gaseous phases are in equilibrium for a given temperature, as indicated by the line between the liquid and gaseous phases in the state diagram. B, Vapor pressure data for a number of common anesthetics. Note that the vapor pressure of desflurane is much higher at a given temperature than the vapor pressure of the other agents, and that the vapor pressure of desflurane reaches 760 mm Hg (or 1 atm) at approximately 22.8°C (its boiling point), indicating that it will boil in a warm room.

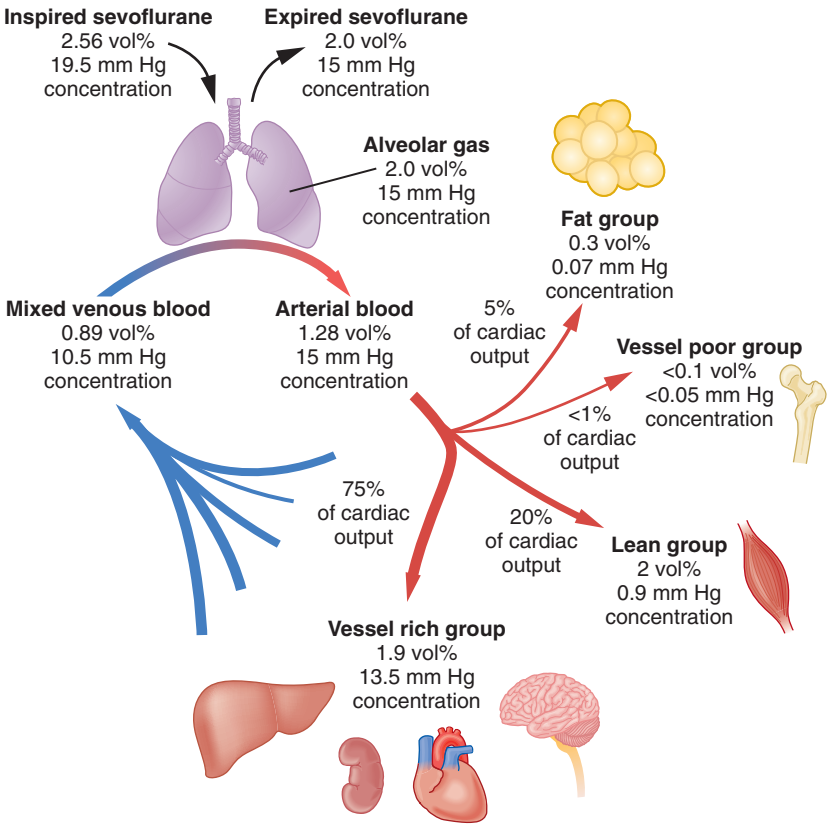
that depend largely on their biochemical composition. This determines relative anesthetic uptake and concentrations in each tissue. Because of differing partition ratios, the actual concentrations can be very different between various tissues at equilibrium even though the partial pressure will eventually be the same, and even two agents with low blood:gas partition ratios, such as nitrous oxide and desflurane, will differ in their rate of uptake into the central nervous system (CNS) because their CNS:blood partition ratios differ.[2] Fig. 3.4 demonstrates that even after a 10-minute wash-in period the differences in partial pressure are pronounced as the different tissue compartments take up the agent.

Measuring Anesthetic Potency as MAC

The potency of inhaled anesthetics is commonly expressed using the concept of minimum alveolar concentration (MAC) as described by Eger and colleagues.[3] The MAC of an anesthetic vapor is the steady-state concentration at which 50% of "normal" (healthy, nonpregnant, adult) human subjects under standard conditions (normal body temperature, 1 atm, no other drugs) do not move (are immobile) in response to a defined stimulus (surgical incision; laboratory studies often substitute application of a tail clamp to rodents). Although MAC is defined in terms of a gas concentration in volume percent or fractional atm at 1-atm ambient pressure, it is the partial pressure and resultant concentration at the effect site that is critical to the pharmacologic response (immobility). Thus anesthetic potency expressed in terms of alveolar partial pressure or tissue concentration is constant for a given physiologic state. MAC is expressed as a gas concentration at 1-atm ambient pressure. The vaporizer setting in volume percent delivers an equivalent alveolar partial pressure that varies with atmospheric pressure; this is significant at high altitudes where higher inspired concentrations



• **Fig. 3.3** Blood:gas partitioning of inhaled anesthetics at 37°C. At equilibrium, the partial pressures of the anesthetics in the gas and liquid (blood) phases (100 mL of each) are equal (15 mm Hg for 2 vol% at standard atmospheric pressure of 760 mm Hg). In contrast, blood concentrations differ depending on the drug specific blood:gas partition ratios (λ). Note that λ increases ~4% per 1°C decrease in temperature.



• **Fig. 3.4** Tissue partial pressures of anesthetics. Results of a Gas Man simulation (Med Man Simulations, Inc., Boston, MA) of a 70-kg patient administered sevoflurane for 10 minutes at 2.56 vol% in 8 L/min of 100% O_2. The delivered inspiratory and measured end-tidal concentrations of sevoflurane are shown, together with the partial pressure and concentration of anesthetic in arterial blood, mixed venous blood, the vessel-rich, vessel-poor, lean, and fat groups. If allowed to run until full equilibration between compartments, the partial pressures of anesthetic would equalize, while the concentrations measured as volume percent will differ according to the tissue:gas partition ratios.

are required to produce a given tissue partial pressure/concentration. The MAC of an inhaled agent is analogous to the EC_{50} (effective concentration in 50% of subjects) of intravenous agents; hence, more potent agents have lower MAC values. MAC is defined using only one behavioral component of anesthesia—the lack of a motor response (immobilization) to a painful stimulus—and reflects primarily spinal effect sites (see Chapter 11). The MAC concept has been extended to other endpoints including MAC awake (for emergence),[4] MAC blunted autonomic response, and so on.

Although MAC was originally developed as a simple method of comparing the potency of inhaled anesthetics, it has emerged as an important clinical tool. Anesthesiologists often formulate an anesthetic plan by targeting a certain MAC multiple for a given patient, procedure, and anesthetic technique (although strictly

speaking MAC is a single point on a nonlinear curve, so there are limitations to this approach). The pervasive influence of MAC in the daily practice of anesthesia makes it one of the most important unifying concepts in anesthetic pharmacology. Further consideration of the factors that influence MAC (e.g., age, body temperature, adjuvant drugs, genetics) is provided in Chapter 11.

Monitoring Inhaled Anesthetic Delivery

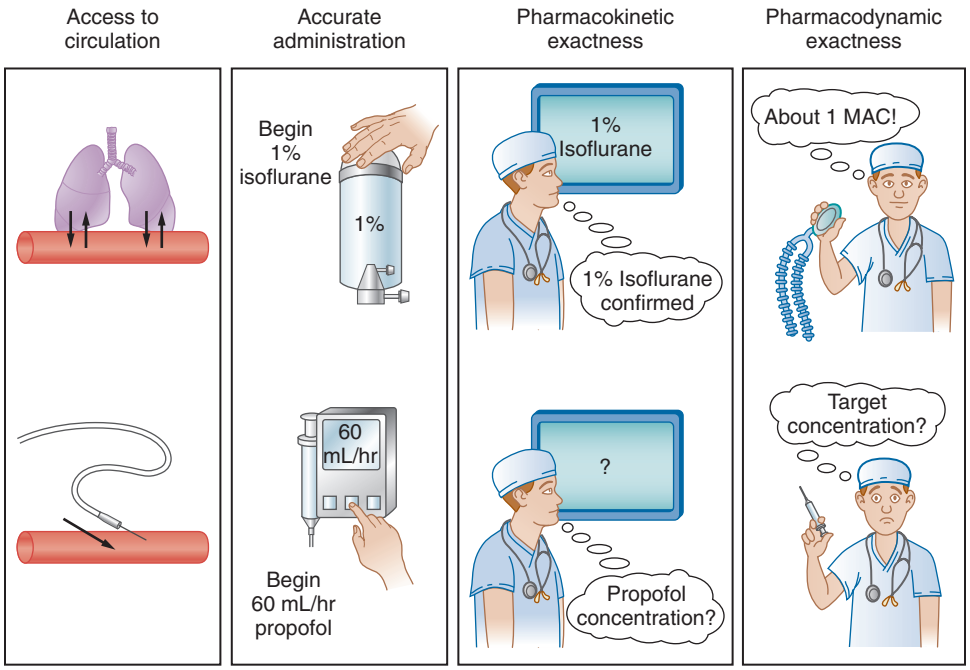
Differences Between Inhaled and Intravenous Anesthetic Delivery

Administering volatile anesthetics by inhalation using a calibrated vaporizer affords several fundamental advantages compared with intravenous drug delivery (Fig. 3.5). Because uptake of inhaled anesthetic diminishes as equilibrium between alveolar and pulmonary venous partial pressures is approached, the vaporizer setting reflects the anesthetic concentration in blood and therefore at the site of drug action owing to rapid uptake in well-perfused tissues (including the CNS). This enables accurate administration of the inhaled drug to a target concentration (with an upper limit above which the partial pressure cannot rise). Moreover, the end-expired concentration can be measured and confirmed by respiratory gas monitoring, ensuring that the targeted concentration has been achieved (pharmacokinetic exactness). The pharmacodynamic significance of the measured concentration is standardized in terms of MAC, providing pharmacodynamic exactness.

In contrast, direct access to the circulation as required in intravenous anesthesia delivery does not prevent indefinite uptake of drug (see Fig. 3.5, lower panel). Without the aid of a computer model, the infusion rate of an intravenous anesthetic does not reveal much about the resulting concentration in blood, preventing accurate administration targeted to a known concentration. There is currently no commercially available device to measure the concentration of intravenous anesthetics in real time, preventing equivalent pharmacokinetic exactness (delivering a targeted concentration). Even if concentrations of intravenous drugs were measurable in the clinical setting, the meaning of a given concentration is not common knowledge to most practitioners who practice without target controlled infusion technology (e.g., practitioners based in the United States; see Chapter 2). In contrast to the early days of total intravenous anesthesia, the therapeutic windows for most intravenous anesthetics are now well characterized (e.g., the steady-state propofol concentrations required to achieve adequate anesthesia in 50% of patients, among many others).[5,6] Despite these advances, available computer-controlled pumps, although accurate and sophisticated, fall short of the theoretical appeal and practical convenience associated with the delivery of volatile anesthetic via the lung. Target-controlled infusion technology (see Chapter 2) partly addresses these shortcomings.

Agent Analysis

A number of technologies can be used to analyze the amount of agent being delivered to the patient. These are usually implemented in a sidestream, or diverting, system that takes a sample of gas from as close to the patient as feasible. In contrast, mainstream systems require attaching the analyzer hardware directly to the end of the endotracheal tube. Delivered volatile anesthetic concentration can be determined using mass spectrometry, Raman spectral analysis, infrared spectrometry, refractometry, or oscillating crystal technology. Nitrous oxide can be detected with mass spectrometry, Raman analysis, or infrared spectrometry.[7] Monitoring of delivered anesthetic concentration allows detection of volatile anesthetic



• **Fig. 3.5** Comparison of delivery of anesthetics by inhalation *(upper panel)* or intravenous infusion *(lower panel)* at the beginning of the total intravenous anesthesia era (circa 1995). Inhalational delivery provides both pharmacokinetic and pharmacodynamic accuracy because known concentrations can be titrated by adjusting the vaporizer to known target concentrations (minimum alveolar concentration *[MAC]*) without accumulation and usually with minimal metabolism. (Modified from Egan TD. Intravenous drug delivery systems: toward an intravenous "vaporizer." *J Clin Anesth.* 1996;8(3 suppl):8S–14S.)

uptake and elimination, vaporizer malfunctions, and estimation of anesthetic depth based on MAC values and age-derived nomograms. Additionally, low-flow anesthesia can be more easily implemented if the delivered anesthetic concentration is being monitored. That said, prediction of arterial/effect site concentrations of anesthetic from end-tidal concentrations is difficult and subject to inaccuracies owing to dead-space ventilation, for example,[8] which can have significant effects on uptake times in the beginning of an anesthetic.[2]

Monitoring Neurophysiologic Effect

Although hemodynamic stability under anesthesia is relatively straightforward to monitor, it is surprisingly difficult to monitor the neurophysiologic effect of a given end-tidal concentration of an inhaled anesthetic. This is of particular concern in patients also receiving neuromuscular blockers, who could potentially be aware but unable to move.[9] Monitoring methods focus on the complexity of the electroencephalogram (EEG), which transitions from rapid disorganized activity during wakefulness to slow coherent activity with decreasing levels of arousal. A number of measures of the complexity of EEG, such as dimensional complexity, spectral edge, and spectral entropy, have all been proposed as valuable measures of arousal or awareness. The most frequently used commercial system currently is the BIS (Medtronic, Boulder, CO), which uses a proprietary algorithm to measure electromyography and correlations in power between different frequency bands of the EEG to develop an index that the manufacturer claims can predict awareness under anesthesia. That said, alternative systems that rely on processed EEG, such as the SedLine (Masimo, Irvine, CA), are making inroads into the market. Initial reports suggested that use of the BIS within an anesthetic protocol leads to an absolute risk reduction of awareness under anesthesia of 0.74% compared with anesthesia care outside of the protocol (B-Aware trial).[10] Subsequent studies that did not use BIS within an anesthetic protocol failed to reproduce this result.[11] Another randomized clinical trial that compared a structured anesthetic protocol based on the BIS with an anesthetic protocol based on end-tidal anesthetic gas concentration (B-Unaware trail) found that BIS neither lowered the incidence of anesthesia awareness nor reduced the administration of volatile anesthetic gas.[12] This conclusion was then confirmed in a separate study using patients at high risk of awareness under general anesthesia.[13] This led the study group to discourage anesthesiologists from attempting to use BIS values to titrate anesthesia.[14] The 5th National Audit Project (NAP5) of the Royal College of Anaesthetists and the Association of Anaesthetists of Great Britain and Ireland addressed accidental awareness during general anesthesia in 2014. This audit showed that practitioners in the United Kingdom were selectively using depth of anesthesia monitors, which were used in only 1% of cases involving volatile anesthetics without neuromuscular blockade but in 23% of cases involving total intravenous anesthesia with neuromuscular blockade (which had an almost fourfold increase in risk of accidental awareness during general anesthesia).[15]

Metabolism and Degradation

Metabolism

Metabolism of volatile anesthetics varies up to 1000-fold between specific agents and is catalyzed chiefly via cytochrome P450 enzymes in the liver (Table 3.2), primarily by CYP 2E1.[16,17] Hence patients exposed to agents that induce cytochrome P450 2E1 (CYP 2E1; e.g., ethanol, barbiturates) can have increased metabolism (see Chapter 4). Metabolism is inhibited by the agents themselves at the higher concentrations present during anesthesia, but it is enhanced during elimination of residual anesthetic during the recovery phase, which is more prolonged and extensive for the soluble agents.[18]

TABLE 3.2 Degree of Metabolism, Metabolites, and Enzymes Involved for Various Agents

Agent	Degree of In Vivo Metabolism (%)	Metabolites	Enzymes Catalyzing Metabolism
Halothane	15–40	Inorganic bromide, fluoride	CYP 2E1 and, to a lesser extent, CYP 3A4 and CYP 2A6
Enflurane	2.4	Inorganic fluoride	CYP 2E1
Isoflurane	0.2	Trifluoroacetic acid, inorganic fluoride	CYP 2E1
Sevoflurane	2–5	Inorganic fluoride	CYP 2E1
Desflurane	0.02	Inorganic fluoride	CYP 2E1

CYP, Cytochrome P450.
(Modified from Kharasch ED, Thummel KE. Identification of cytochrome P450 2E1 as the predominant enzyme catalyzing human liver microsomal defluorination of sevoflurane, isoflurane, and methoxyflurane. *Anesthesiology*. 1993;9:795–807; Restrepo JG, Garcia-Martín E, Martínez C, et al. Polymorphic drug metabolism in anaesthesia. *Curr Drug Metab*. 2009;10: 236–246.)

Halothane is the most extensively metabolized of the modern agents. Its extensive metabolism (up to 40% of absorbed dose) has a significant impact on its elimination kinetics, in contrast to other agents.[19] It is also unique among volatile agents in undergoing significant reductive metabolism by CYP 2A6 and 3A4, although this is minor compared with its oxidative metabolism.[20] Nitrous oxide and xenon are not metabolized.

Although the agents themselves have certain adverse effects (e.g., cardiac depression), a number of other adverse reactions to anesthesia, particularly hepatic and renal toxicity, are mediated by their metabolites. As a result, agents that undergo little metabolism have become more popular, whereas agents that undergo more metabolism, such as halothane and methoxyflurane, have fallen into disuse. Discussion of specific metabolites and their organ toxicity is found in Chapter 11.

Chemical Degradation

At temperatures exceeding 50°C in the presence of soda lime carbon dioxide (CO_2) absorbent, and somewhat even at 40°C as often exists in absorbents, sevoflurane undergoes base catalyzed degradation to produce the vinyl ether compound A (fluoromethyl-2,2-difluoro-1-(trifluoromethyl), or FDVE) and trace amounts

of compound B (2-(fluoromethoxy)-3-methoxy-1,1,1,3,3-pentafluoropropane).[21] FDVE causes renal tubular necrosis in rats, but toxicity is species-dependent. Human exposure has no clinically significant effects even with low-flow sevoflurane generating FDVE exposures of more than 400 ppm hours, although biochemical markers of renal injury have been reported with high compound A exposure in some studies.[22–25] More modern CO_2 absorbents based on lithium hydroxide have been designed to minimize production of compound A during normal use.[26]

Carbon Monoxide Production

The passage of volatile anesthetics through dry CO_2 absorbents can produce potentially life-threatening concentrations of carbon monoxide.[27,28] Severe carbon monoxide poisoning with carboxyhemoglobin levels approaching 40% has been reported in association with desflurane.[29] Carbon monoxide production is insignificant with sevoflurane and halothane, intermediate with isoflurane, and highest with desflurane and enflurane.[30] The quantity of carbon monoxide produced depends on fresh gas flow, the quantity of dry absorbent, and the water content of the absorbent; barium hydroxide–containing absorbent (Baralyme) produces more carbon monoxide than soda lime. No carbon monoxide is produced when the water content of soda lime exceeds approximately 4.8%, or the water content of Baralyme exceeds 9.7%. Baralyme has been removed from the market. With modern absorbents, this concern is largely obviated, with only small amounts of carbon monoxide production (peak concentrations <116 ppm) with desiccated Drägersorb (Dräger, Lübeck, Germany); Medisorb (Vyaire Medical, Lake Forest, IL); and Spherasorb (Intersurgical, East Syracuse, NY), and no appreciable formation with Amsorb (Armstrong Medical Ltd., Coleraine, Northern Ireland); LoFloSorb (Intersurgical, Wokingham, England); Superia, or lithium hydroxide.[26] The reaction by which carbon monoxide is produced is unclear; for desflurane the cascade probably begins with base-catalyzed extraction of a proton from the difluoromethyl ethyl group. The absence of this moiety in sevoflurane, methoxyflurane, and halothane thus explains the insignificant production of carbon monoxide by these agents.[31]

Uptake and Distribution

General Principles

During the wash-in period, the partial pressure of an inhaled gas in the alveoli increases exponentially to approach that of the inspired fresh gas concentration. This ratio reflects the uptake of anesthetic from the inhaled gas into the blood as well as from blood into the tissues. Assuming no uptake of gas, the alveolar concentration (F_A) approaches the inspired gas concentration (F_I) with first-order kinetics:

[1]

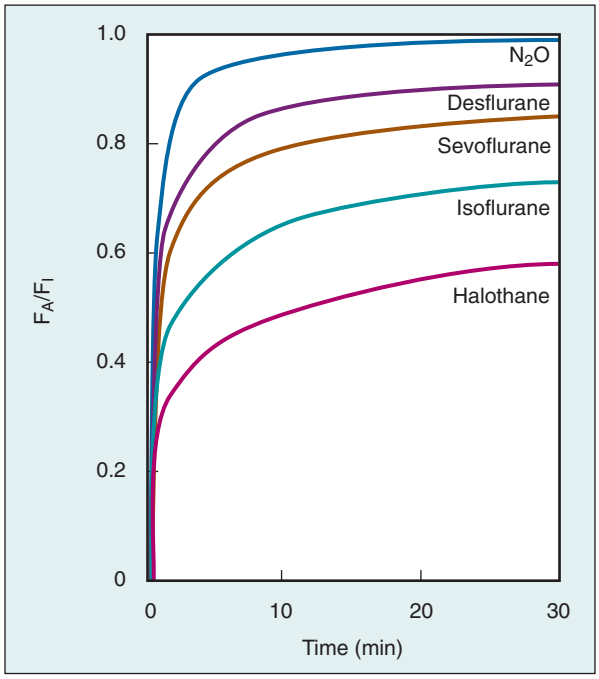
$$\frac{d}{dt}\left(\frac{F_A}{F_I}\right) = -\frac{t}{\tau},$$

where t is time and τ is the wash-in time constant, which is the ratio of the capacity of the reservoir into which the gas is delivered (the circuit volume plus the lung volume of the patient) to the flow rate at which it is delivered. Thus τ is the time it takes to fill the system once at the current fresh gas flow. If the circuit starts with no anesthetic at time zero and the inspired gas concentration does not change, then

[2]

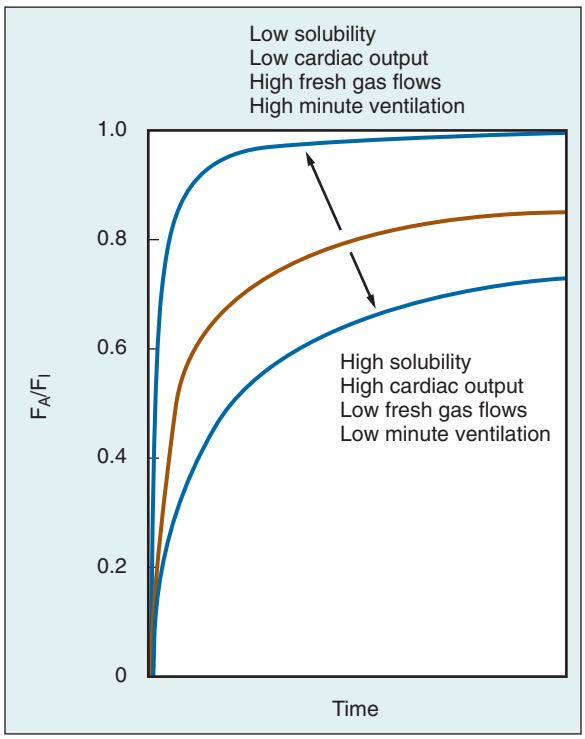
$$\frac{F_A}{F_I} = 1 - e^{-t/\tau}$$

where e is Euler's number. After a single time constant has elapsed (when $t = \tau$), F_A is 0.63 F_I; at time $t = 2\tau$, $F_A = 0.86\ F_I$; at $t = 3\tau$, $F_A = 0.95\ F_I$; and at $t = 4\tau$, $F_A = 0.98\ F_I$ (Fig. 3.6).

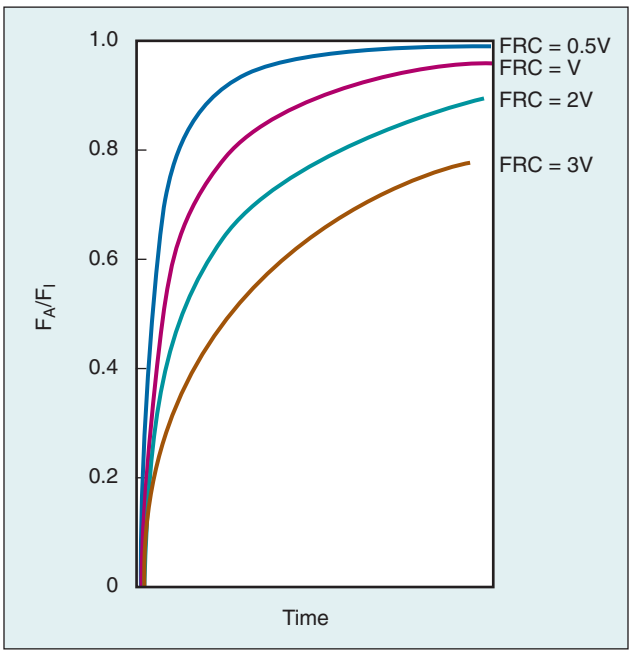


• **Fig. 3.6** Wash-in of nitrous oxide *(N_2O)*, desflurane, sevoflurane, isoflurane, and halothane. The rate at which the alveolar concentration (F_A) approaches the inhaled concentration (F_I) for a fixed minute ventilation and cardiac output reflects the solubility of the drug in blood, with wash-in of the least soluble (nitrous oxide and desflurane) being the fastest. (Modified from Yasuda N, Lockhart SH, Eger EI 2nd, et al. Comparison of kinetics of sevoflurane and isoflurane in humans. *Anesth Analg.* 1991;72: 316–324.)

The response to a drug depends on the concentration of the drug at its effect site (e.g., a receptor expressed in brain or spinal cord) and is usually not the plasma concentration (see Chapter 1). This is typically modeled by considering the human body as being made up of multiple compartments, one of which is the effect site. The concentration of an inhaled anesthetic in brain, for example, depends on the relative solubilities of the drug in brain and blood (the brain:blood partition ratio), which in turn depends on the partial pressure of the anesthetic in the alveoli measured as the end-tidal concentration. At equilibrium, the end-tidal anesthetic concentration reflects the concentration of anesthetic in the blood, and for these highly lipid-soluble drugs that easily cross membranes, at the effect site. The effect of an inhaled anesthetic thus depends on its concentration at its effect site and not on total absorbed mass of drug. The total absorbed mass is a significant determinant of the kinetics of uptake and elimination, however.



• **Fig. 3.7** Factors affecting the rate of anesthetic wash-in (equilibration between the inspired fraction and the expired fraction) include solubility, cardiac output, fresh gas flow, and minute ventilation. F_A, Alveolar concentration; F_I, inhaled concentration.



• **Fig. 3.8** Effect of functional residual capacity *(FRC)* on wash-in for a fixed minute ventilation *(V)* and cardiac output. Patients with lower FRCs relative to their minute ventilation have more rapid wash-in. F_A, Alveolar concentration; F_I, inhaled concentration.

Determinants of Wash-In

The rate of wash-in of the anesthetic is determined by both the rate of delivery to the alveoli and the rate of removal from the alveoli by uptake into blood. Factors that affect the rate of delivery to the alveoli include the inspired concentration, the time constant of the delivery system (which is determined by fresh gas flow and circuit volume), anatomic dead space, alveolar minute ventilation, and functional residual capacity (FRC). Factors affecting the rate at which anesthetic is removed from the alveoli include the solubility of anesthetic in the blood, cardiac output, and the partial pressure gradient between alveolar gas and mixed venous blood. These concepts are illustrated in the classic uptake curves shown in Fig. 3.7.

The gradient between inspired and alveolar anesthetic concentrations drives the increase in alveolar concentration of inhaled drugs. Alveolar ventilation determines the rate at which alveolar gas concentration equilibrates with the concentration in the circuit. A change in FRC changes the total volume of the system and thereby alters τ. As a result, an obese patient with reduced FRC will have faster wash-in (Fig. 3.8). The early rapid increase in F_A/F_I represents the equilibration of anesthetic with the circuit and airways unopposed by alveolar uptake. The rate of change in F_A/F_I slows as alveolar concentrations increase and uptake into blood and tissues lead to increased venous concentration, which reduces the alveolar-to-venous concentration gradient and slows uptake. For more soluble agents with greater uptake, the knee in the curve occurs at lower F_A/F_I ratios.

Special Factors

For a fixed cardiac output, a left-to-right shunt (which recycles blood through the lungs) does not affect wash-in unless it alters the ventilation to the perfused lung. A right-to-left shunt (where systemic venous blood bypasses the lungs), however, can significantly slow the rate of wash-in. Right-to-left shunt effects are much more prominent with poorly soluble anesthetics (i.e., nitrous oxide and desflurane).

A number of differences contribute to the faster wash-in observed in infants and children compared with adults. Volatile anesthetics are less soluble in neonates, likely secondary to lower serum protein and lipid concentrations. Tissue solubilities, particularly in the muscle group, are also lower in children than in adults. Finally, the cardiac output in neonates is disproportionately distributed to the vessel-rich group compared with adults, enhancing drug delivery to the CNS.

Tissue Uptake

Initially during wash-in, hydrophobic anesthetics are avidly taken up by the tissues and the anesthetic partial pressure of venous blood returning to the lungs is low. As anesthetic partial pressure in the tissues approaches the alveolar partial pressure, venous anesthetic partial pressure increases to approach alveolar partial pressure. As a result, the anesthetic partial pressure gradient between alveolar gas and venous blood decreases, diminishing the rate of uptake.

Factors that govern tissue uptake of anesthetics are analogous to those that govern uptake from the alveoli: tissue solubility, tissue blood flow and the arterial blood:tissue partial pressure gradient. Tissues can be classified into four groups based on their relative

blood flow: vessel-rich group (brain, heart, kidney, and liver; contributing 10% to body mass and receiving 75% of cardiac output); lean group (muscle and skin; contributing 50% to body mass and receiving 20% of cardiac output); vessel-poor group (bones and connective tissue; contributing 20% to body mass and receiving <1% of cardiac output); and fat (contributing 20% to body mass and receiving ~5% of cardiac output). The time constant (τ) for wash-in of each group is defined as follows:

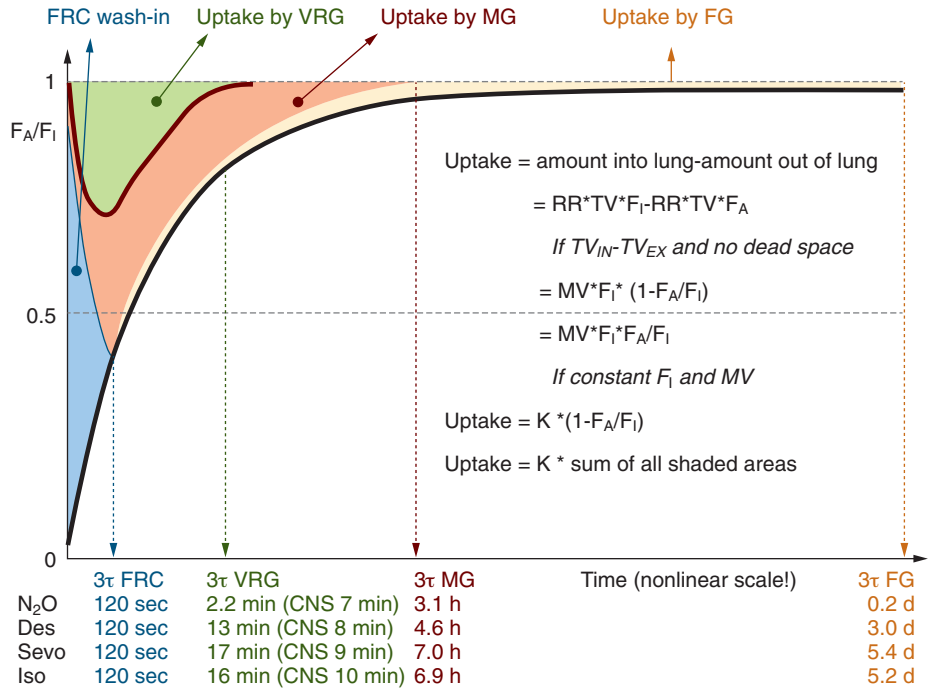
[3]

$$\tau = \frac{V\lambda}{Q}$$

where V is the volume of tissue, Q is the tissue blood flow, and λ is the tissue:blood partition ratio. Based on tissue-specific differences in each of these factors, equilibration times from shortest to longest are vessel-rich group (VRG), lean tissue group, vessel-poor group, and fat (which has such low blood flow that it usually fails to equilibrate on a clinical time scale). The large mass of the lean tissue group makes it the largest tissue reservoir, and its lower blood flow relative to the VRG means that it continues to take up anesthetic after the VRG approaches equilibrium. Again, more soluble agents have longer time constants as the result of more extensive tissue uptake. The rate of rise of the F_A/F_I curve thus is determined by the amount and rate of uptake of the different compartments of interest. (Fig. 3.9) The slower rate of rise in the second phase of uptake evident in the F_A/F_I relationship reflects saturation of the VRG and slower equilibration of other (mainly lean) tissue groups. In practice, the rate of rise of anesthetic is rarely a significant issue, however, since most anesthetic techniques begin with administration of a bolus of intravenous agent.[2]

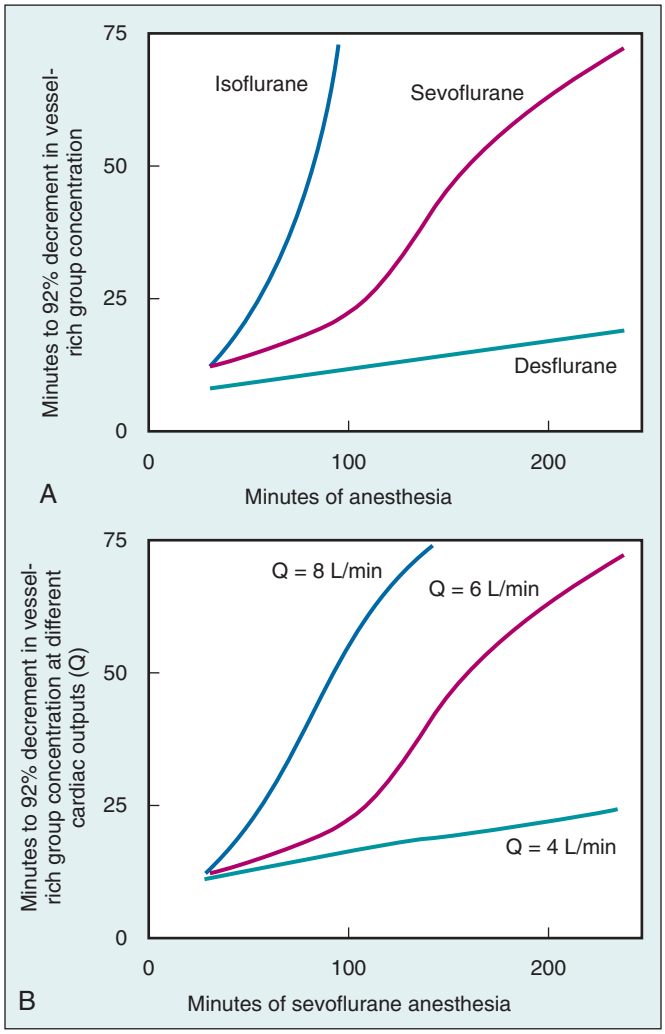
Recovery and Elimination

Recovery from anesthesia follows elimination of the inhaled anesthetic agent from the effect site. Most anesthetic is eliminated from the blood via exhalation from the lungs; other routes include transcutaneous and visceral losses (both minor) and a more significant agent-specific metabolic component. Biodegradation has a significant effect on the elimination of the most extensively metabolized agents (in decreasing order of biodegradation: methoxyflurane, halothane, sevoflurane, enflurane, isoflurane, desflurane).[32] The extensive metabolism of methoxyflurane (~75% of absorbed drug) and halothane (~40% of absorbed drug) contributes to the faster decay in alveolar concentration for these drugs compared with less metabolized drugs such as isoflurane and desflurane.[33]



• **Fig. 3.9** The *F/F*curve is determined by uptake of different compartments, for fixed *F*, minute ventilation, and cardiac output. Uptake is proportional to 1 – *F/F*, which is the area above the *F/F*curve. Each colored area thus represents schematically a different compartment: functional residual capacity *(FRC, blue)*, vessel-rich group *(VRG, green)*, muscle group *(MG, orange)*, fat group *(FG, yellow)*. *FA*, Alveolar conl centration; *FI*, inhaled concentration; *Iso*, isoflurane; *MV*, minute ventilation; *NO*, nitrous oxide; *RR*, respiratory rate; *Sevo*, sevoflurane; *TVA*, inspired tidal volume; *TVI*, expired tidal volume. (Modified from Hendrickx J, Peyton P, Carette R, et al. Inhaled anaesthetics and nitrous oxide: complexities overlooked. *Eur J Anaesthesia.* 2016;33:611–619.)

Washout of inhaled anesthetics follows a multiexponential decay time course. As with wash-in, the lower the solubility, the faster is elimination owing to the increased efficacy of ventilation in eliminating anesthetic from the blood. In contrast to wash-in, wherein the inhaled concentration can be raised above the desired target (overpressure) to speed induction by overcoming the effect of solubility to hinder the rise in alveolar concentrations, during washout the alveolar concentration of anesthetic can never be less than zero, limiting the gradient for elimination. Additionally, washout is affected by the differential elimination from the four tissue compartments discussed earlier for uptake. Anesthetics can also redistribute between various tissue groups. For anesthetics with low tissue and blood solubility, duration of anesthesia has relatively little effect on rate of elimination. But for anesthetics with greater solubility, the washout rate is proportional to duration of anesthesia as the result of accumulation in tissues with longer time constants. This can be expressed as context-sensitive decrement times (Fig. 3.10).[34] Evidence for a fifth compartment during washout has been suggested to involve diffusion from highly perfused tissues to adjacent fat that has a much larger time constant than muscle but 10 times faster than bulk fat.[18,35] Compartments with longer time constants (e.g., fat) do not equilibrate during short (<1 hour; longer with desflurane) procedures such that they can continue to take up anesthetic until alveolar elimination reduces arterial anesthetic partial pressure below tissue level. This can accelerate elimination early in recovery, but it eventually slows recovery as tissues continue to unload anesthetic into blood. Complete elimination after a long anesthetic exposure can take days.



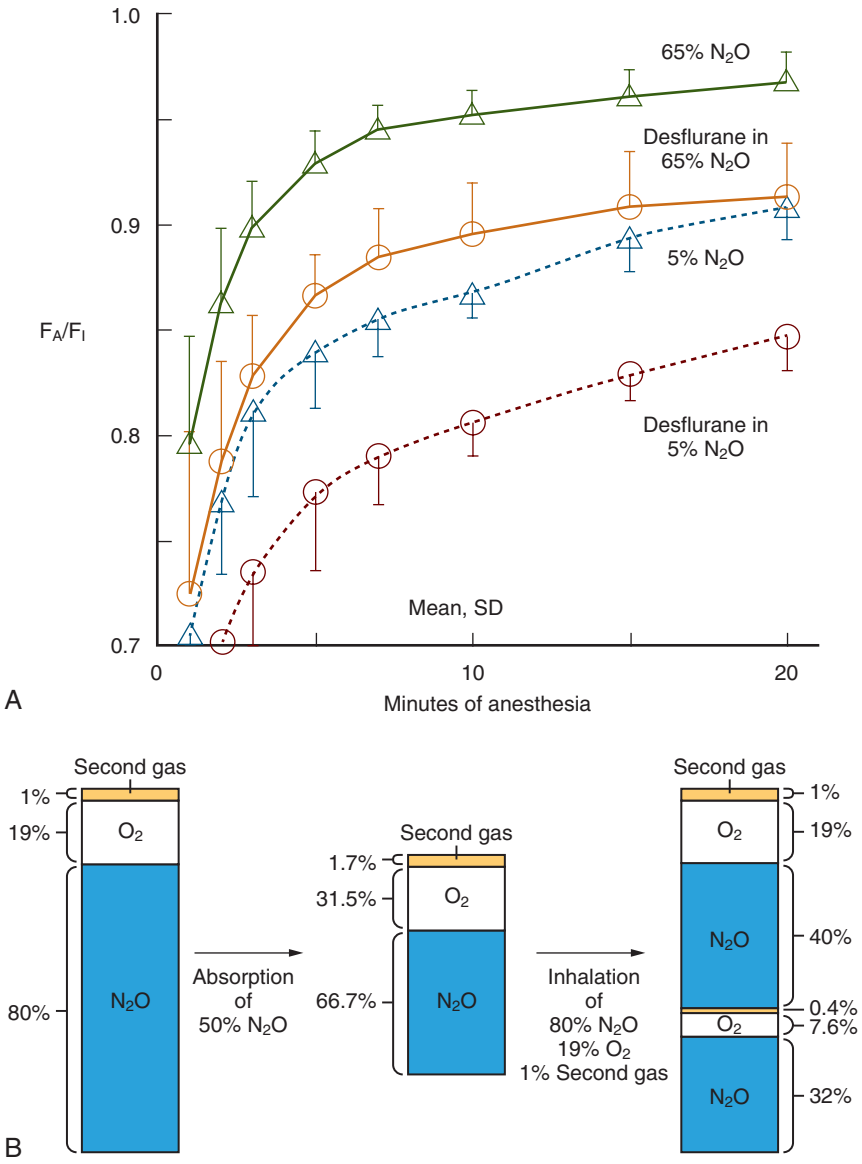
• **Fig. 3.10** Context-sensitive decrement time as a function of total anesthetic time, agent, and cardiac output. A, Time required for the vessel-rich group concentration to decrease 92% from baseline as a function of the duration of the anesthetic. Note that the washout time increases with increasing solubility, as desflurane (the least soluble agent) is the fastest to wash out, whereas isoflurane (the most soluble agent) is the slowest to wash out for all anesthetic durations. B, Increasing cardiac output *(Q)* decreases the time to washout; all curves in this panel are for sevoflurane. (Modified from Eger EI 2nd, Shafer SL. Tutorial: context-sensitive decrement times for inhaled anesthetics. *Anesth Analg.* 2005;101:688–696.)

Nitrous Oxide: Concentration Effect, Second Gas Effect, Diffusion Hypoxia, and Effects on Closed Gas Spaces

The higher the concentration of an inhaled anesthetic, the faster the alveolar concentration approaches the inhaled concentration.[36] This is termed the *concentration effect* and is only of clinical relevance with gases administered at high concentrations such as nitrous oxide and xenon. When an inhaled anesthetic, such as nitrous oxide, is administered in high concentrations, the gas is rapidly taken up into blood (for nitrous oxide, the rate is on the order of 1 L/min). Assuming that the amount of oxygen uptake is approximately balanced by the amount of CO_2 eliminated, anesthetic uptake results in reduced alveolar volume. The absorbed nitrous oxide is replaced by a volume of gas with proportions similar to the initial inhaled mixture, resulting in a more rapid rise in the alveolar concentration of nitrous oxide (the so-called concentration effect). The concentration effect is due to both a concentrating of residual gases and an effective increase in alveolar ventilation due to the large volume of anesthetic gas absorbed, which is replaced by additional inspired gas minimizing the fall in alveolar anesthetic concentration (Fig. 3.11).[37] At the extreme of 100% inspired anesthetic gas, the effects of dilution of alveolar gas during uptake is completely eliminated and uptake is limited only by alveolar ventilation (other factors staying constant).

The concentration effect also affects other gases present in the inspired gas, including the more potent volatile agents. If a second gas is administered at the same time as a low-potency gas that is taken up in large volumes like nitrous oxide, the concentration of the second gas rises faster than it would in the absence of the high-concentration gas. This is termed the second gas effect and is due to the uptake of significant volumes of alveolar nitrous oxide that serves to concentrate the residual gases in the inspired mixture and to increase alveolar ventilation (second gas effect).[37,38] This process can speed induction of inhalational anesthesia. Ironically, perhaps, induction of anesthesia tends to promote ventilation-perfusion scatter, which exaggerates the concentrating effect in those alveoli, because uptake preferentially occurs in areas with a lower ventilation-perfusion ratio. As a result, the second gas effect also has an even more profound effect on arterial than alveolar concentrations.[39]

Analogous to the second gas effect during induction, when a low-potency gas like nitrous oxide is discontinued, it diffuses rapidly



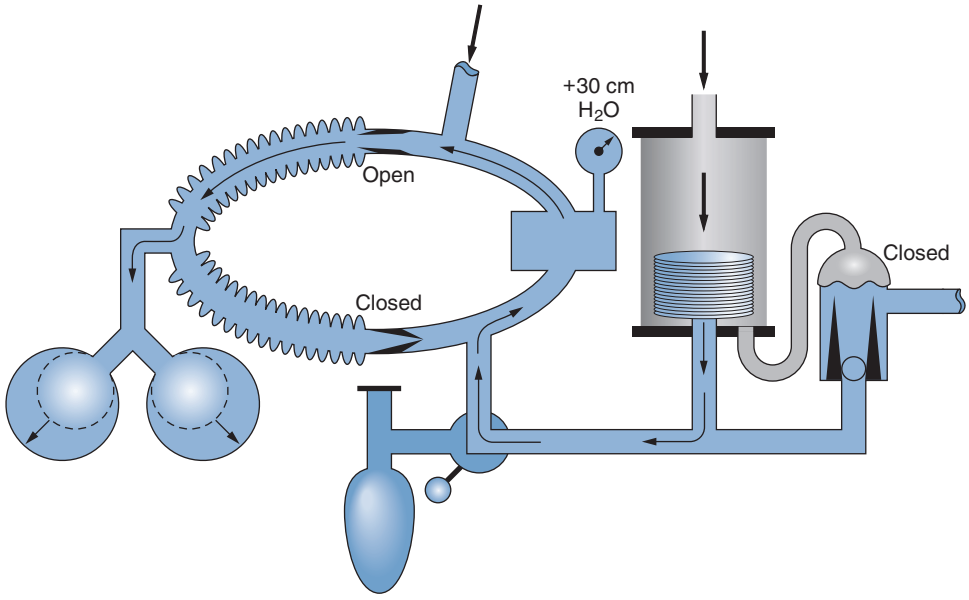
• **Fig. 3.11** Second gas and concentration effects. A, The F_A/F_I of nitrous oxide *(N_2O)* increases to a higher level when delivered at a concentration of 65% (*blue* curve, upper panel) than at a concentration of 5% (*green* curve), a demonstration of the concentration effect. Similarly, the F_A/F_I of desflurane increases to a higher level when delivered with 65% N_2O (*red* curve) than when delivered with 5% N_2O (*brown* curve), a demonstration of the second gas effect. B, Absorption of the very soluble N_2O increases the relative concentration of the second gas. Uptake of 50% of the N_2O does not reduce its concentration by half because the reduction in volume increases its concentration as well as that of the second gases (oxygen and the second gas). A subsequent breath diminishes this effect by mixing the concentrated mixture with the delivered gas, yet the second gas is still more concentrated. *F_A*, Alveolar (end-tidal) concentration; *F_I*, inspired concentration; *N_2O*, nitrous oxide; *O_2*, oxygen. (A, Modified from Taheri S, Eger EI 2nd. A demonstration of the concentration and second gas effects in humans anesthetized with nitrous oxide and desflurane. *Anesth Analg.* 1999;89:774–780. B, Modified from Stoelting RK, Eger EI 2nd. An additional explanation for the second gas effect: a concentrating effect. *Anesthesiology.* 1969;30:273–277.)

into the alveoli, contributing to second gas removal of more potent volatile anesthetics. Nitrous oxide elimination falls exponentially to low rates after about 5 minutes. The large volumes of dissolved nitrous oxide can also cause diffusion hypoxia by diluting alveolar oxygen. Up to 30 L of nitrous oxide can accumulate in the body within 2 hours, and this volume is added to the expired volumes.[40] This eliminated nitrous oxide mixes with alveolar gas, reducing the concentration of oxygen and potentially generating a hypoxic mixture (diffusion hypoxia); this can be minimized by increasing inhaled oxygen during initial recovery. The large volumes of nitrous oxide can also dilute alveolar CO_2, leading to arterial hypocarbia and reduced respiratory drive.[41] The second gas effect has also been shown to occur in reverse during emergence, where the rapid elimination of nitrous oxide dilutes alveolar partial pressure of the potent volatile anesthetic to speed emergence.[42]

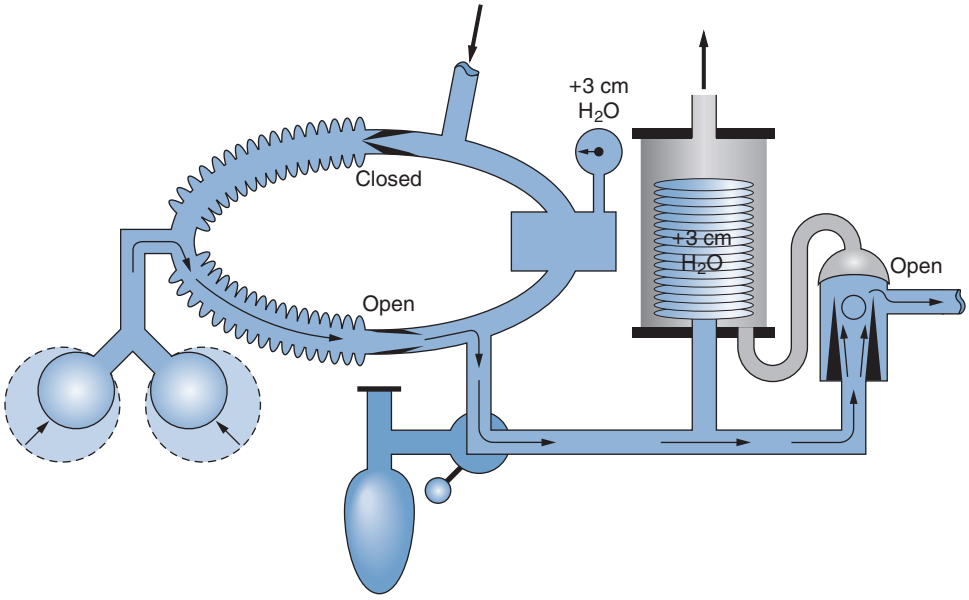
Nitrous oxide (blood:gas partition ratio of 0.47) is roughly 30 times as soluble in blood as nitrogen (blood:gas partition ratio of 0.015). As a result, nitrous oxide accumulates in closed gas spaces that contain nitrogen faster than the nitrogen can diffuse out. This can lead to distention of closed air-containing spaces such as the middle ear, bowel, pneumothorax, air emboli, or tracheal tube cuff. The volume of distensible spaces increases to the extent that the nitrous oxide concentration is equal to the alveolar, and in turn, blood nitrous oxide concentration in volume percent. Hence, the extent of this increase is proportional to the concentration of alveolar nitrous oxide at low (i.e., single-digit concentrations), but is about twofold for 50% nitrous oxide and threefold for 75% nitrous oxide. Expansion is time-dependent but can be rapid for air emboli. For poorly compliant spaces like the middle ear, diffusion of nitrous oxide can cause a potentially deleterious increase in pressure proportional to its alveolar concentration.

Gas Delivery Systems

Inhaled anesthetics are delivered to the lungs using an anesthesia circuit. This serves several functions: delivering oxygen and inhaled drugs to the patient, maintaining temperature and humidity of inhaled gases, removing exhaled CO_2, and ultimately removing



A **Inspiratory phase**



B **Expiratory phase late**

• **Fig. 3.12** The anesthetic circle system. Fresh gas flow enters the inspiratory limb, which has a one-way valve that allows flow toward the patient. The inspiratory limb meets the expiratory limb at the T-piece. The circuit dead space is determined by the volume of everything between the patient and the T-piece. A second one-way valve in the expiratory limb limits flow away from the patient. The bag and ventilator bellows affect circuit pressure on the expiratory side of the circuit. A switch valve gives the user choice between manual and mechanical ventilation. When manual ventilation is selected, an adjustable pressure-limiting valve vents excessive pressure to the scavenging system. When the ventilator is in operation, the scavenger system is cyclically opened. *Arrows* indicate direction of gas flow. During inspiration, oxygen compresses the ventilator bellows and seals the scavenger system. As a result of the one-way valves in the circuit, the increased pressure forces gas into the lungs. Release of the pressure in the ventilator bellows opens the scavenger system and allows gas to return from the patient.

drugs from the patient. Three broad classes of circuits are in use: rebreathing circuits where inspired and exhaled gases mix (Bain circuit), non-rebreathing circuits in which one-way valves separate inhaled from expired gases (self-inflating resuscitation bag-valve system), and circuits that use a CO_2 absorbent (circle systems with both inspiratory and expiratory valves). The most common inhaled drug delivery system used in modern anesthesia machines is a circle system (Fig. 3.12).

Circle systems consist of inspiratory and expiratory limbs, a reservoir bag, a canister of CO_2 absorbent (e.g., soda lime), one-way

valves to direct gas flows (one each on the inspiratory and expiratory limbs), a Y-piece that attaches the inspiratory and expiratory limbs to the respiratory tract via a mask or tracheal tube, a fresh gas inlet, and a relief valve. The CO_2 absorbent removes CO_2 in an exothermic reaction by producing water and a carbonate:

Reaction of CO_2 With Barium Hydroxide Lime (Baralyme, Obsolete)

$$Ba(OH)_2 + 8\,H_2O + CO_2 \leftrightarrow BaCO_3 + 9\,H_2O + \text{heat}$$

$$9\,H_2O + 9\,CO_2 \leftrightarrow 9\,H_2CO_3$$

$$9\,H_2CO_3 + 9\,Ba(OH)_2 \leftrightarrow 9\,BaCO_3 + 9\,H_2O + \text{heat}$$

Reaction of CO_2 With Lithium Hydroxide (in Current Use)

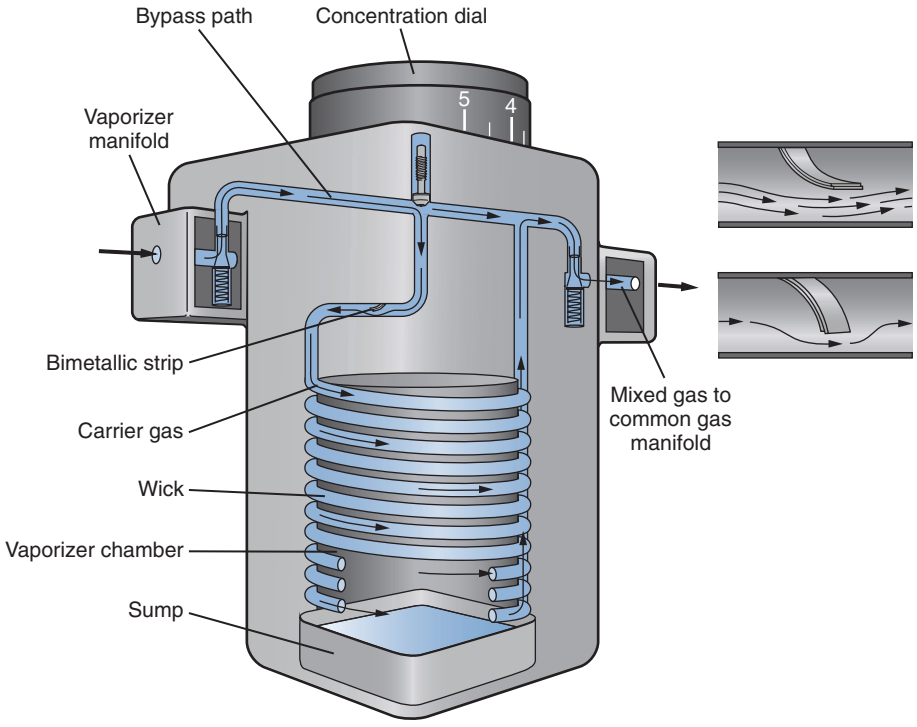
$$2\,LiOH + 2\,H_2O \leftrightarrow 2\,LiOH \cdot H_2O$$

$$2\,LiOH \cdot H_2O + CO_2 \leftrightarrow Li_2CO_3 + H_2O + \text{heat}$$

CO_2 absorbent can degrade inhaled anesthetics to potentially harmful breakdown products. Desiccated soda lime and barium hydroxide–based absorbents degrade sevoflurane (see earlier text); this can be avoided by eliminating monovalent bases from soda lime or by using a lithium hydroxide–based absorbent. Additionally, the heat produced by desiccated absorbent can be sufficient to ignite combustible degradation products, leading to absorbent canister explosion.[43,44] A number of proprietary absorbents (e.g., Amsorb, Drägersorb) have been developed that do not contain monovalent bases to minimize degradation of sevoflurane and desflurane.

Vaporizers are devices that add desired anesthetic concentrations to the fresh gas flow and ultimately to the anesthetic circuit and patient. Most modern vaporizer designs, with the notable exception of common desflurane vaporizers, use temperature-compensated variable bypass manifolds that are concentration calibrated for use with a single anesthetic agent (Fig. 3.13). These devices function by diverting a portion of the fresh gas flow through a vaporizing chamber where the flow is saturated with volatile anesthetic; the amount of flow that bypasses the chamber is determined by the ambient temperature and the desired concentration (in volume percent) of anesthetic in the vaporizer output. In contrast, desflurane vaporizers compensate for the very high vapor pressure of desflurane at room temperature by using an electric heater to warm and pressurize the desflurane into a vapor that is injected into the fresh gas flow at a rate to deliver the set desflurane concentration in the vaporizer output.

The anesthetic circuit has significant effects on the kinetics of inhaled drug delivery and elimination by determining inspired gas concentrations (F_I). Rebreathing allows mixing of inspired and expired gases (with depleted anesthetic concentration resulting



• **Fig. 3.13** A variable bypass anesthetic vaporizer. Fresh gas flows through the vaporizer and a portion of the flow is diverted through the vaporizer chamber. This carrier gas flows over a wick that ensures equilibration of the anesthetic with the carrier gas. The carrier flow, saturated with anesthetic, is then mixed back with the fresh gas that bypasses the reservoir to achieve the desired anesthetic concentration (volume percent). A temperature-compensating valve adjusts the amount of gas flow that is diverted to ensure stable temperature because vapor pressure is temperature-dependent. Note that the portion of flow diverted through the vaporizer chamber, as well as the temperature-compensation valve, must both be calibrated for each individual agent. Filling a variable bypass vaporizer with an agent other than the one for which it is calibrated can lead to delivery of a dangerous concentration of anesthetic. (Adapted from Morgan GE, Mikhail MS, Murray MJ. *Clinical Anesthesiology.* 4th ed. New York: McGraw-Hill; 2006.)

from uptake) and thus reduces delivered anesthetic concentration below that delivered by the vaporizer. This is minimized when the fresh gas flow exceeds minute ventilation. The circuit itself has a time constant (τ) for equilibration with the gas delivered from the machine (τ = volume of the breathing system/fresh gas flow). This determines the wash-in kinetics of the circuit. If the delivered gases immediately mix with the circuit gases, the anesthetic concentration in the breathing system reaches 95% of the delivered concentration in 3τ; however, more efficient circuit designs are commonly used.[45] Increased gas flow or reducing circuit volume accelerates this equilibration and speeds the rate of induction.

Low-Flow Anesthesia

The choice of fresh gas flow in the circuit can dramatically affect the amount of agent used, and hence the cost of anesthetic drugs, particularly for long cases. The lowest cost approach is to use a closed circuit, where there are no leaks in the circuit, the pressure limiting valve is closed, and the fresh gas flow uses 100% fraction of inspired oxygen (FIO_2) to exactly offset the uptake/consumption of oxygen by the patient (roughly 2.5–3 mL O_2/kg per minute for adults, or approximately 200 mL/min for a typical 70-kg adult). Closed-circuit administration minimizes the cooling and drying effects of the fresh gas flow for the patient but leaves little margin for error; any change in anesthetic concentration requires temporarily increasing the gas flow to speed equilibration. With slightly higher flow rates, small leaks in the circuit can be overcome and gradual changes in the anesthetic concentration are possible while still keeping costs down. As the fresh gas flow increases, times to equilibration of changes in inhaled anesthetic concentration are faster, but the patient is exposed to cooler and drier gases potentially compromising their pulmonary function, and more agent and inhaled gases are wasted.[46] Wasted inhaled anesthetics in the operating room are typically collected and then scavenged through a wall suction system to be vented into the atmosphere. For cost reasons, anesthesia systems using xenon actively recover as much xenon is possible from the waste gas stream before venting the residual. Anesthetic agents have substantial greenhouse gas and ozone depletion potential, so minimizing venting to the atmosphere is appropriate.[47] Sevoflurane is usually used at gas flows greater than 2 L/min out of concern for compound A production, but as discussed earlier there is minimal evidence of clinically significant nephrotoxicity in humans.[25]

As an alternative to traditional low-flow semi-closed anesthesia systems, one commercially available device, the AnaConDa (Sedana Medical, Danderyd, Sweden), inserts a filter between the patient and the Y-piece that selectively adsorbs and desorbs volatile anesthetics with each breath while passing oxygen, nitrogen, and CO_2 freely.[48] This functionally results in a breathing system that is closed with respect to volatile anesthetics but open for the remainder of the gas stream.

Pharmacoeconomic Considerations

The cost of inhaled anesthetic consumed during an anesthetic is determined by four principal factors: the cost of liquid anesthetic per milliliter, the volume of vapor that results from each milliliter of liquid, the volume percent of anesthetic delivered (determined largely by the potency), and the chosen fresh gas flow rate.[49] The volume percent delivered is determined by two factors: anesthetic potency and solubility. While potency determines the vaporizer setting at steady state (when $F_A = F_I$), solubility affects the vaporizer setting during wash-in as some degree of overpressure might be required to speed induction before equilibration to steady state occurs. The significance of the solubility issue is illustrated by a study that used a 10-minute wash-in period before initiating controlled fresh gas flows for delivery of anesthetic. Desflurane consumption was governed by fresh gas flow, and although there was a trend toward increased consumption of sevoflurane and isoflurane at higher fresh gas flows, halothane consumption was totally independent of the fresh gas flow.[50]

For most institutions in the United States, isoflurane is the least expensive anesthetic on a per milliliter basis and desflurane the most expensive, with sevoflurane slightly less expensive than desflurane. However, the lesser potency of desflurane (with an MAC of 6% compared with an MAC of 2% for sevoflurane) means that at steady state significantly more desflurane is consumed per hour for a given anesthetic depth at the same flow rates. Because most anesthesiologists are comfortable with using low flow rates for desflurane, but not sevoflurane, the cost differential for longer cases favors desflurane if low flows are used.

Emerging Developments

Intravenous Delivery of Volatile Anesthetics

Early reports suggested that intravenous delivery of liquid volatile agents incurs significant morbidity with risk of pulmonary damage or death.[51–54] Subsequently, several groups have reported that volatile anesthetics, including halothane, isoflurane, and sevoflurane, can be successfully delivered intravenously as a lipid emulsion.[52,55–58] Initial reports of nonlethal intravenous delivery of anesthetics used lipid emulsion as the carrier vehicle, but ongoing research to increase anesthetic concentrations in the emulsion has led to the development of fluoropolymer-based vehicles.[59] Volatile anesthetic emulsions can be delivered by bolus or continuous infusions, and preserve respiratory drive while causing a rapid loss of consciousness in animals. Intravenous delivery appears to preserve most properties of volatile agents, including early and late cardiac preconditioning.[58,60] The principal advantage of these preparations is the rapid onset, because there is no need to wait for uptake through the lungs and the resultant slow rise in alveolar concentration. However, intravenous delivery gives up the advantages of inhalational delivery. For example, inhalational anesthetic delivery results from equilibration with a (measurable) delivered concentration of anesthetic, and there is no accumulation of agent beyond the inhaled concentration or need for continuous adjustment of delivery rate to ensure a given blood-tissue concentration. As a result, a large amount of research has gone into developing target-controlled infusions for intravenous agents to make their use more akin to use of a vaporizer for an inhaled agent (see earlier text).[61] Adverse effects of the accumulating vehicle are also potentially problematic.

Volatile Anesthetics in the Intensive Care Unit

Volatile anesthetics offer the intensivist an additional tool for sedation in the intensive care unit (ICU). Although this may require placing an anesthesia machine in the ICU, the AnaConDa device (see the previous discussion in the "Low-Flow Anesthesia" section) will allow anesthetic delivery with a normal ICU ventilator, with potential advantages for patients requiring nontraditional ventilation modes. Volatile anesthetics are established lifesaving interventions for refractory status asthmaticus[62] and status epilepticus.[63] A recent meta-analysis showed that volatile anesthetics can shorten the

duration of mechanical ventilation,[64] presumably based on their fast washout and reduced awakening time. This should offer the advantage of minimizing complications of mechanical ventilation, with a presumed benefit in mortality and ICU length of stay. Further study will be required to justify a broad adoption of volatile anesthetics for long-term sedation, however, as all of the usual cautions with interpreting meta-analyses apply. Only one of the included trials was blinded; most of the trials had small or moderate enrollments; the majority of the studies included in the meta-analysis did not include clinically relevant outcomes such as delirium, major morbidity, or mortality; and volatile anesthetics were not compared against dexmedetomidine, which is known to have several benefits of reduced time to extubation, reduced ICU length of stay, and reduced incidence of delirium.[65,66]

Key Points

- The effects of inhaled anesthetics depend on the anesthetic concentration at their effect sites. This parallels the alveolar anesthetic concentration and not the total amount of absorbed anesthetic.
- The potency of different agents can be compared using the MAC, the minimum alveolar concentration of anesthetic required to prevent movement (immobilization) in 50% of subjects in response to a standardized surgical stimulus.
- Blood and tissue concentrations of a gas are determined by the partial pressure of the gas and its blood:gas or tissue:gas partition ratio (an index of its solubility).
- The physical properties of inhaled anesthetics, in particular solubility, determine many aspects of their pharmacokinetic behavior.
- Blood solubility is a major determinant of the rate of inhaled anesthetic uptake and elimination from the alveoli; both are faster with less soluble agents.
- Physiologic factors that govern inhaled anesthetic uptake and elimination include primarily alveolar ventilation and cardiac output.
- Extrinsic factors that affect inhaled anesthetic uptake and elimination, by determining changes in the alveolar concentration, include minute ventilation, fresh gas flow, and inspired concentration.
- Inhaled anesthetic tissue distribution depends on relative perfusion, the gradient between arterial and venous anesthetic concentration, and intertissue distribution.
- Volatile anesthetics in use today are minimally metabolized; most of this metabolism is by the cytochrome P450 system.

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Physics: Liquids, Vapors, Gases, and the Gas Laws

Kai Kuck

OUTLINE

Background
Liquids, Gases, and Vapors
Liquefaction and Vaporization
Gas Laws
Humidity
Gas Conditions

Background

Anesthesiology involves management of medications in both liquid and gaseous forms. Thus, knowledge of the gas laws that govern the behavior of liquids, gases, and vapors—and the transitions between these states—is critical to anesthetists.

Liquids, Gases, and Vapors

Substances can exist in 3 states, or phases (solid, liquid, and gaseous). The difference between these states is a matter of the kinetic energy of the molecules and the degree of their interaction.

Liquids are, for all practical purposes, incompressible. Their volume depends largely on their temperature and the structure and mass of their molecules. These properties determine the interaction between the molecules. While the molecules in a liquid can move freely within the liquid, the kinetic energy of molecules in a liquid is too low to overcome the intermolecular attractive forces, preventing transition into the gas phase.

Gases, in contrast, are compressible. Like liquids, they take on the volume of their container. Molecule kinetic energy is higher than for liquids; in fact, molecular kinetic energy in gases is so high that intermolecular interactions are much less important. **Pressure** is the force per area that a gas exerts on the walls of its container.

Vapor describes the gas form of a substance when it exists in equilibrium with its liquid form, for example, when the temperature is low enough such that the substance can exist in gaseous or liquid form.

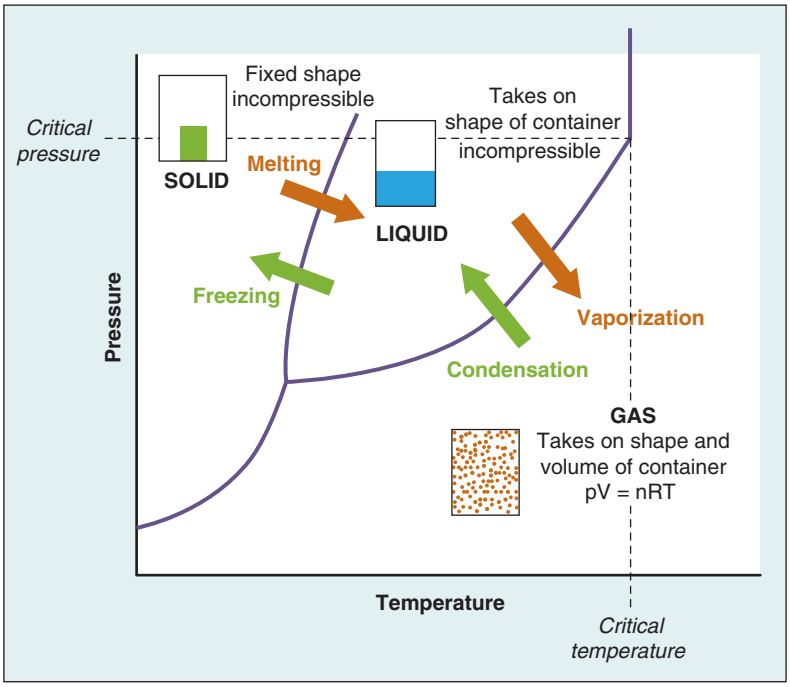
Liquefaction and Vaporization

When gases are cooled and compressed, they will at some temperature and pressure condense into liquids. The liquefaction occurs at the point when the kinetic energy of the gas molecules is insufficient to overcome the forces of intermolecular attraction. The exact temperature and pressure at which this happens depends on the molecular mass and molecular structure. The **critical temperature** is the temperature above which a gas cannot be liquefied, regardless of how much it is compressed (Fig. P1.1). The **critical pressure** is the pressure needed to liquefy a gas at exactly its critical temperature. Above its critical temperature, a substance will exist only in its gaseous form and it is commonly referred to as a gas. Below its critical temperature, a substance can exist as a solid, liquid, or gas. When below its critical temperature and gaseous, a substance is commonly referred to as a vapor**.** At room temperature, pressurized cylinders of O_2, N_2, or air contain gases only, while cylinders of CO_2 or N_2O contain both liquid and gas states in equilibrium (Table P1.1).

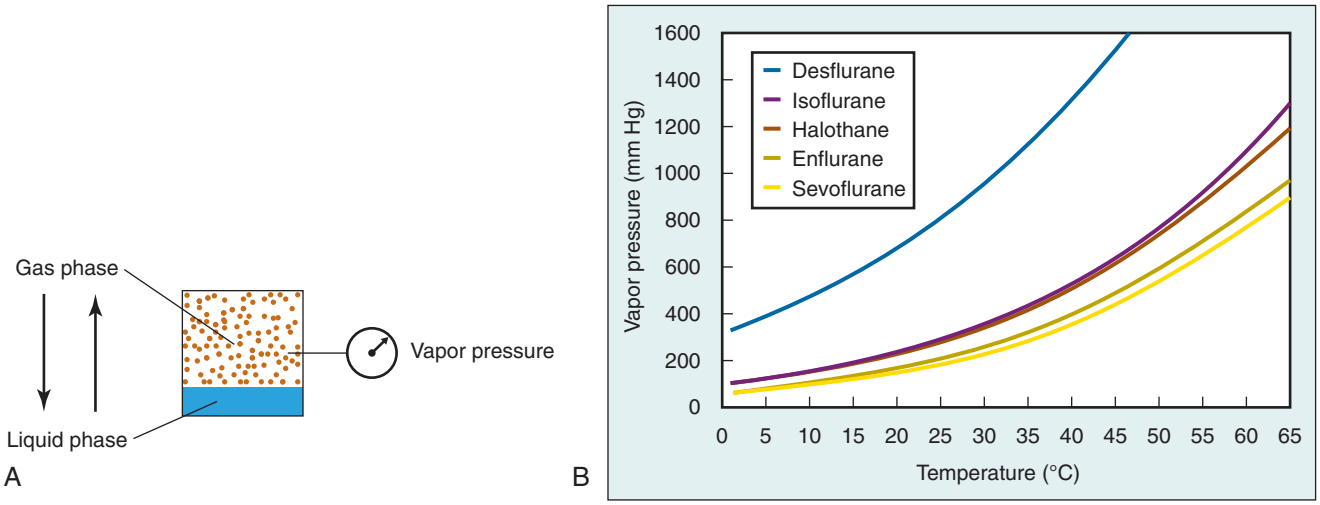
Vapor pressure is the pressure in a closed container at which the liquid and vapor phases are in equilibrium (when the vapor phase is said to be **saturated**). Vapor pressure depends on the substance itself (its molecular structure, mass, and so on) and temperature (Fig. P1.2).[3] The temperature at which vapor pressure equals atmospheric pressure is called the atmospheric **boiling point**. It takes heat for a substance to change state (e.g., from liquid to gas). The heat needed to vaporize a specific mass (1 kg) of a substance at a given temperature is known as the **specific latent heat**. Often, the vaporization process draws heat from the liquid itself or from the environment, cooling them. Since vaporization

TABLE P1.1 Critical Temperatures and Pressures of Selected Gases[1,2]

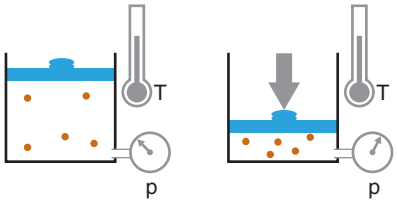
	Critical Temperature (°C)	Critical Pressure (bar)
O_2	–118.2	50.4
N_2	–147	34
CO_2	30.9	73.8
N_2O	36.5	72.5
Air	–140.7	37.86



• **Fig. P1.1** Diagram of solids, liquids, and gas phases. Substances change depending on temperature and pressure. Arrows signify the transition from one phase to another. Substances require external energy to melt and vaporize (endothermic, *red*), while condensation and freezing give off energy (exothermic, *green*). Not shown are sublimation, the transition from solid phase to gas phase, and deposition, the transition from gas phase to solid phase.



• **Fig. P1.2** (A) Diagram of vapor pressure. The vapor pressure is the pressure in a closed container in which a substance's liquid and vapor phases are in equilibrium. It depends on the substance and increases with temperature. (B) Vapor pressures of volatile anesthetic agents.[3] Desflurane exhibits not only a much higher vapor pressure than other agents—desflurane's vapor pressure also changes faster when its temperature changes and reaches the atmospheric pressure (e.g., 760 mm Hg at sea level) close to room temperature (22.8°C). This necessitates fundamentally different vaporizer designs for desflurane than for other volatile agents. (From Andrews JJ, et al. Consequences of misfilling contemporary vaporizers with desflurane. *Can J Anaesth.* 1993;40(1):71–76.)



• **Fig. P1.3** Diagram of Boyle's Law. Assuming the number of molecules and the temperature (T) of a gas do not change, its volume changes inversely with its pressure (p).

itself is dependent on temperature, vaporizers have temperature-compensation mechanisms to prevent cooling from reducing vaporizer output.

Gas Laws

The gas laws describe relationships between pressure, volume, temperature, and amount of gases. The ideal gas law describes the behavior of a gas in which molecules move randomly and do not interact with each other, except for their collisions. Many of the gases in anesthesia behave as ideal gases, with notable exceptions. An important exception is when a gas is close to its transition between the liquid and gas phases or when it exhibits strong intermolecular interactions (e.g., water).

In 1662, Boyle described Boyle's Law (Fig. P1.3): *as long as the number of molecules and the temperature of a gas do not change, its volume changes inversely with its pressure.*

$$p_1 \times V_1 = p_2 \times V_2, \text{ or}$$

$$V \propto \frac{1}{p}$$

Consider, for example, an E cylinder with an internal volume of 5.1 L (Fig. P1.4). If it is completely filled with oxygen, its internal pressure is 131 bar (or 1900 psi) at room temperature (70°F or 21°C). Boyle's law can be used to determine the volume of the oxygen in that cylinder, if the oxygen is released into an atmospheric pressure of 14.69 psi (1.013 bar) without changing temperature:

$$131\ bar \times 5.1\ L = 1.013\ bar \times V$$

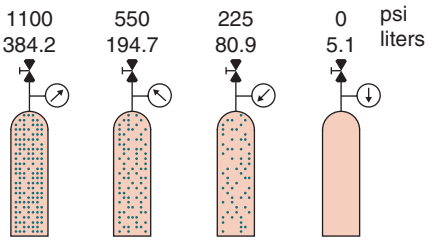
$$\rightarrow V = \frac{131\ bar \times 5.1\ L}{1.013\ bar} = 660\ L$$

In the 1700s, when hot air balloons enjoyed increasing popularity in prerevolutionary France, Charles described **Charles's Law**, sometimes also called **Charles and Gay-Lussac's Law** (Fig. P1.5), from the scientist who first published[4] Charles' discovery in the early 1800s: *as long as the number of molecules and the pressure of a gas do not change, its volume changes linearly with absolute temperature (in °K).*

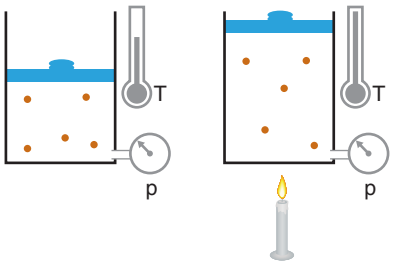
$$\frac{V_1}{T_1} = \frac{V_2}{T_2}, \text{ or}$$

$$V \propto T$$

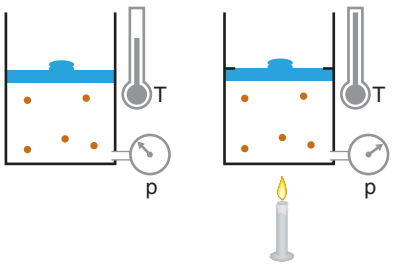
For example, in a hot air balloon, as temperature increases, the volume of the gas in the balloon expands and it becomes less dense, eventually causing enough buoyancy to float the balloon.



• **Fig. P1.4** Boyle's Law applied to E-sized cylinders. The pressure (above atmospheric pressure, measured in pounds per square inch, psi) inside of an oxygen E cylinder is linearly related to the volume of oxygen when released into atmospheric pressure.



• **Fig. P1.5** Diagram of Charles's Law. Assuming that the number of molecules and the pressure (p) of a gas do not change, its volume changes linearly with absolute temperature (T, measured in Kelvin).



• **Fig. P1.6** Diagram of Amonton's Law. The pressure (p) of a fixed amount of gas in a fixed volume container changes linearly with absolute temperature (T, measured in Kelvin).

Another example is the expansion of an inflatable laryngeal mask airway's cuff when it is heated in an autoclave (or by the patient's body heat).

Amonton's Law,[5] sometimes also referred to as **Gay-Lussac's Law**, describes the relationship between the temperature and the pressure of a gas (Fig. P1.6): *the pressure of a fixed amount of gas in a fixed-volume container changes linearly with absolute temperature (in °K).*

$$\frac{p_1}{T_1} = \frac{p_2}{T_2}, \text{ or}$$

$$p \propto T$$

This law explains how after driving some distance, when the tires of a car heat up, the tire pressure is higher compared to the pressure in cold tires.

Combining Boyle's Law, Charles's Law, and Amonton's Law yields the **General Gas Law**, or Combined Gas Equation (Fig. P1.7): *for a fixed amount of gas, its volume changes linearly*

with the change in its absolute temperature and reciprocally with the change in its pressure:

$$\frac{p_1 \times V_1}{T_1} = \frac{p_2 \times V_2}{T_2}, \text{ or}$$

$$V \propto \frac{T}{p}$$

(where T is absolute temperature in °K).

Avogadro's Law (Fig. P1.8) states that *as long as the pressure and temperature of a gas stay constant, its volume will change linearly with the number of molecules:*

$$\frac{V_1}{n_1} = \frac{V_2}{n_2}, \text{ or}$$

$$V \propto n$$

(where T is absolute temperature in °K).

The variable "n" is the amount of gas in mol, where 1 mol is the amount of a substance that contains 6.02×10^{23} molecules of that substance (Avogadro's number).

At a temperature of 0°C and a pressure of 760 mm Hg (Standard Temperature and Pressure [STP]), 1 mol of a gas occupies exactly 22.4 L.

The **Ideal Gas Law** results from combining Avogadro's Law with the General Gas Law (Fig. P1.9), which relates all the state variables of an ideal gas to each other:

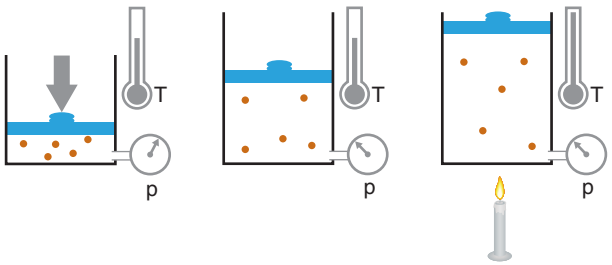
$$p \times V = n \times R \times T = N \times k \times T$$

where

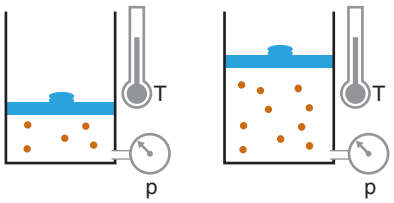
p = pressure (Pa)
V = volume (m^3)
n = amount of gas (mol)
N= number of molecules (1)
R= Universal Gas Constant 8.3145 J/(mol × K)
K = Boltzmann constant 1.381×10^{-23} J/K
T = Absolute Temperature in Kelvin (°K)

The number of molecules in 1 mol is constant and called **Avogadro's Number**, $N_{Avogadro}$:

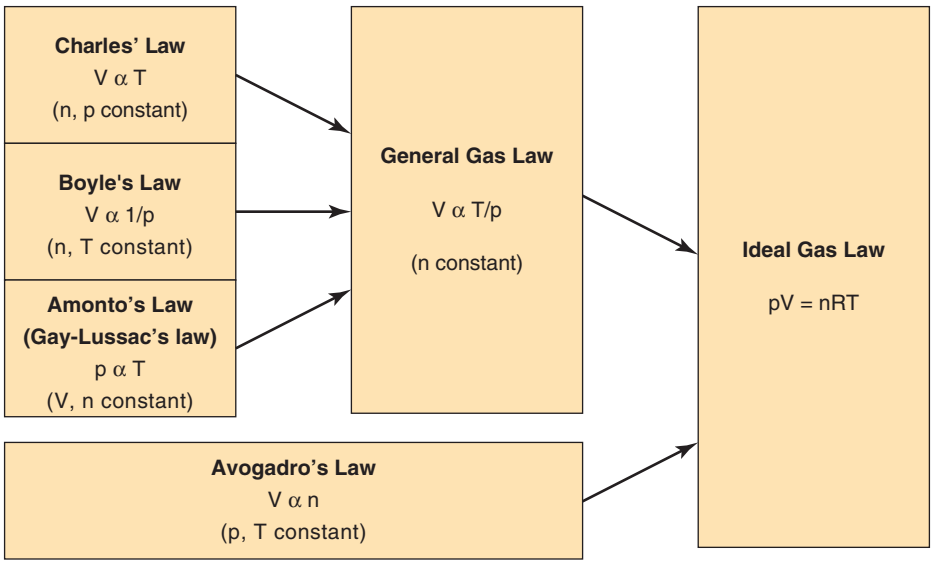
$$N_{Avogadro} = \frac{N}{n} = \frac{R}{k} = 6.02212 \times 10^{23}$$



• **Fig. P1.7** Diagram of the General Gas Law. For a fixed amount of gas, its volume will change linearly with the change in its absolute temperature (T, measured in Kelvin) and reciprocally with the change of its pressure (p).



• **Fig. P1.8** Diagram of Avogadro's Law. Assuming constant pressure (p) and temperature (T) in a gas, its volume will change linearly with the number of molecules.



• **Fig. P1.9** Diagram of the Gas Laws. The gas laws describe the relationships between the pressure, volume, temperature, and amount of gases. *n,* Amount of gas (mole); *p,* pressure (Pa); *R,* universal gas constant (8.314 J/(K × mol)); *T,* temperature (K); *V,* volume (m^3).

Avogadro hypothesized that the behavior of gases as described in the ideal gas law is independent of the identity of the gas:

$$p \times V = (n_{Gas1} + n_{Gas2}) \times R \times T.$$

From this, Dalton's Law of Partial Pressures follows directly: *the total pressure of a gas mixture is the sum of partial pressures of the constituent gases.*

$$p_{Total} = p_{Partial_{GAS1}} + p_{Partial_{GAS2}}$$

Dalton's Law, combined with Boyle's Law, allows the conversion from volume percent to partial pressures and vice versa:

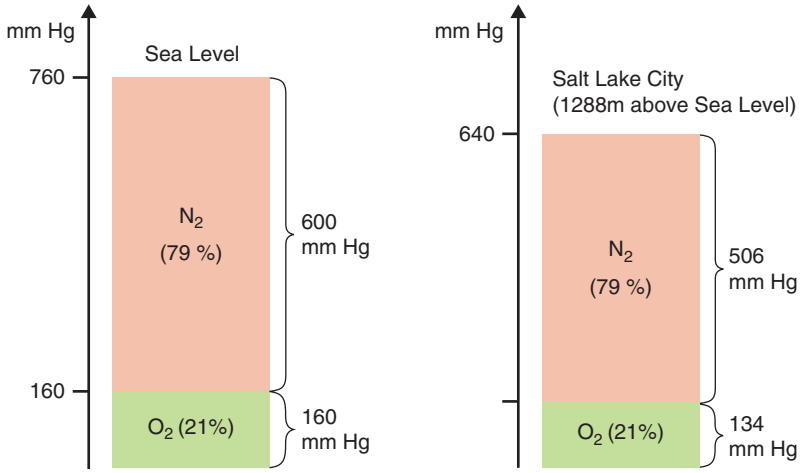
$$p_{Partial_{GAS1}} = \frac{V_{GAS1}}{V_{TOTAL}} \times p_{TOTAL}$$

Dalton's law describes, for example, how the partial pressure of oxygen in air is lower at altitude than at sea level, even though the volume percent is the same (Fig. P1.10).

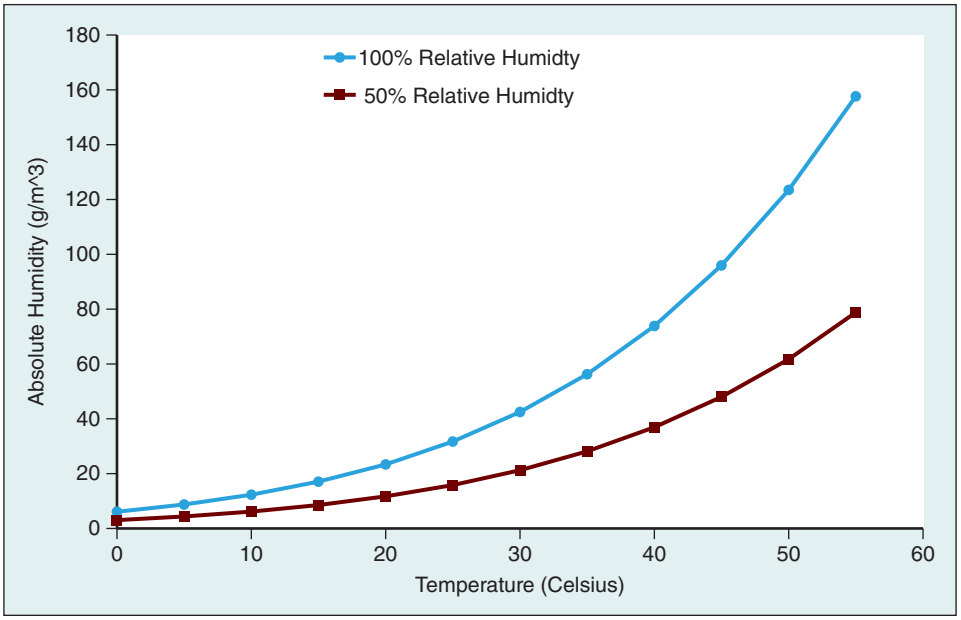
Humidity

The humidity and temperature of gas delivered to a patient are important determinants of how much moisture and heat the patient loses through respiration. Humidity can either be expressed as absolute or relative humidity.

Absolute humidity simply describes the total mass of water vapor in a given volume of gas, measured, for example, as g/m^3 or mg/L. There is a maximum capacity of gas to hold water vapor; when it is reached, the gas is said to be fully saturated.



• **Fig. P1.10** Example of Dalton's Law of Partial Pressures. The volume percent of nitrogen (N_2) and of oxygen (O_2) in ambient air do not change when going from sea level to altitude. However, because the total ambient pressure decreases (in this example, from 760 mm Hg at sea level to 640 mm Hg in Salt Lake City), the partial pressures of both gases also decrease.



• **Fig. P1.11** Maximum absolute humidity and relative humidity as a function of temperature.

TABLE P1.2 Most Commonly Used Gas Conditions

	STPD	BTPS	ATPS
Temperature	0°C (273.15 K)	37°C (310.15 K)	(Ambient Temperature)
Pressure	760 mm Hg	760 mm Hg	(Ambient Pressure)
Humidity	Dry (partial pressure of water vapor: 0 mm Hg)	Saturated (partial pressure of water vapor: 47.1 mm Hg)	Saturated (partial pressure of water vapor depends on the ambient temperature)

ATPS, Ambient temperature and pressure, saturated; *BTPS,* body temperature and pressure, saturated; *STPD,* standard temperature and pressure, dry.

The maximum amount of water that can be in a given volume of gas increases with temperature (Fig. P1.11). At room temperature (20°C or 68°F), fully saturated air contains 17 mg/L water vapor. Expiratory gas, that is, fully saturated and at body temperature (37°C or 98.6°F), contains 44 mg/L of water vapor.

Relative humidity is the total mass of water vapor in a given volume of gas but expressed as a percentage of the maximum amount of water vapor the gas can hold at that temperature. The amount of water vapor is linearly related to n, the number of moles of water. Applying the gas laws (see earlier discussion), the relative humidity can also be calculated as the ratio of the actual water vapor pressure divided by the water vapor pressure of saturated gas at the given temperature. The vapor pressure of water at room temperature (20°C or 68°F) is 17.5 mm Hg and at body temperature (37°C or 98.6°F) 47.1 mm Hg.

An important function of the upper respiratory tract is to humidify inspiratory gas. With the use of an endotracheal tube, the upper respiratory tract is not involved in respiration, which can lead to drying of the lower airways. Humidifiers and heat moisture exchangers (HME) are often used to avoid this. If gas in the anesthesia breathing circuit is at higher temperatures (e.g., close to body temperature) and saturated, liquid water can condense out of the gas in parts of the breathing circuit that have lower temperatures. Because humidification of dry air (as occurs in the lungs) requires energy to vaporize the water, patient temperature can fall under anesthesia as a result of this humidification process (among other more influential reasons).

Gas Conditions

Volumes and concentrations of gases in mixtures are, as described in the gas laws, affected by the temperature, pressure, and water vapor of the gas. These conditions can differ dramatically between different parts of the anesthesia breathing circuit and between inspiration and expiration. Thus, it is customary to describe the conditions under which gas measurements are taken. The most commonly used conditions are **STPD** (Standard Temperature and Pressure, Dry), **BTPS** (Body Temperature Pressure, Saturated), and **ATPS** (Ambient Temperature and Pressure, Saturated; Table P1.2).

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Physics: Monitoring Gas Concentrations

Kyle Burk and Kai Kuck

OUTLINE

Background

Calibration and Preparation Before Use

Monitoring Methods
- Sidestream
- Mainstream

Technologies
- Infrared Absorption
- Paramagnetic Oxygen Sensor
- Electrochemical Oxygen Sensor
- Mass Spectrometry
- Raman Scatter Analysis

Background

This section introduces gas monitoring methods commonly or historically used during anesthesia and reviews the physics principles underpinning these methods. Monitoring of oxygen and carbon dioxide (CO_2) concentrations is a basic and well-entrenched monitoring standard in anesthesia.[1] Volatile anesthetic agent concentrations are also routinely monitored and clinicians have come to rely on this capability as an essential feature of anesthesia workstations.

Commonly derived variables of gas monitoring include fraction of inspired oxygen (FiO_2), end-tidal oxygen concentration, inspired CO_2 concentration, end-tidal carbon dioxide concentration, respiratory rate, and end-tidal volatile anesthetic concentration, where end-tidal refers to the measurements made at the end of expiration. These measurements provide valuable information about the adequacy of oxygen delivery and ventilation. Monitoring CO_2 can indicate adequacy of ventilation, confirm correct positioning of a tracheal tube or laryngeal mask airway, and allow conclusions about metabolism and cardiorespiratory performance. Perhaps the most important function of real-time measurement of airway gases is confirmation of the integrity of the oxygen delivery system. An important nuance of airway gas monitoring relates to nitrogen. If nitrogen concentration is detected in a patient breathing 100% oxygen, it can indicate air emboli (e.g., during sitting intracranial procedures) or a circuit leak.

As with the other measured variables, such as end-tidal CO_2 concentrations, measurement of end-tidal anesthetic agent concentrations has substantial clinical utility. It enables clinicians to confirm that the targeted minimum alveolar concentration (MAC) fraction of anesthetic vapor has been achieved.[2] These measurements also have important patient safety implications. Anesthetic gas measurement detects inadvertent filling of a vaporizer with the wrong anesthetic agent and unintentional excessively high or low vaporizer settings. Monitoring inhaled anesthetic thresholds (with alarms activated) has also been demonstrated to reduce the incidence of awareness with recall after general anesthesia.[3]

Calibration and Preparation Before Use

Gas monitors should be calibrated regularly according to the manufacturer's specifications to ensure accuracy. Calibration can be performed using a calibration canister that contains a precise, set mixture of gases. Some gas monitoring technologies require warm-up time before they can accurately display gas concentrations. The length of warm-up time necessary varies depending on the technology used.

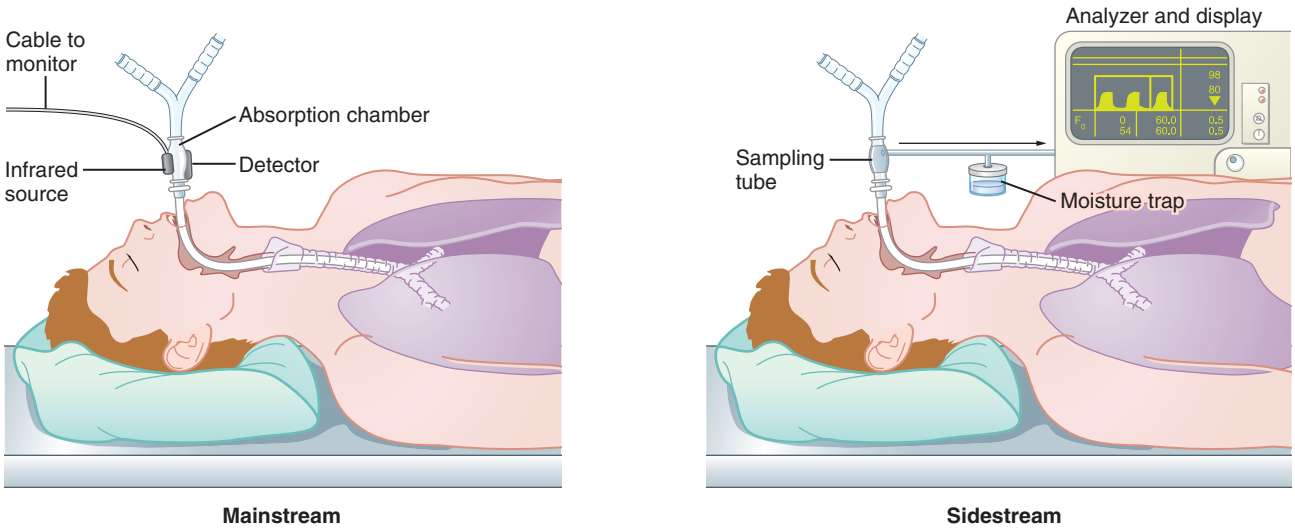
Monitoring Methods

Gas monitoring is done using one of two methods (Fig. P2.1): either diverting (i.e., **sidestream**) or nondiverting (i.e., **mainstream**).

Sidestream

Most anesthesia gas monitoring techniques use the sidestream technique to sample gas. Sidestream measurement is also commonly used with a nasal cannula to measure CO_2. A sidestream monitor uses a pump to sample gas from the breathing circuit and draw the sample into the sensor within the monitor. The length of tubing through which the sample is drawn affects the delay in the gas measurements. Because sidestream monitoring is delayed relative to flow measurements, gas monitoring using the sidestream method allows only measurement of gas concentration and not the flow rate of the gases. One advantage of sidestream monitors is that they can measure both CO_2 and anesthetic agent concentrations.

Certain compounds commonly found in breathing circuits can artifactually interfere with gas measurements. For example, water has a wide infrared (IR) absorption band and can affect the accuracy of gas monitoring. For this reason, a water trap is typically used in sidestream monitors to prevent excessive humidity in the optical measurement chamber. Similarly, the aerosol propellants in bronchodilator inhalers have overlapping absorption spectra for



• **Fig. P2.1** Mainstream gas monitors *(left)* measure gas concentrations directly in the breathing circuit. Sidestream gas monitors *(right)* use a pump that samples the gas from the main circuit and draws the sample into the sensor in the monitor.

TABLE P2.1 Gas Measurement Technologies and Their Capabilities

	Oxygen	Nitrogen	Carbon Dioxide	Volatile Anesthetics
Infrared absorption			Yes	Yes
Electrochemical oxygen analysis	Yes			
Paramagnetic oxygen analysis	Yes			
Mass spectrometry	Yes	Yes	Yes	Yes
Raman scatter analysis	Yes	Yes	Yes	Yes

carbon dioxide and certain inhaled anesthetics and can thus be misinterpreted by these monitors.[4] For example, use of an albuterol inhaler during anesthesia can result in a transient halothane reading on the gas monitor.

Standard sidestream monitors typically sample gas at 200 mL/min. Microstream monitors sample gas at 60 mL/min, allowing sidestream monitoring during very small tidal volumes (e.g., neonatal ventilation). Some monitors, especially those that are integrated with anesthesia machines, return the sampled gas back into the breathing circuit.

Mainstream

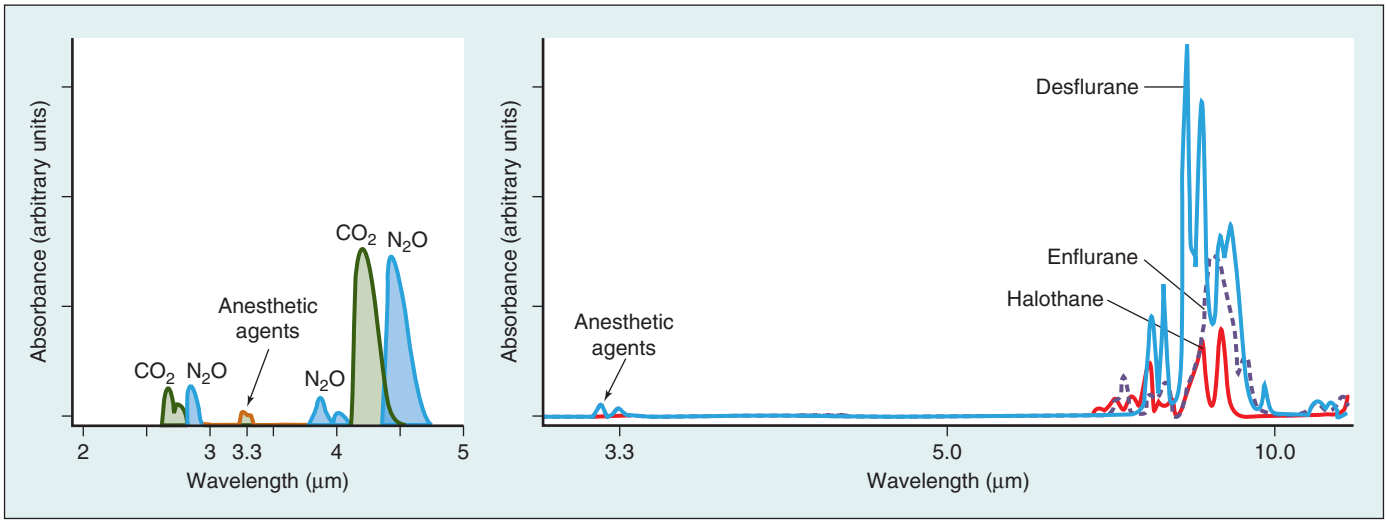
Mainstream gas monitors measure gas concentrations directly in the breathing circuit, typically close to the patient (e.g., between the endotracheal tube and the Y piece). Most mainstream monitors measure only CO_2. Mainstream monitoring coupled with flow measurements allows monitoring of volumetric excretion of CO_2. Placing a mainstream adapter in the breathing circuit increases dead space and can become problematic when delivering small tidal volume.[5]

Technologies

Several technologies exist for measuring gas concentrations. Table P2.1 contrasts the different gas measurement technologies in terms of the gases that they can measure.

Infrared Absorption

Infrared absorption is the most common technology in use today. It is based on the **Lambert-Beer Law**, which explains that when light passes through a gas, absorption increases with the optical path length through the gas, the gas concentration, and an extinction coefficient (which is specific to the gas and the light's wavelength). The gas concentration is measured by determining the amount of IR light that is absorbed (Fig. P2.2) and comparing that to a reference measurement. Each gas has a specific absorption spectrum (e.g., the amount absorbed over a spectrum of wavelengths). These spectra are the basis for the measurement techniques. The approach assumes that only a limited number of compounds will be present in the measured gas (i.e., too many compounds interfere with the reliability of the measurements because of overlapping absorption spectra).

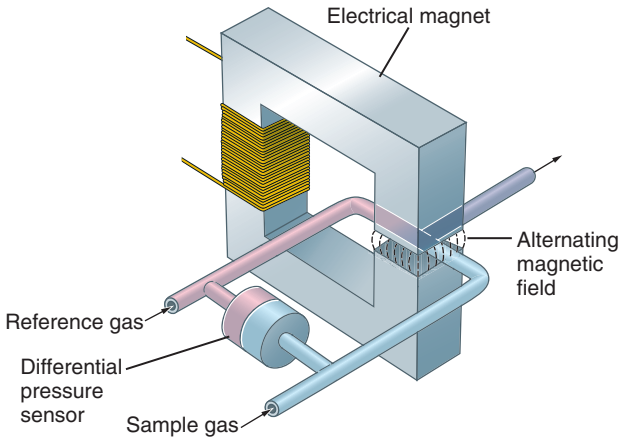


• **Fig. P2.2** Absorption spectra for gases commonly found when providing anesthesia care. *Left:* Carbon dioxide (CO_2) and nitrous oxide (N_2O) have pronounced absorption characteristics for light of smaller wavelengths. *Right:* Volatile anesthetics show some absorption for light around a wavelength of 3.3 micrometers (μm) but show much stronger absorption spectra for light of wavelengths between 5 μm and 10 μm. (Modified from Eisenkraft JB, Reich D. Respiratory gas monitoring. In: Reich D, ed. *Monitoring in Anesthesia and Perioperative Care*. Cambridge: Cambridge University Press; 2011; and modified from Levin PD, Levin D, Avidan A. Medical aerosol propellant interference with infrared anaesthetic gas monitors. *Br J Anaesth*. 2004;92(6):865–869.)

IR absorption is useful for determining concentrations of CO_2 and volatile anesthetics whose molecules have dipolar characteristics and can be excited into vibrations by light of certain wavelengths, thereby absorbing some of the light's energy. However, IR absorption cannot be used to measure concentrations of nondipolar molecules such as nitrogen and oxygen. Water molecules' strong dipoles absorb IR light so well that it can interfere with the measurement of anesthetic gases or CO_2. Recent technological advances have enabled the development of a small, lightweight IR mainstream analyzer that is capable of measuring CO_2, N_2O, isoflurane, sevoflurane, and desflurane.[6]

Paramagnetic Oxygen Sensor

Oxygen is a paramagnetic gas. When introduced into a magnetic field, oxygen positions itself in the strongest part of the field. A gas sample containing oxygen in a switched magnetic field generates a pressure signal that is proportional to the partial pressure of oxygen. Adding a reference gas increases the accuracy of the oxygen analysis (Fig. P2.3). The typical gas monitoring setup in modern anesthesia machines includes sidestream IR analysis of CO_2 and anesthetic agents along with paramagnetic analysis of oxygen.



• **Fig. P2.3** A sample containing oxygen in a switched magnetic field generates a pressure signal that is proportional to the partial pressure of oxygen.

Electrochemical Oxygen Sensor

Electrochemical sensors are made up of a hydrophobic membrane and two electrodes, anode and cathode, surrounded by an electrolyte solution. Oxygen passes through the membrane and electrolyte solution and is reduced at the cathode. Electrons for the reduction are supplied by the anode, which is oxidized in the process. The electrons travel through an external circuit from anode to cathode. This current is proportional to the concentration of oxygen. The response time of most of these sensors is slow and cannot be used to determine end-tidal concentrations. They are primarily placed in the inspiratory limb of anesthesia machines for monitoring of inspiratory oxygen concentration (FiO_2). Because the anode in these *galvanic cells* is oxidized, they have a limited lifespan, often measured in % oxygen-hours (% oxygen concentration times the number of hours the sensor is exposed to that concentration; a sensor specified with a lifetime of 500,000 % oxygen-hours should last 1000 hours exposed to 100% oxygen or 2000 hours exposed to 50% oxygen). Replacing these oxygen sensors is an important component of the proper maintenance of anesthesia workstations.

Mass Spectrometry

Mass spectrometry is no longer routinely used in anesthesia gas monitoring but is of significant historical importance. It is composed of gas sample tubing, a sample pump, vacuum pump, an ion source, and a mass spectrometry analyzer. Accelerated electrons are used to ionize the molecules in the sample gas. These ions are then separated in accordance to their mass-charge ratio, (e.g., by deflecting the moving ions in an electrical or magnetic field). The ionized molecules hit the detector at different places depending on their mass-charge ratio, creating a "spectrum." The spectrum is characteristic for different molecules and is used to determine the composition of the gas sample.

Mass spectrometry technology is expensive and cumbersome. Because of the considerable expense, only one mass spectrometry machine was typically used for numerous operating rooms. This meant that the sampled gas had to travel some distance through the sampling tubing to finally arrive at the central mass spectrometry machine for gas measurement. In addition, the machine was "time shared" with all the connected operating rooms. The resulting measurement delay was problematic for the dynamic needs of anesthesia practice. The substantial expense was another important drawback. Because of these suboptimal features, IR techniques gradually replaced mass spectrometry as IR technology improved.

Raman Scatter Analysis

Raman scatter analysis is another technology that is of some historical significance but is no longer commonly used in modern operating rooms. When the gas sample enters the analysis chamber, it is exposed to monochromatic light generated by an argon laser. The light interacts with the gas molecules, producing light at new wavelengths, a phenomenon known as Raman scattering. The wavelength shift and amount of scattering can be used to determine the gas composition of the gas sample, because specific compounds have characteristic Raman scattering behavior. A key clinical advantage of Raman scattering analysis is that it is the only gas analysis approach besides mass spectrometry that is capable of detecting nitrogen, which can be important in the diagnosis of air embolism. The inability to detect nitrogen is a key disadvantage of the IR spectroscopy method.

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4

Drug Metabolism and Pharmacogenetics

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CHAPTER OUTLINE

Evolutionary Perspective

Pharmacogenetics, Pharmacogenomics and Variability in Drug Responses

Pharmacokinetic Considerations
- Classification of Drug Metabolism Reactions
  - *Phase I Metabolism*
  - *Phase II Metabolism*
- Phase I Enzymes
  - *Cytochrome P450*
  - *Flavin-Containing Monooxidases*
  - *Amine Oxidases, Including Monoamine Oxidase Esterases, Including Butyrylcholinesterase (Pseudocholinesterase)*
- Phase II Enzymes
- Sites of Drug Metabolism
  - *Liver*
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Pharmacogenomics and Drugs Commonly Used in Anesthesia
- Neuromuscular Blockers
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  - *Increased Butyrylcholinesterase Activity*
- Opioids
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  - *Pharmacodynamic Alterations*
- Intravenous Anesthetics
  - *Pharmacokinetic Alterations*
  - *Pharmacodynamic Alterations*
- Inhalational Anesthetics
  - *Pharmacokinetic Alterations*
  - *Pharmacodynamic Alterations*
- Serotonin Receptor Antagonists

Emerging Developments

Evolutionary Perspective

The biotransformation of foreign substances is based on ancient evolutionary defense mechanisms. Hundreds of millions of years ago, animals evolved to terrestrial life and began ingesting new varieties of plant life with nutrient and toxic potential. These early organisms had to detoxify and eliminate any novel toxic compounds or perish. Enzyme systems that originally existed to maintain homeostatic functions gradually adapted to process exogenous toxins.[1] The genetic heterogeneity of these metabolic enzymes exponentially increased as animals survived exposures to evermore diverse xenobiotics. The genetics of human metabolic enzymes today reflect both the foundational homeostatic role they played and the diversity of ancient evolutionary pathways. This has resulted in a wide range of interindividual variation in phenotypic responses to both xenobiotics and endogenous organic compounds. In this age of targeted drug development and precision medicine, the study of pharmacokinetics, pharmacodynamics, and pharmacogenomics has become increasingly interconnected to better understand the variation in drug effects (Tables 4.1 and 4.2).

Pharmacogenetics, Pharmacogenomics, and Variability in Drug Responses

Pharmacogenetics arguably began with Pythagoras, the sixth-century BCE mathematician who reported an association between the ingestion of fava beans and hemolytic anemia in certain individuals. The field grew rapidly in the 1950s, with the first reports of genetically determined responses to succinylcholine (scoline apnea) in 1956 and the birth of the term *pharmacogenetics* in 1959, coined by the German geneticist Friedrich Vogel. Subsequent investigations focused on identifying single-gene associations with variable drug responses: an early focus of study was the apparent bimodal half-life of isoniazid, an antituberculosis treatment, resulting from polymorphisms in N-acetyltransferase.

With the sequencing of nearly the entirety of the human genome in 2003, deeper analysis of the relationships between multiple genes and drug responses became possible (Fig. 4.1). This has led to the evolution of *pharmacogenomics,* the study of the relationships between the entire genome, drug responses and human diseases (see Table 4.1). Although conditions with single-gene associations still exist (Fig. 4.2), it is increasingly evident that many unexplained variations in drug efficacy result from sources affecting multiple steps in the gene expression and biotransformation pathway (Tables 4.2 and 4.3; Fig. 4.3 and 4.4).

Pharmacokinetic Considerations

Classification of Drug Metabolism Reactions

Pioneering studies in drug metabolism in the 1800s focused on identifying altered forms of ingested substances that were excreted in the urine. It was not until the 1950s that the enzyme systems responsible for these chemical reactions were identified. In 1959, R.T. Williams, a Welsh pharmacologist, first proposed

Abstract

Biotransformation is an ancient and vital process that governs a drug's pharmacokinetics and pharmacodynamics. The enzymes and transporters that control each step in the metabolic pathway are highly polymorphic. This can cause significant variability in drug effects between individuals, or when certain drugs are given in combination. Specific pharmacogenomics considerations apply to the majority of medications that are in clinical use today, including those particularly relevant to the practice of anesthesiology such as neuromuscular blockers, opioids, anesthetic agents and anti-emetics. Future developments in the fields of precision medicine, systems biology and bioinformatics can produce new models for characterizing complex genome-phenome associations, and improve understanding of interindividual variability in drug responses.

Keywords

drug metabolism
drug transporters
pharmacogenetics
pharmacogenomics
systems pharmacology
cytochrome P450
phase I metabolism
phase II metabolism

TABLE 4.1 Key Definitions

Biotransformation: Chemical alteration of a foreign molecule by the body
Drug metabolism: The alteration of a drug by the body to allow for excretion
Xenobiotics: A substance that is foreign to the body
Pharmacokinetics: Study of the disposition of a drug within the body
Pharmacodynamics: Study of the effects of the drug on the body
Pharmacogenetics: Study of genetic (often single-gene) causes of variability in drug responses
Pharmacogenomics: Genome-wide study of the determinants of variability in drug responses

TABLE 4.2 Outcomes of Drug Metabolism

Cessation of active drug effect
Conversion of prodrug to active form
Enhance suitability for elimination
Conversion to toxic form

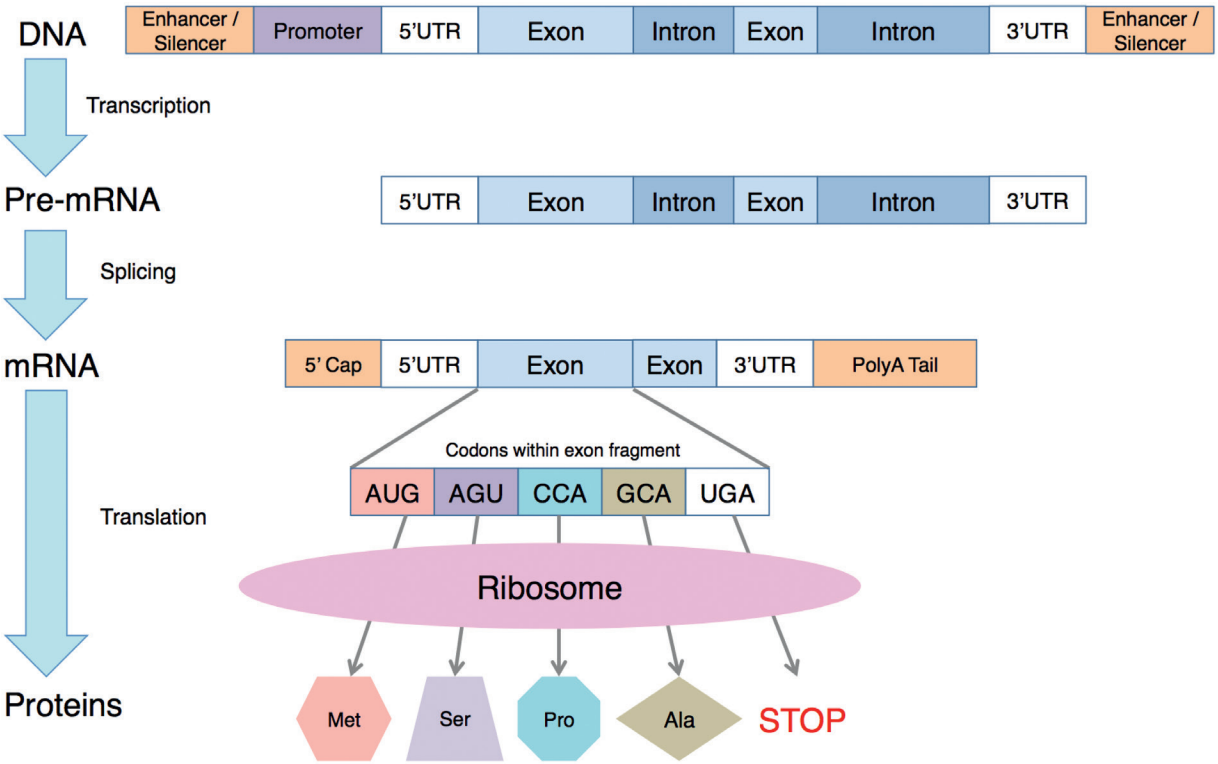
organizing these chemical processes into two phases of drug metabolism (Table 4.4).

Phase I Metabolism

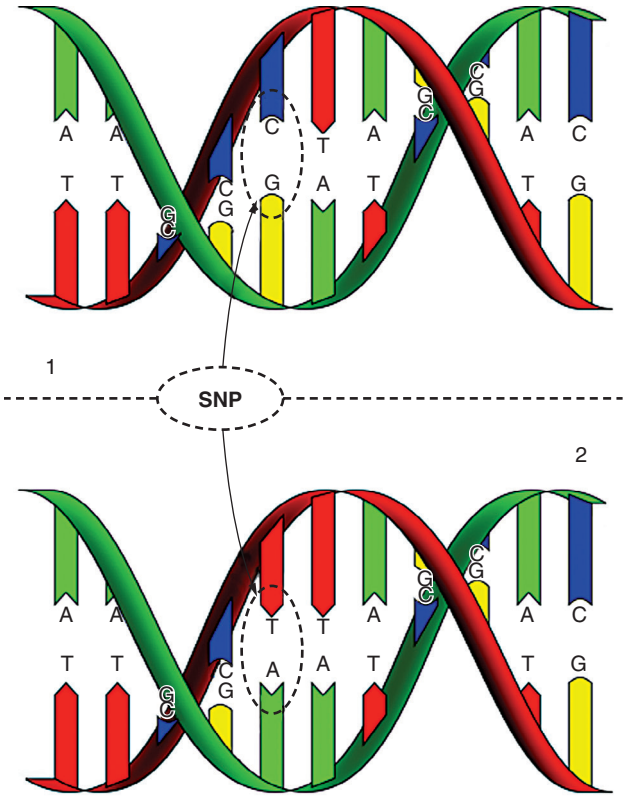
Phase I metabolism broadly describes enzymatic reactions that alter biologic activity via the addition or alteration of a functional molecular group. For lipophilic compounds, this usually introduces a polar functional group that forms a substrate for subsequent metabolic handling. These alterations can inactivate or enhance the biologic effects of the parent drug, or they can introduce new activity such as in the case of prodrugs and certain carcinogenic compounds.

Phase II Metabolism

Phase II metabolism involves the addition of a cofactor to a compound. This typically results in a molecule that is highly water-soluble and amenable to excretion within the urinary or biliary tract. These enzymes usually require specific functional groups on their substrates for conjugation to occur: products of phase I metabolism are often good candidates for subsequent phase II reactions. However, it is not necessary for drugs to undergo both phase I and II metabolism, such as in the case of morphine, oxymorphone, and hydromorphone, which are readily glucuronidated by uridine diphosphate (UDP)-glucuronyltransferase (Fig. 4.5).



• **Fig. 4.1** Schematic of gene, messenger ribonucleic acid *(mRNA)* and codon structures. Information within a gene must be transcribed into mRNA, which interacts with ribosomes to form proteins. During DNA transcription, regulatory regions within the DNA strand determine the genes to be transcribed and the amount of mRNA to produce. This initial pre-mRNA contains information from both exons and introns: once the introns are spliced out, the final mRNA is transported into the cytosol. Ribosomes on the endoplasmic reticulum then translate this mRNA into amino acids. Triplets of bases within mRNA, called *codons*, encode a single amino acid. Codons can also have regulatory functions in protein synthesis. There are 64 possible codon combinations and 20 amino acids; a single amino acid can have one or more corresponding codons. *UTR,* Untranslated region.



• **Fig. 4.2** Single-Nucleotide Polymorphisms (SNPs). An SNP is a form of genetic variation in which one base pair is substituted for another. In diploid organisms, this results in more than two genetic alleles for each locus, which, if expressed, can lead to the formation of a protein with altered function.

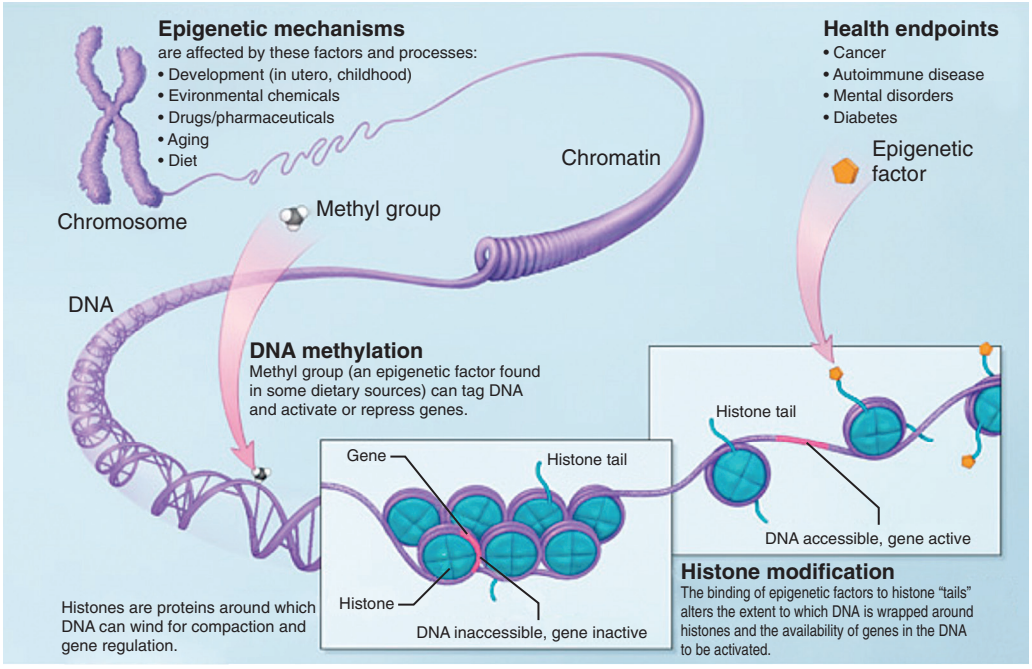
Phase I Enzymes

Cytochrome P450

A group of major biotransformational enzymes in many organisms, including humans, is the cytochrome P450 (CYP) system. The CYPs are a superfamily of heme-containing proteins that contain several hundred distinct forms, located in cellular membranes in the endoplasmic reticulum and the inner mitochondrial membrane. Genetic studies of CYP DNA across a variety of organisms suggest that all currently known CYP originated from a common ancestor over two billion years ago, around the time that single-celled life forms evolved into complex, multi-organellar eukaryotes.[1] This long history has led to a vast array of genetic subfamilies within the CYP system.

In humans, approximately 50 to 100 CYP enzymes are encoded by 57 functional genes and 58 pseudogenes spread across multiple autosomal chromosomes.[8] These gene sequences are the basis for the classification of CYP families and subfamilies (Tables 4.5 and 4.6). This diversity is also seen in the vast array of CYP variants, which together with age, gender, and disease, is a major contributor to the variability in drug responses between individuals.

CYPs are highly versatile enzymes capable of catalyzing numerous reactions, including reduction and hydrolytic reactions. This, combined with their affinity for many different substrates, makes CYPs the key biotransformational enzymes for a vast array of both xenobiotics and endogenous signaling molecules. More than 95% of oxidative metabolic processes in the body are performed by CYPs.[9] In humans, a core cluster of enzymes in the CYP1, 2, and 3 families is responsible for the biotransformation of about 75% of all drugs currently used in clinical practice[8] (see Figs. 4.4 and 4.5). CYPs are the primary metabolic enzyme for numerous drug groups commonly used in anesthesia, including volatile anesthetics,



• **Fig. 4.3** Epigenetic Modifications. Epigenomics is the study of inherited chromosomal changes that resulted in changes in phenotype without alteration in DNA sequences. The most common events are in form of DNA methylation and histone modification.

TABLE 4.3 A Brief Review of Genetics

Proteins are pivotal in sustaining life: enzymes, receptors, second-messenger systems, and cellular structural components are all proteins. The blueprint to individual protein structures is encoded by a specific sequence of DNA. DNA is composed of a deoxyribose backbone containing complementary base pairs, arranged in a double helical, ladder-like structure with 5′ to 3′ directionality. These base pairs are made up of adenine-thymine and cytosine-guanine. The DNA strand is coiled into chromosomes, which are found in the cell nuclei.

Within the DNA strand, there are sequences that code for proteins and those that do not. DNA sequences that encode proteins are termed ***genes***. Noncoding sequences can have structural or regulatory roles in gene expression or no function at all. A gene is organized into regulatory regions bracketing the open reading frame, consisting of exons and introns with 5′ to 3′ directionality (see Fig. 4.1).

The human genome has approximately 20,000 protein-coding genes, accounting for less than 2% of the human genome.[2] Variations in pre-mRNA splicing, with selective inclusion of exons, result in many alternate mRNA sequences potentially coded from a single gene. This allows for a great many more proteins than the number of protein-coding genes currently identified.

Mutation vs. Polymorphism vs. Variant

The human genome has been highly preserved through the ages, with only 0.5% discordance between two unrelated individuals.[3] In its simplest definition, a ***genetic mutation*** is any variation in the DNA base sequence within a gene. By convention, mutations are rare (<1% of a population), allowing for the existence of a putative normal genotype. ***Polymorphisms*** are also mutations; however, they are much more common (>1% of a population) and can be considered "normal variant" forms resulting from natural selection. The use of the term ***genetic variant*** is considered neutral. Variant forms of genes are called ***alleles***, with the common allele termed ***wild-type*** and lesser forms termed ***minor alleles***. Humans are diploid organisms (with two sets of paired chromosomes) and therefore carry two alleles of the same gene. Allelic variation in a single locus is responsible for the patterns described by simple Mendelian inheritance, but the addition of polygenic traits, polyallelic loci, and non-Mendelian patterns of inheritance add substantial complexity to the ultimate phenotype.

The most common type of allelic variation is the ***single-nucleotide polymorphism*** (SNP), accounting for >70% of variations.[4] This involves the variation in a single nucleotide base pair within the DNA strand (see Fig. 4.2). Sequence variants, including SNPs, are classified according to the affected domain (DNA, RNA, protein), their location in the sequence, and the alteration.[5] There is currently no consensus nomenclature system established, which leads to potential confusion as the same variant can be described in multiple ways.

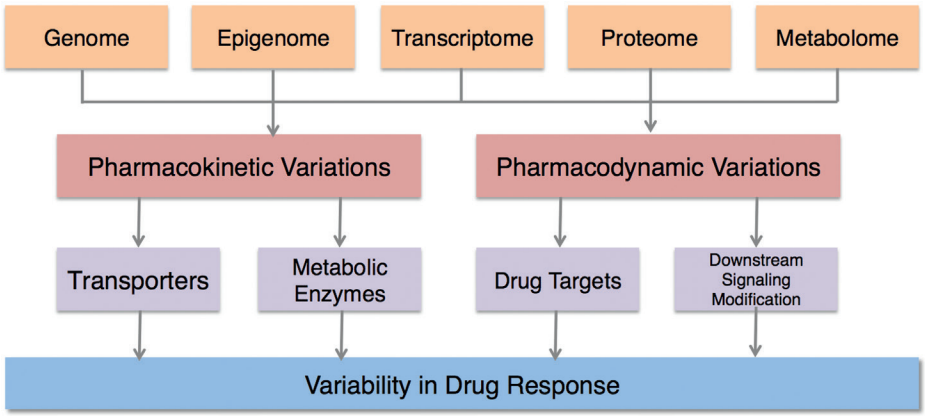
SNPs can occur in coding and noncoding regions; coding region SNPs can be synonymous (not affecting the protein sequence) or nonsynonymous (affecting protein sequence). Nonsynonymous SNPs can be either missense or nonsense types; missense SNPs result in the substitution with an alternate amino acid, whereas nonsense SNPs usually result in a prematurely truncated, nonfunctional protein. As of 2017, more than 10 million SNPs have been identified,[6] which corresponds to an average of one SNP for every 300 base pairs in the human genome.

Genotype vs. Phenotype vs. Clinical Effect

Most genetic variants do not result in any appreciable change in phenotype. The large proportion of noncoding sequences within the genome and the redundancy of translation systems reduce the possibility of clinically apparent sequelae. Conversely, heritable phenotypic differences can result between two populations without apparent alterations in their respective DNA sequences. This latter phenomenon is often the result of **epigenetic modifications**—that is, inherited variants in the chromosome rather than the DNA sequence itself. Epigenetic mutations result from events such as DNA methylation (which alters DNA transcription) and histone modification (which affects the packaging of DNA into chromatin) (see Fig. 4.3).

Integrative "Omics": Epigenomes, Transcriptomes, Proteomes, Metabolomes

As genetic assaying and sequencing technology continues to advance, additional fields of study have opened to detail the steps along the path of genetic expression. **Epigenomics** is the study of heritable chromosomal alterations resulting in phenotypic changes, while **transcriptomics** investigates the total mRNA transcripts generated by a cell or organism under defined conditions. A **proteome** refers to the entire collection of proteins expressed by a particular cell or organism, which may greatly outnumber the genome; **proteomics** is the study of the proteins produced by the cell under different physiologic states, and the factors that determine the translation and post-translational modifications. Finally, **metabolomics** focuses on the dynamic array of metabolites formed by the enzymes coded within an organism's genome. The integration of these fields into **systems pharmacology and quantitative biology** allows for large-scale modeling of complex physiologic or disease states, which has enormous potential to inform the study of drug interactions, and drug design, in the decades to come[7] (see Fig. 4.3).



• **Fig. 4.4** Systems Pharmacology and Variable Drug Responses. Systems pharmacology integrates knowledge from multiple fields of quantitative biology and bioinformatics to fully understand the factors contributing to interindividual variations in drug response.

TABLE 4.4 The Phases of Drug Metabolism

	Broad Function	Specific Reactions	Typical Enzymes
Phase I	Alteration of a functional group (addition, or removal) Alters biologic activity (decrease, or increase)	Oxidation	Oxidases Dehydrogenases
		Reduction	Reductases CYP
		Hydrolysis	Esterases Phosphatases Hydrolases Lipases
Phase II	Alters water solubility for excretion	Glucuronidation	UDP-glucuronyltransferase
		Sulfonation	Sulfotransferase
		Acetylation	N-Acetyltransferase
		Glutathione conjugation	Glutathione S-transferase
		Methylation	Methyltransferase

CYP, Cytochrome 450; *UDP,* uridine diphosphate

TABLE 4.5 Cytochrome P450: Essential Facts

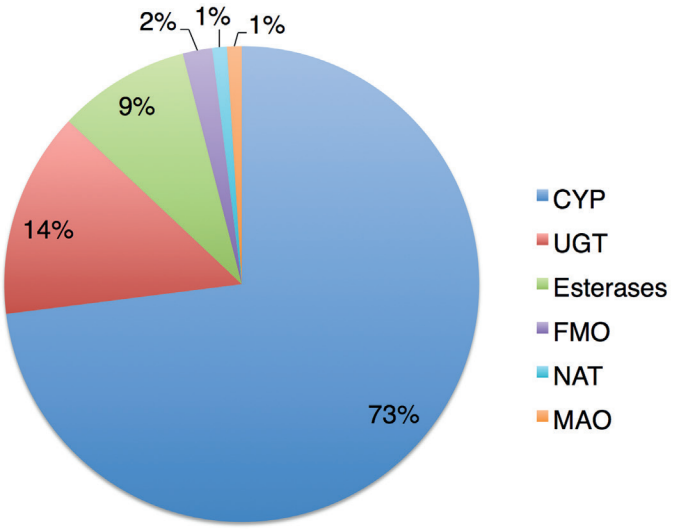
Cytochrome P450

- First discovered in the 1960s.
- Named for their appearance; when reduced and bound to carbon monoxide has a pinkish hue, with peak ultraviolet light absorption at 450 nm.
- Humans have ~50–100 CYP enzymes across 18 families and 44 subfamilies; many of them have homeostatic or unknown functions.
- Isoform families are designated by letter, subfamilies by number.

Homeostatic Roles of Cytochrome P450

1. Biosynthesis of lipophilic hormones and signaling molecules, including:
   - Steroid hormone
   - Prostaglandins, Thromboxane, Eicosanoids
   - Bile and fatty acids
   - Retinoids
   - Vitamin D derivatives
   - Porphyrins
2. Defensive detoxification against reactive intermediates and xenobiotic toxins
3. Potential unknown endogenous roles
   - 13 CYP families with unknown "orphan" substrates

CYP, Cytochrome 450.



• **Fig. 4.5** Contributions of Different Enzymes to Drug Metabolism. Cytochrome P450 enzymes are responsible for the vast majority of biotransformation reactions for drugs currently used today. This is closely followed by the uridyl-glucuronyltransferases and esterases. The flavin-containing oxygenases and monoamine oxidases *(MAOs)* make up a comparatively small percentage of overall drug metabolism, although limited research data suggest that their contribution is likely underestimated. *CYP,* Cytochrome P450; *FMO,* flavin-containing monooxidase; *NAT,* N-acetyltransferase; *UGT,* uridine phosphate-glucuronosyltransferase. (Data from Guengerich FP. Human cytochrome P450 enzymes. In: Ortiz de Montellano PR, ed. *Cytochrome P450*, 4th ed., Vol. II. Cham, Switzerland: Springer International Publishing; 2015: 523–785.)

intravenous hypnotics, opioid analgesics, and local anesthetic agents (see Table 4.6 and Fig. 4.6).

Inducers and inhibitors influence the function of many CYPs. CYP inhibition is possible in almost all isoforms and can be reversible, irreversible, or partially irreversible. Conversely, only a select group of CYPs are inducible. Reversible inhibition is typically a result of competition at the substrate-binding active site. Other drugs can affect downstream oxygen-transferring functions of the CYP, which causes fully or partially irreversible enzyme inhibition. In contrast, CYP induction occurs in a time-dependent manner, usually as a result of a stimulus to increasing gene transcription and enzyme production, but the exact mechanism is unknown. This is believed to be an evolutionary defensive mechanism to toxin exposure by increasing the capacity to degrade the offending substance. In the case of toxins and certain drugs, this leads to a diminution of effect. For prodrugs and substances with active metabolites, however, enzyme induction can confer the risk of exaggerated drug effects and potential harm.

Flavin-Containing Monooxidases

Flavin-containing monooxidases (FMOs) are a second major family of enzymes important in oxidative drug metabolism. Long-overlooked because of technologic constraints limiting their study, the role of FMOs in drug metabolism and homeostasis is increasingly being recognized, and is now shown to be responsible for approximately 2.5% of all metabolic reactions in the human body and about 6% of phase I metabolic reactions.[10]

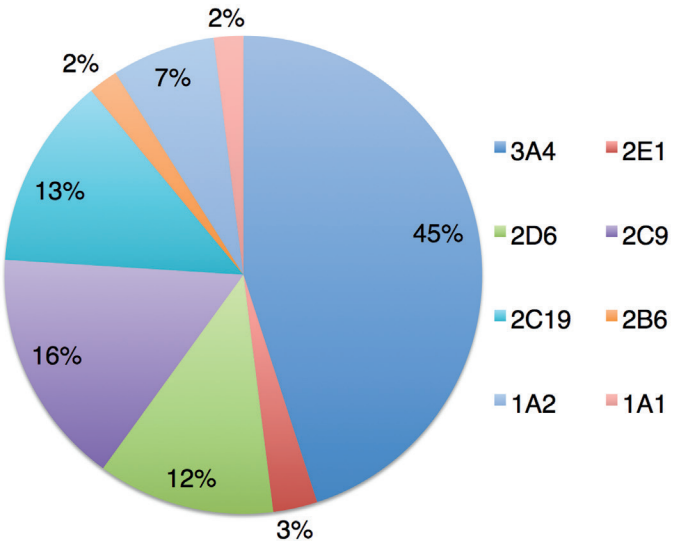
FMOs contain a flavin adenine dinucleotide prosthetic group, which catalyzes oxidative reactions with reduced nicotinamide adenine dinucleotide phosphate as a cofactor. FMOs are found in all eukaryotes and appear to have followed an evolutionary development similar to CYPs[11]; however, in contrast to the vast genetic variety of CYPs, the six known human FMOs are encoded by six genes and six pseudogenes located on chromosome 1 (Table 4.7). Of the FMO subtypes, *FMO3* has both the highest expression in the adult liver and the highest functional activity, and as a result is a major focus for pharmaceutical development.

FMOs are distinct from CYPs in that they have a narrow specificity but high catalytic activity (Table 4.8). Whereas CYPs

TABLE 4.6 Cytochrome P450 Subfamilies, Substrates, Inhibitors, and Inducers

Family	Subfamily	Major Substrates Relevant to Anesthetic Practice	Inhibitor	Inducer
CYP1	1A2	Local anesthetics Acetaminophen Cyclobenzaprine Ondansetron Haloperidol Olanzapine Warfarin	Ciprofloxacin Fluvoxamine	Cigarette smoke Omeprazole Phenytoin
CYP2	2A6	Halothane Methoxyflurane Dexmedetomidine Nicotine		
	2B6	Alfentanil Methadone Propofol Sertraline	Clopidogrel	Rifampicin Carbamazepine
	2C9	Ketamine Propofol Diclofenac Ibuprofen Parecoxib Celecoxib	Amiodarone	Aprepitant Carbamazepine Barbiturates Rifampicin
	2C19	Diazepam Barbiturates Clopidogrel Warfarin Proton pump inhibitors	Fluconazole Fluvoxamine Fluoxetine Omeprazole	Barbiturates Rifampicin
	2D6	Codeine Oxycodone Tramadol Methadone Duloxetine β-Blockers Metoclopramide Ondansetron	Bupropion Duloxetine Fluoxetine Paroxetine Sertraline Quinidine Amiodarone Labetalol Celecoxib	
	2E1	Halothane Enflurane Sevoflurane Isoflurane Methoxyflurane Ethanol Caffeine Acetaminophen		Ethanol Isoniazid
CYP3	3A4	Midazolam Alprazolam Diazepam Temazepam Lidocaine Methadone Fentanyl Alfentanil Sufentanil Amiodarone Nifedipine Verapamil	Grapefruit juice Aprepitant Ranitidine Clarithromycin Erythromycin Ketoconazole Verapamil Diltiazem	Barbiturates Phenytoin Carbamazepine Rifampicin Dexamethasone St John's wort

Data from Guengerich FP. Human cytochrome P450 enzymes. In: Ortiz de Montellano PR, ed. *Cytochrome P450,* 4th ed., Vol. II. Cham, Switzerland: Springer International Publishing; 2015:523–785; and Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol. Ther.* 2013;138:103–141.



• **Fig. 4.6** Contribution of Cytochrome P450 (CYP) Isoforms to Drug Metabolism. The CYP 3A family is responsible for the oxidative metabolism of almost half of the drugs currently in common use. The next CYP isoforms most involved in drug metabolism are 2C9, 2C19, and 2D6. While there are genetic variants associated with CYP 3A4 and 2C9, they are of insufficient frequency to contribute to any notable clinical effect. By contrast, polymorphisms in CYP 2D6 and 2C19 have significant clinical sequelae. (Data from Guengerich FP. Human cytochrome P450 enzymes. In: Ortiz de Montellano PR, ed. *Cytochrome P450*, 4th ed, Vol. II. Cham, Switzerland: Springer International Publishing; 2015: 523-785.)

TABLE 4.7 Flavin-Containing Monooxygenases

	Location	Known Substrates
FMO1	Fetal liver **Adult kidney**	Chlorpromazine Imipramine
FMO2	Adult lung **Adult kidney**	Non-functional
FMO3	**Adult liver** Adult lung	Methamphetamine Ranitidine Diphenhydramine Olanzapine
FMO4	**Adult liver** Adult kidney	Insufficient data
FMO5	**Adult liver** Adult intestine	Insufficient data

FMO, Flavin-containing monooxidase.
Bold type indicates the dominant enzyme location.
Data from Cruciani G, Valeri A, Goracci L, et al. Flavin monooxygenase metabolism: why medicinal chemists should matter. *J Med Chem.* 2014;57:6183–6196; Cashman JR, Zhang J. Human flavin-containing monooxygenases. *Ann Rev Pharmacol Toxicol.* 2006;46:65–100; and Krueger SK, Williams DE. Mammalian flavin-containing monooxygenases: structure/function, genetic polymorphisms and role in drug metabolism. *Pharmacol Ther.* 2005;106:357–387.

can bind readily to a broad variety of substrates, FMOs have a selective affinity for nucleophilic molecules (those containing a free pair of electrons, such as amines, sulfites, phoshites) but with approximately double the catalytic velocity of CYPs.[11] Another characteristic of FMOs is that they are resistant to induction or inhibition, making them less prone to drug interactions and an attractive target for drug design.

TABLE 4.8 Characteristics of Cytochrome P450 and Flavin-Containing Monooxygenases

Cytochrome P450	Flavin-Containing Monooxygenases
Catalyzes ~75% of all metabolic reactions	Catalyzes ~1%–2% of all metabolic reactions
Can catalyze broad range of substrates	Narrow substrate range
Substrate affinity varies between isoforms	High affinity for nucleophilic molecules (containing N, S, P, Se)
Neutralize molecules via electrophilic reactions	Neutralize molecules via nucleophilic addition
Lower catalytic rate	High catalytic rate
Highly inducible and inhibited	Resistant to inducers and inhibitors
50–100 CYP enzymes, encoded by 57 genes and 58 pseudogenes	6 FMO enzymes, encoded by 6 genes and 6 pseudogenes

CYP, Cytochrome 450; *FMO,* flavin-containing monooxygenase.

To date, FMOs have been identified as key metabolic enzymes for antidepressants, antipsychotics, and antihistamines. Although the primary role of FMOs continues to be defined, they are known to play a complementary role to CYPs.[12] In particular, FMO3 has been shown to work in tandem with CYP3A4,[10] performing the same reactions on similar substrates but with a higher reaction capacity and velocity. It has been speculated that FMOs may play a role in mitigating CYP3A4 drug interactions and interindividual variations in activity.[12]

Amine Oxidases, Including Monoamine Oxidase

Amine oxidases catalyze oxidative deamination reactions, producing ammonia and an aldehyde. These enzymes are critical to both homeostatic and xenobiotic metabolic pathways and are involved in the biotransformation of aminergic neurotransmitters (such as catecholamines, histamine, and serotonin) as well as toxins and carcinogens in foods and the environment.

The **monoamine oxidases (MAOs)** are well studied and have been targets for drug therapy for more than 60 years. MAOs are flavin-containing mitochondrial enzymes distributed throughout the body. In humans, two isoenzymes of MAO have been identified, encoded by two genes located on the X chromosome: *MAO-A* and *MAO-B.* Each isoenzyme can be distinguished by certain substrate specificities and anatomic distribution (Table 4.9), although MAO-A has the distinction of being the sole catecholamine metabolic enzyme in sympathetic neurons. In neural and other selective tissues, MAOs catalyze the first step in the degradation of catecholamines into their aldehyde intermediaries, which is further processed by catechol-*O*-methyltransferase.

The ubiquity of biogenic amines and their central role in neural and cardiovascular function make MAOs highly relevant to clinical anesthesia. The interactions between MAO inhibitors and drugs commonly used in anesthesia have been well described. Although genetic polymorphisms in MAO genes exist and are of great interest in the fields of neurology and psychiatry, to date none have been identified that specifically concern the handling of anesthetic agents.

TABLE 4.9 Monoamine Oxidases

	MAO-A	MAO-B
Location	CNS: sympathetic and catecholaminergic neurons Liver Pulmonary endothelium Gastrointestinal tract Placenta	CNS: glia, serotoninergic neurons Platelets
Specific Substrates	Serotonin Melatonin Epinephrine Norepinephrine	Dopamine Phenylethylamine Benzylamine
Substrates for both MAO-A and MAO-B	Dopamine Tyramine Tryptamine	

CNS, Central nervous system; *MAO,* monoamine oxidase.

Further details on the agents that alter the function of MAO, and their effects on biotransformation of catecholamines, can be found in Chapter 12).

Esterases, Including Butyrylcholinesterase (Pseudocholinesterase)

Esterases catalyze hydrolysis of specific molecules containing the R1-CO-O-R2 ester group, as well as amides, hydrazides, and carbamates. In human physiology, esterases are distributed in the liver, erythrocytes, plasma, and the gastrointestinal tract. Proteases are specialized esterases and are involved in the activation of proenzymes such as those secreted by the pancreas.

Cholinesterases are serine hydrolases with particular relevance to the practice of anesthesiology. Two types of cholinesterases have been identified, each encoded by a single gene: acetylcholinesterase (AChE) and butyrylcholinesterase (BChE, also known as plasma cholinesterase or pseudocholinesterase). AChE has a key physiologic role in regulating cholinergic transmission and is a target for drug therapy in autonomic, central nervous system, and neuromuscular disorders (see Chapters 13, 14, and 21).[13]

BChE has been of great interest to anesthesiologists since the first description of variable responses to succinylcholine in the 1950s. Widely expressed in the liver, lung, brain, heart and plasma, it is also involved in the metabolism of mivacurium, cocaine, chloroprocaine, and tetracaine. Although the BChE gene shares 54% of the same amino acids as AChE,[13] BChE appears to have a separate, albeit undefined, biologic role. Discussion of pseudocholinesterase deficiency continues later in this chapter (also see Chapter 21).

Phase II Enzymes

Transferases are the predominant enzyme type for phase II drug reactions. Functionally, transferases attach water-soluble sugars, amino acids, or salts to their substrates. This forms a metabolite that is more easily excreted by the kidneys or the biliary tract.

Phase II reactions are classified according to the endogenous conjugate being catalyzed by its specific transferase enzyme (see Table 4.4). In the adult, glucuronidation is the most common phase II process and is involved in the metabolism of approximately 40% to 70% of drugs in current clinical use.[14] In the fetus and neonate, glucuronidation activity is nearly absent and does not reach adult levels until 2 to 6 months of age.[15] This increases the risk of toxicity of compounds dependent on this pathway for metabolism, such as morphine and chloramphenicol. Sulfonation is well developed in the newborn and is the dominant conjugation pathway until UDP-glucuronyltransferase activity matures; this is demonstrated by the metabolism of acetaminophen, which is metabolized into sulfate conjugates in the first months of life, after which glucuronides become the major metabolite.

Drug interactions involving the transferases are rare, but they are subject to genetic and environmental variations that are of clinical relevance. The **UDP-glucuronyltransferases** (UGTs) are involved in the metabolism of many drugs as well as endogenous substances, such as bilirubin, steroid hormones, bile acids, and fat-soluble vitamins. UGTs are membrane enzymes that are most concentrated in the liver and gastrointestinal tract but are also active in kidney, brain, pancreas, and placenta. Four UGT enzyme families have been identified in humans, with UGT1 and UGT2 the most heavily involved in drug metabolism. UGT 2B7 is the main isoform responsible for opioid glucuronidation, and although genetic polymorphisms have been identified for this enzyme, the large overlap in substrate specificity between the UGT enzymes has minimized any substantive phenotypic manifestation of these variants.[14]

Arylamine N-acetyltransferases (NATs) are cytosolic enzymes found in many tissues throughout the body and are associated with the metabolism of hydralazine, caffeine, procainamide, sulfonamides, and isoniazid. In humans, this enzyme family is encoded by the *NAT1* and *NAT2* genes, which are highly polymorphic. *NAT2* gene polymorphisms have a higher degree of functional variation than *NAT1* and multiple mutations result in three distinct phenotypes: **fast (or wild-type), intermediate, and slow acetylators**[16] (Table 4.10). "Slow acetylators" carry at least one reduced-function allele and are much more susceptible to drug toxicity. For example, slow acetylators who are administered hydralazine experience not only a greater degree of hypotension and tachycardia, but they are also at increased risk of hydralazine-induced lupus erythematosus. The current understanding is that in those with the slow-acetylator phenotype, the parent drug accumulates and is diverted to oxidative metabolic pathways. This produces reactive intermediaries, haptens, and carcinogens at levels that would be much lower in the intermediate- and fast-acetylator counterparts. This mechanism has been attributed to not only the development of drug-induced autoimmune disorders such as those seen with hydralazine and sulfonamides, but also the pathogenesis of bladder, breast, and colorectal cancer with chronic exposure to environmental carcinogens[17] (Table 4.10).

The **methyltransferases** include thiopurine S-methyltransferase (TPMT) and **catechol *O*-methyltransferase (COMT)**. COMT is a magnesium-dependent enzyme that exists in soluble and membrane-bound forms found throughout the body. The soluble form is highly concentrated in the liver, while the membrane-bound form is predominantly found in the central nervous system and the chromaffin cells of the adrenal glands. It is one of the major metabolic pathways of catecholamines and related compounds such as levodopa and α-methyldopa. COMT is also a target for drug therapy: entacapone, a reversible inhibitor of COMT, is used in the treatment of Parkinson disease to increase the duration of action of levodopa (see Chapter 12).

TABLE 4.10 Variant N-Acetyltransferase Phenotypes

Phenotype	Genotype	Approximate Frequency	Clinical Effect Example
Fast (wild-type)	Two copies of the increased function allele	70% East Asians 70% Native Americans	Normal activity of hydralazine
Intermediate	One copy each of an increased-function and a reduced-function allele		Mild decrease in serum hydralazine levels, no recommendation for dose adjustment
Slow	Two copies of the reduced function allele	>80% Scandinavians >80% Egyptians 70% South Asians 40%–70% Western Europeans 40%–70% African Americans	Exaggerated drug effect of hydralazine Increased risk of hydralazine-induced lupus

Data from McDonagh EM, Boukouvala S, Aklillu E, et al. PharmGKB summary: very important pharmacogene information for N-acetyltransferase 2. *Pharmacogenet Genomics*. 2014;24:409–425; and Patin E, Barreiro LB, Sabeti PC, et al. Deciphering the ancient and complex evolutionary history of human arylamine N-acetyltransferase genes. *Am J Hum Genet*. 2006;78:423–436.

TABLE 4.11 Drug Transporters

Functionally, drug transporters mediate the uptake of drugs into cell, and the export of drugs and metabolites outside of cells. There are two major drug transporter superfamilies in humans: **ABC (ATP-binding cassette)** and **SLC (solute carrier)**, each containing hundreds of transporter proteins whose function as yet is not fully understood (see Table 4.12).

Phylogenetically, **the ABC superfamily** is among the oldest proteins associated with earth-bound life: member transporters are found across all current extant prokaryotic and eukaryotic life forms. They are especially important in oncologic pharmacogenomics as they determine the uptake and efficacy of chemotherapeutics. The **P-glycoprotein (P-gp) efflux transporter** is an ATP-dependent drug transport protein from the ABC transporter superfamily encoded by the *ABCB1* gene, located in close proximity to the genes for the cytochrome P450 (CYP) 3A enzymes. It is located in the apical membranes of many epithelial cell types, including those of the gastrointestinal tract and brain and cerebrospinal fluid capillary endothelium. It is theorized that the wild-type P-gp works synergistically with CYP 3A enzymes within the gastrointestinal tract as a defense mechanism against xenobiotics and other toxic compounds, preventing their entry. They also likely contribute to maintaining the integrity of the blood-brain barrier. This efflux transporter has a broad specificity and extrudes a wide variety of substrates from cells, including opioids, β-blockers, calcium channel blockers, dexamethasone, ondansetron, digoxin and tricyclic antidepressants, as well as endogenous compounds such as conjugated bilirubin.

The ***ABCB1* gene** is highly polymorphic, with more than 100 single-nucleotide polymorphisms currently identified in humans.[20] Patients with loss of function mutations in the ABCB1 gene can have increased clinical effects of P-gp substrates, and this finding is supported by several human studies. Similarly, many inducers and inhibitors of P-gp exist and can alter their function. For example, loperamide is a substrate for P-gp and is normally excluded from the enterocyte, which localizes its effect in the gastrointestinal tract. When coadministered with the P-gp inhibitors, the central effects of loperamide, such as sedation and respiratory depression, can occur.

Organic anion-transporting peptides (OATPs), organic cation transporters (OCTs), and organic anion transporters (OATs) belong to the SLC transporter superfamily. These are genetically and structurally heterogeneous structures that are united by their function as uptake (and occasionally bidirectional) transporters.[21] SLC transporters are located widely throughout the body in the liver, intestine, brain, heart, kidney and placenta. Drug-drug interactions are best described for orally administered medications, and those with a renal site of action or excretion such as diuretics and antihypertensives.

One of the challenges in studying the effects of drug transporter variants in vivo is the overlapping substrate range of transporters and downstream metabolic enzymes. An example of this is the close genetic and functional relationship between P-glycoprotein and CYP 3A enzymes, and between several members of the SLC family and uridyl-glucoronyltransferase (UGT) 1A1.[21] It is anticipated that with ongoing improvements in bioinformatics, these complex relationships will be unraveled and understood in the near future.

ATP, Adenosine triphosphate.

Variants of the *COMT* gene, located on chromosome 22, are typified by a complex spectrum of neuropsychological associations commensurate with the central role that catecholamines play in human behavior. The G472A polymorphism results in a methionine for valine substitution within the enzyme that diminishes its activity by approximately 25%.[18] This increases the cortical neuronal levels of dopamine and has been linked to various disorders of executive functioning and cognition, including autism, attention deficit disorders, and schizophrenia.[18,19] Anesthetic considerations for the G472A polymorphism are discussed further later in the chapter.

Sites of Drug Metabolism

Traditional thinking in pharmacokinetics and pharmacology summarize the factors influencing the disposition of a drug into four phases: absorption, distribution, metabolism, and excretion (ADME). This convenient but linear mnemonic overlooks the overlapping mechanisms that govern these processes. Drug transporters (Table 4.11) involved in absorption are essential for substrate delivery in metabolism and for drug excretion (Table 4.12). Biotransformational enzymes are widely present throughout the body and influence the absorption of certain drugs well before

TABLE 4.12 Selected Drug Transporter Systems

Family	Transporter	Substrates	Inducer	Inhibitor
ABC	P-glycoprotein (ABCB1 gene)	Opioids, including • Morphine • Fentanyl • Methadone • Sufentanil Cardiovascular drugs, including • Calcium channel blockers • β-Blockers • Statins • Digoxin Antiemetics, including • Ondansetron • Dexamethasone	St. John's wort Trazodone Aspirin Rifampin	Midazolam Amiodarone Dronedarone Carvedilol Lidocaine Verapamil Grapefruit juice
SLC	OATP	Antihypertensives, including • Aliskiren • ACE inhibitors • Angiotensin II receptor blockers		Clarithromycin Erythromycin Grapefruit juice Pravastatin
	OAT	Diuretics, including • Furosemide • Bumetamide		Probenecid Benzylpenicillin
	OCT	Antiarrhythmics, including • Procainamide • Dofetilide		Cimetidine Trimethoprim
		Other • Metformin • Ranitidine		

ABC, Adenosine triphosphate-binding cassette; *ACE,* angiotensin-converting enzyme; *OAT,* organic anion transporter; *OATP,* organic anion-transporting peptide; *SLC,* solute carrier.
Data from König J, Müller F, Fromm MF. Transporters and drug-drug interactions: important determinants of drug disposition and effects. *Pharmacol. Rev.* 2013;65:944–966.

they reach the circulation and biophase. Although the liver remains an important site for drug metabolism, many other locations are heavily involved in the metabolism of oral, inhaled, and intravenous drugs.

Liver

The liver is the largest organ in the body and the principal site of drug metabolism (see Chapter 31), and has a sinusoidal structure that creates a large blood-tissue interface. Almost all known metabolic enzymes are located in the smooth endoplasmic reticulum of the hepatocyte, including the major oxidases (see later). It receives 25% to 30% of total cardiac output and almost the entirety of portal vein flow, which carries substances absorbed through the gastrointestinal tract to the liver. This so-called first-pass exposure to enterally absorbed drugs functions as an important metabolic barrier between the gut and the systemic circulation. "First pass" may be a misnomer, as before this there is significant drug metabolism that occurs in the intestinal enterocyte. The total hepatic clearance of a specific compound is a function of the liver's intrinsic capacity to metabolize and excrete that substance, the fraction of unbound drug, and hepatic blood flow (Table 4.13). The **hepatic extraction ratio** expresses hepatic clearance as a ratio of hepatic blood flow and is an indicator of the amount of drug removed during one pass through the liver.

Active, energy-requiring drug transport is required for both entry into the hepatocyte (sometimes termed **phase 0 metabolism**)

TABLE 4.13 Hepatic Clearance and Extraction Ratio

$$\text{Hepatic clearance} = Q \times \frac{[(\text{Unbound drug} \times \text{Metabolic capacity})]}{[(Q + \text{Unbound drug} \times \text{Metabolic capacity})]},$$

where Q = hepatic blood flow.

Drugs with high hepatic extraction ratio (> 0.7):
- Will have high first pass metabolism with oral administration
- Are highly sensitive to changes in liver blood flow: **"flow-limited" clearance**
- Less sensitive to alterations in drug binding or "intrinsic clearance"
- Examples: Morphine, lidocaine, verapamil, and nitroglycerin

Drugs with low HER (<0.3):
- Minimal first pass metabolism with oral administration
- Highly sensitive to changes in drug binding or "intrinsic clearance": **"capacity-limited" clearance**
- Insensitive to changes in liver blood flow
- Examples: Warfarin, phenytoin

Drugs with Intermediate HER (0.3–0.7):
- Examples: Aspirin, codeine, and nortriptyline

and for biliary excretion. The expression of these transporter systems is subject to genetic polymorphisms, which can contribute to variations in drug effect, some of which are summarized in Table 4.12.

Intestinal Mucosa

Orally administered medications must first withstand chemical and bacterial degradation before they are absorbed from the gut. Absorption occurs via diffusion, pinocytosis, or transport. Active transport across gut epithelium involves similar drug transporter systems found in the liver and in other organs (Table 4.12).

Gastrointestinal mucosal epithelium contains many of the metabolic enzymes seen in the liver and other organs, and is the first site of biotransformation for many ingested compounds before they reach the portal circulation. Enzymes present in enterocytes include CYPs, FMOs, carboxylesterases, and the transferases.[22] While the gut has a much lower overall enzyme content compared with the liver, the enormous surface area and the obligatory exposure of orally absorbed compounds results in small intestinal intrinsic clearance rates that may be two to three times that of the liver.[23]

As with the liver, CYPs contribute to the largest portion of intestinal drug metabolism. Clinically important enzymes in the gut include CYP3A (making up 80% of small intestinal CYP content).[24] The highest levels of metabolic enzyme activity occur in the villi of duodenal (50% that of liver) and jejunal (30%) mucosal epithelium.[22] Together with the liver, these enzymes contribute to the first-pass metabolism of orally administered midazolam, calcium channel blockers, statins, and calcineurin inhibitors.

Grapefruit and other citrus fruits such as pomelos and certain orange varieties (bergamot, Seville) contain a number of compounds that can cause inadvertent variations in oral drug bioavailability when ingested. There are two identified compounds responsible, each with different effects on intestinal absorption. **Furanocoumarins** are toxic phytochemicals produced by these plants as a defense mechanism against predators and are found throughout the fruit, with the highest concentration in the peel.[25] Furanocoumarins are potent, irreversible inhibitors of CYP3A4 and 3A5[26]; because grapefruits are usually ingested orally, their effects are most marked on intestinal CYP3A activity. This increases the oral bioavailability of drugs that have extensive first-pass metabolism by intestinal CYP3A4 (see Table 4.6). Normal CYP activity is restored following the physiologic turnover of gut epithelium, which can take up to 3 days.[26] **Flavonoids** are a second group of compounds found in these fruits that contribute to their color and flavor. They are inhibitors of key drug transporters including P-glycoprotein and organic anion-transporting polypeptide, which results in a decrease in oral bioavailability of drugs dependent on these transporters for gut absorption (see Tables 4.11 and 4.12).[26]

Lung

The lungs participate in both the biotransformation and uptake of therapeutic compounds. Pulmonary endothelial cells contain low levels of the monooxidases, transferases, and esterases.[22] These have been exploited in the pharmaceutical design of inhaled corticosteroids and bronchodilators to limit their systemic absorption and extend their local activity.[27] The cytochromes are also involved in the biotransformation of the many substances found in tobacco and cannabis smoke, which are also CYP inducers.[28] Aside from these few examples, the lungs do not significantly contribute to the overall systemic clearance of xenobiotics.

The lungs metabolize many endogenous substances with therapeutic effects. They are a site of angiotensin-converting enzyme (ACE) activity, which metabolizes angiotensin I to angiotensin II, and bradykinin to its degradation products. The lungs also inactivate prostaglandins $F_{2\alpha}$ (dinoprost) and E_1 (alprostadil, misoprostol) and are an important location for the inactivation of biogenic amines, albeit with a unique selectivity that is not fully explained. Pulmonary tissues contain high levels of MAO but remove approximately 98% of all serotonin and 30% of norepinephrine in first-pass pulmonary clearance while leaving epinephrine, isoproterenol, and dopamine unaffected.[29] Since MAO has little to no selectivity in its metabolism of biogenic amines, this points to an unknown selective uptake mechanism in pulmonary endothelium prior to metabolism.

The lungs exert a significant first-pass uptake effect on certain drugs, many of which are commonly used in anesthesia (Table 4.14). Passive diffusion of low-molecular-weight (100–1000 Da) molecules is known to occur, but the exact cellular pathways remain unclear.[30] Increasing lipophilicity of small compounds enhances transcellular diffusion and may be the primary mechanism of transient pulmonary uptake of unionized fractions of amide local anesthetics.[31] Organic cation and cation/carnitine transporters (OCT, OCTN) from the SLC superfamily are present in luminal aspect of tracheobronchial and alveolar epithelium.[32,33] P-glycoprotein and other ATP-binding cassette (ABC) family efflux transporters are also present on the basolateral membrane of respiratory epithelium as well as alveolar macrophages.[32] However, the exact roles that these and other drug transporters play in mediating pulmonary drug uptake are unclear.

Blood

Several drugs commonly used in anesthetic practice are metabolized via organ-independent biotransformation pathways. **Esterases**, which degrade bioactive molecules by splitting their ester bonds, are widely distributed in red blood cells and plasma. Esterases terminate the actions of succinylcholine, remifentanil, and esmolol (discussed in greater detail later). **Monocytes and macrophages** are involved in the clearance of unfractionated and low-molecular-weight heparins, as well as colloid intravenous fluids such as dextran

TABLE 4.14 Anesthetic Drugs With Significant First-Pass Pulmonary Uptake

Local anesthetics	Lidocaine Bupivacaine Mepivacaine Prilocaine
Intravenous anesthetics	Propofol Thiopental Ketamine Diazepam
Opioids	Fentanyl Sufentanil Pethidine Methadone Morphine Codeine
Biogenic amines	Norepinephrine Dopamine

Data from Boer F. Drug handling by the lungs. *Br J Anaesth.* 2003;91:50–60.

TABLE 4.15 Pharmacogenomic Alterations With Anesthetic Significance

	Pharmacokinetic Alteration	Pharmacodynamic Alteration
Neuromuscular blockers	• Pseudocholinesterase deficiency	• Malignant hyperthermia
Inhalational agents	• Halothane hepatitis • CYP 2E1 variants and volatile anesthetic metabolism	• Malignant hyperthermia • 5,10-Methylene-tetrahydrofolate reductase (MTHFR) gene mutation and nitrous oxide • Melanocortin-1 receptor (MC1R) gene mutation and MAC requirements
Intravenous agents	• CYP 2C19 variants and diazepam metabolism • UGT 2B15 variants and oxazepam, lorazepam metabolism	
Opioids	• P-glycoprotein transporter variants and opioid sensitivity • CYP 2D6 variants and codeine, tramadol, oxycodone metabolism	• *OPRM1* gene variants and opioid requirements • COMT gene variants and altered pain perception

COMT, Catechol *O*-methyltransferase; *CYP,* cytochrome P450; *MAC,* minimum alveolar concentration; *UGT,* uridine phosphate-glucuronosyltransferase.

and hydroxyethylated starches. **Hofmann elimination** is a series of spontaneous chemical degradation steps that break down quaternary amines into a tertiary amine and an alkene. It is enzyme-, organ- and age-independent but is affected by pH and temperature. Hofmann elimination is the main metabolic pathway for atracurium and cisatracurium.

Pharmacogenomics and Drugs Commonly Used in Anesthesia (Table 4.15)

Neuromuscular Blockers

Butyrylcholinesterase Deficiency

Congenital BChE (or pseudocholinesterase) deficiency was one of the first pharmacogenetic disorders described in the medical literature. It is a result of a single mutation in the *BChE* gene on chromosome 3q26 and follows Mendelian inheritance patterns. Depending on the genotype, BChE deficiency results in prolongation of the effects of succinylcholine and mivacurium.

Currently more than 60 allelic variants of the *BChE* gene have been identified[34]; a selection of clinically important alleles is summarized in Table 4.16. In the past, different forms of BChE deficiency were identified based on phenotypic studies. These measured the inhibition of BChE activity by dibucaine (an ester local anesthetic) and fluoride. Normal BChE activity is decreased by 80% on exposure to dibucaine and 60% with fluoride; this degree of inhibition is reported as *dibucaine and fluoride numbers,* respectively (Table 4.17). Since then, the phenotypic BChE deficiency has been further defined as a qualitative or quantitative defect in BChE activity.

The overall prevalence of mild heterozygous BChE deficiency is highest in Caucasian populations (4%), which results in modest prolongation of succinylcholine activity (up to 1 hour). More severe heterozygous variants causing apnea lasting 1 hour or longer are rare, and homozygous forms, with complete absence of BChE activity, are rarer still.

Increased Butyrylcholinesterase Activity

Inherited conditions causing increased BChE activity have been described, which result in either a quantitative or qualitative change in the enzyme.[35] Two rare but distinct genetic variants were identified in the 1960–1970s that are associated with 30% and 400% increased activity compared with wild-type BChE and inherited in an autosomal dominant pattern.[36,37] The latter Cynthiana variant was later found to be due to increased production of enzyme.[36,37] An additional isoform discovered in the 1970–1980s appears to have

TABLE 4.16 Genetic Variants Associated With Butyrylcholinesterase (Plasma Cholinesterase) Deficiency

Name	Phenotype	AA Alteration	DNA Alteration
Usual	Normal	None	None
Atypical	Dibucaine-resistant	70 Asp→Gly	nt 209 (GAT→GGT)
Silent 1	Silent, no activity	117 Gly→Frameshift	nt 351 (GGT→GGAG)
Silent 2		6 Ile→ Frameshift	nt 16 (ATT→TT)
Silent 3		500 Tyr→ Stop	nt 1500 (TAT→TAA)
Fluoride 1	Fluoride-resistant	243 Thr → Met	nt 728 (ACG→ATG)
Fluoride 2		390 Gly→Val	nt 1169 (GGT→GTT)
K variant	66% Normal BChE levels	539 Ala→ Thr	nt 1615 (GCA→ACA)
H variant	33% Normal BChE levels	142 Val→Met	nt 424 (GTG→ATG)
J variant	10% Normal BChE levels	497 Glu→ Val 539 Ala→Thr	nt 1490 (GAA→GTA) nt 1615 (GCA→ACA)

AA, amino acid; *BCHe,* butyrylcholinesterase; *nt,* nucleotide,
Data from Bartels CF, Jensen FS, Lockridge O, et al. DNA mutation associated with the human butyrylcholinesterase K-variant and its linkage to the atypical variant mutation and other polymorphic sites. *Am J Hum Genet.* 1992;50:1086–1103; and Bartels CF, James K, La Du BN. DNA mutations associated with the human butyrylcholinesterase J-variant. *Am J Hum Genet.* 1992;50:1104–1114.

TABLE 4.17 Phenotypic Variants of Butyrylcholinesterase (Plasma Cholinesterase) Deficiency

Name	Genotype	DN	FN	% UU Enzyme Levels	Average Activity (kU/L)	Apnea Duration	Average Frequency
Usual	UU	80	60	—	8	1–5 min	94%
Atypical	UA	60	50	—	8	10 min	1:25
	AA	20	20	—	1–5	2 hr	1:3000
Silent	US	80	60	—	1–5	10 min	1:25
	SS	—	—	—	~0	8 hr	1:100,000
Fluoride-resistant	UF	75	50	—	1–5	10 min	1:300,000
	FF	65	40	—	1–5	2 hr	1:150,000
K-variant	KK	80	60	66%	5	Insufficient data	1:100
J-variant	JJ	—	—	33%	Insufficient data	Insufficient data	1:150,000
J-variant	UJ	80	60	—	7	Insufficient data	Insufficient data
H-variant	HH	-	-	10%	Insufficient data	Insufficient data	Insufficient data

DN, dibucaine number; *FN,* fluoride number; *UU,* usual butyrylcholinesterase genotype.

Data from Parnas ML, Procter M, Schwarz MA, et al. Concordance of butyrylcholinesterase phenotype with genotype. *Am J Clin Pathol.* 2011;135:271–276; Bartels CF, Jensen FS, Lockridge O, et al. DNA mutation associated with the human butyrylcholinesterase K-variant and its linkage to the atypical variant mutation and other polymorphic sites. *Am J Hum Genet.* 1992;50:1086–1103; and Bartels CF, James K, La Du BN. DNA mutations associated with the human butyrylcholinesterase J-variant. *Am J Hum Genet.* 1992;50:1104–1114.

TABLE 4.18 Variant CYP 2D6 Phenotypes

Phenotype	Genotype	Approximate Frequency	Codeine Effects
Ultrarapid	More than two functional copies of the gene	1%–2% (29% in Ethiopia and Saudi Arabia)	Significantly higher amounts of morphine risks overdose: avoid codeine due to potential for toxicity
Extensive	Two copies of a normal- function allele	77%–92%	Normal activity, normal metabolism to morphine
Intermediate	One copy of a reduced- function allele One copy of a normal- function allele	2%–11%	Decreased efficacy; if no response, consider alternate analgesic
Poor	Two copies of a reduced-function allele	5%–10%	Avoid codeine due to lack of analgesic effect

Data from Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. *Pharmacogenomics J.* 2005;5:6–13, and Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin Pharmacol Ther.* 2014;95:376–382.

normal levels of a hyperactive enzyme.[38] Patients with these variants are resistant to the paralytic effects of succinylcholine and mivacurium and display normal inhibition when exposed to dibucaine and fluoride.

Opioids

Pharmacokinetic Alterations

Opioid Absorption and Distribution

The P-glycoprotein (P-gp), encoded by the *ABCB1* gene, is an important transporter of macromolecules across not only the intestinal epithelium but also brain capillary endothelium, which forms the functional blood-brain barrier. Substrates for P-gp include morphine, fentanyl, sufentanil, methadone, oxycodone, and buprenorphine; both oral and brain uptake are affected by polymorphisms in the *ABCB1* gene. The few human studies investigating the impact of ABCB1 polymorphisms on opioid effect have some contradictory results. ABCB1 C3435T, G2677T/A, and C1236T polymorphisms are associated with variations in the analgesic and respiratory depressant effects of morphine and fentanyl,[39,40] and differences in efficacy and side effects in patients on chronic oral morphine.[41] However, the same single-nucleotide polymorphisms (SNPs) were not associated with differences in morphine or fentanyl dose requirements or pain scores in postoperative patients.[42,43]

Opioid Metabolism

CYP 2D6 is responsible for handling approximately 25% of all drugs in current usage[44] and is highly involved in the metabolism of opioids to both active and inactive forms. There are currently more than 100 allelic variants of CYP 2D6; in addition, multiple gene duplications and multiplications can exist in an individual, resulting in up to 13 copies of the *2D6* gene and an overexpression of the enzyme. The population can be divided into four phenotypic groups based on their enzyme activity (Table 4.18).

Codeine achieves its analgesic effect only after it has been demethylated by CYP 2D6 to morphine, which has 200 times the affinity and 50 times the intrinsic activity at the μ-opioid receptor. In extensive metabolizers, approximately 10% of an administered codeine dose is metabolized to morphine; the remainder is converted to codeine-6-glucuronide and norcodeine, which are both inactive metabolites. In comparison, ultrarapid metabolizers, who make up 1% to 2% of Caucasians but up to 29% of people from Ethiopia and Saudi Arabia, can have approximately 50% higher plasma concentrations of morphine.[46] This can result in respiratory depression and death, especially in the postoperative pediatric tonsillectomy population.[47,48] These effects are also important for breastfeeding mothers who are ultrarapid metabolizers. It should be noted, however, that significant variability exists even within the extensive metabolizer phenotype, with some patients producing plasma morphine levels approaching or exceeding those found in ultrarapid metabolizers.[46] Poor metabolizers do not experience analgesic effect from codeine owing to lack of 2D6-mediated metabolism to morphine, but they can still experience side effects from non-2D6 mediated metabolites such as codeine-6-glucuronide.[49]

CYP 2D6 is also important in the metabolism of tramadol and oxycodone. **Tramadol** exerts analgesic effects via the μ-opioid receptor as well as serotonin and noradrenaline reuptake inhibition. It is also metabolized by CYP 2D6 to O-desmethyltramadol, which has a much higher affinity for the μ-receptor than its parent compound.[45] In cases of fatal tramadol overdose, the number of functional CYP 2D6 alleles strongly correlates with the ratio of tramadol metabolite to the parent compound.[50]

Oxycodone is metabolized by CYP 2D6 to oxymorphone, which has three times the half-life of oxycodone but makes up only 15% of total oxycodone metabolites. Oxycodone consumption in postsurgical patients correlates with the number of functional CYP 2D6 alleles, although there was no difference in pain scores.[51] For reasons similar to codeine, tramadol and oxycodone should be avoided in ultrarapid metabolizers to avoid unexpected opioid overdose.

Pharmacodynamic Alterations

Opioid Receptors

Variants of the *OPRM1* gene, which encodes for the μ-opioid receptor, are associated with variations in experimental and clinical pain responses as well as opioid side effects. The A118G SNP has an allelic frequency of 10% to 30% in Caucasians[52] and up 36% to 60% in East Asians.[53] Compared with the wild-type OPRM1 gene, this variant increases the affinity and intrinsic activity of β-endorphin for the μ-receptor approximately threefold.[54] In vitro animal experiments also suggest that this SNP alters receptor binding and signal transduction at the level of the sensory neurons.[55] Human trials, however, have not clearly linked this or other SNPs with alterations in pain perception or opioid efficacy. In studies investigating East Asian women undergoing gynecologic surgery, the 118GG genotype is associated with statistically significant but clinically modest increases in intravenous morphine and fentanyl consumption to achieve pain relief in the first 24 hours, but no difference in opioid side effects.[56,57] These findings were supported in a study of adult Japanese patients, 57% of whom were male, undergoing colorectal surgery under general and epidural anesthesia.[58]

Western European women receiving *intrathecal fentanyl for labor analgesia* have a 1.5- to 2-fold difference in the effective concentration for 50% effect (ED_{50}) of intrathecal fentanyl depending on the A118G genotype; those who are heterozygous or homozygous for the 118G SNP (termed A304G in those studies) showed an increased sensitivity to the analgesic effects of intrathecal fentanyl.[59] In addition, there is a significant difference in the degree of cervical dilatation at time of request for analgesia, with 118G homozygotes requesting analgesia at a later progression of labor.[59] Although many factors contribute to this difference, it is in keeping with the findings of enhanced β-endorphin binding to the variant μ-receptor *in vitro*.[54] However, a larger multicenter study of including Caucasian, Asian. and African American parturients did not show any difference in the duration of intrathecal fentanyl for labor analgesia, nor in the requirements of supplemental analgesia following cesarean delivery with neuraxial anesthesia and intrathecal morphine.[60] Confounders that may account for the heterogeneity of human clinical data include different mechanisms of noxious stimulus, gender, and ethnicity, all of which are independent predictors of pain perception.[53,61] Furthermore, differences between intravenous and neuraxial routes of opioid administration may contribute to the incongruent findings, as well as the possibility that the A118G SNP may in fact be a marker for, but not the causative mutation of, the observed differences.

Catecholamines including norepinephrine and dopamine are mediators in the central and peripheral pain pathways, and are metabolized by catechol O-methyltransferase. *Variations in the* COMT *gene* on chromosome 22 are postulated to affect pain perception, although almost all human studies suffer from small sample sizes and other methodologic problems. A prospective trial of 221 patients investigating a range of MAO and COMT polymorphisms show a weak genetic contribution to individual variations in acute surgical pain responses.[62] Smaller studies looking specifically at the G472A SNP show decreased COMT activity and increased sensitivity to nociceptive stimuli induced by heat and hypertonic saline solution.[63,64] A broader "low COMT activity" haplotype group made up of varying allelic variations predicted pain catastrophizing behavior following shoulder surgery.[65]

Intravenous Anesthetics

Pharmacokinetic Alterations

Most **benzodiazepines**, with the exception of oxazepam and lorazepam, are metabolized by the CYP system via N-dealkylation or hydroxylation. Midazolam is a highly specific substrate for CYP 3A4/5, and its clearance can vary 5- to 11-fold in Caucasian and African American populations.[66] Despite in vitro evidence to the contrary, this interindividual variability does not appear to result from polymorphisms of CYP 3A4/5.[67] The reasons for this have been attributed instead to gender and environmental factors,[67] the presence of inducers,[68] and alternate pathways of metabolism and excretion.[69]

Diazepam is primarily demethylated into active metabolites by CYP 2C19, an enzyme encoded by a gene with over 25 alleles currently identified.[70] Alleles can confer normal, loss, or gain in enzyme function, resulting in ultrarapid, normal, and poor metabolizer phenotypes (Table 4.19). Poor metabolizers have a fourfold increase in the half-life of diazepam compared with extensive metabolizers,[71] placing them at risk of prolonged sedation.

Oxazepam and lorazepam are metabolized via glucuronidation and have been considered a safe alternative in hepatic impairment, but their handling is also altered by genetic polymorphisms. Compared with wild-type UGT2B15, the UGT2B15*2/*2 genotype reduces systemic clearance of lorazepam by approximately 50%, resulting in higher visual analog scales for sedation.[72] The same polymorphism also causes a decrease in oxazepam glucuronidation,

TABLE 4.19 Variant CYP 2C19 Phenotypes

Phenotype	Genotype	Approximate Frequency	Effect on Diazepam and Clopidogrel
Ultrarapid	Two copies of increased-function allele	5%–30%	**Diazepam**: Increased production of desmethyl-diazepam, with extremely long half-life. Concern for prolonged duration of action, no formal recommendation on dose adjustment **Clopidogrel:** Increased production of active metabolite, increased risk of bleeding
Extensive	Two copies of a normal-function allele	35%–50%	Normal handling of diazepam and clopidogrel
Intermediate	One copy of a reduced-function allele One copy of a normal-function allele	18%–45%	Normal handling of diazepam and clopidogrel
Poor	Two copies of a reduced-function allele	2%–15%	**Diazepam:** Concern for prolonged duration of action, no formal recommendation on dose adjustment **Clopidogrel:** Decreased conversion into active form; risks no treatment effect, suggest change to alternate antiplatelet agent

Data from Scott SA, Sangkuhl K, Gardner EE, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy. *Clin Pharmacol Ther.* 2011;90:328–332.

although correlation with clinical variability in drug response has not been described to date.[73]

Propofol is hydroxylated in the liver primarily by CYP2B6 and, to a lesser extent, CYP2C9.[74] It also undergoes transformation via UGT 1A9 to form propofol glucuronide, an inactive metabolite. The CYP 2B6 c.516G>T polymorphism decreases propofol metabolism and contributes to variations in propofol clearance when corrected for age, height, and weight.[75,76] However, there appears to be little correlation between this and other genotypes with differences in clinical outcome.[77,78] Similarly, the 766G>A SNP of UGT 1A9 decreases the glucuronidation of propofol but does not account for clinical variability in the effects of propofol.[76,78]

Pharmacodynamic Alterations

The *gamma-aminobutyric acid (GABA)$_A$ receptor* is the molecular target for many intravenous and volatile anesthetics (see Chapters 10 and 11). In vitro studies of variant $GABA_A$ receptors with the epsilon subunit, encoded by the *GABRE* gene, show resistance to the effects of benzodiazepines, barbiturates, etomidate and propofol.[79,80] Human studies, however, have so far been unable to show any association between the *GABRE* gene and variations in response to propofol anesthesia.[77,78]

Inhalational Anesthetics

Pharmacokinetic Alterations

The hepatic metabolism of halothane, sevoflurane, isoflurane, and desflurane occurs almost exclusively through CYP 2E1 oxidation.[81] Although there are many known CYP 2E1 variants, to date no polymorphisms have been shown to cause clinically significant effects on the metabolism of volatile anesthetics. This can partly be attributed to the overall low contribution from liver metabolism to the disposition of sevoflurane, isoflurane, and desflurane (see Chapter 3).

Halothane Hepatitis

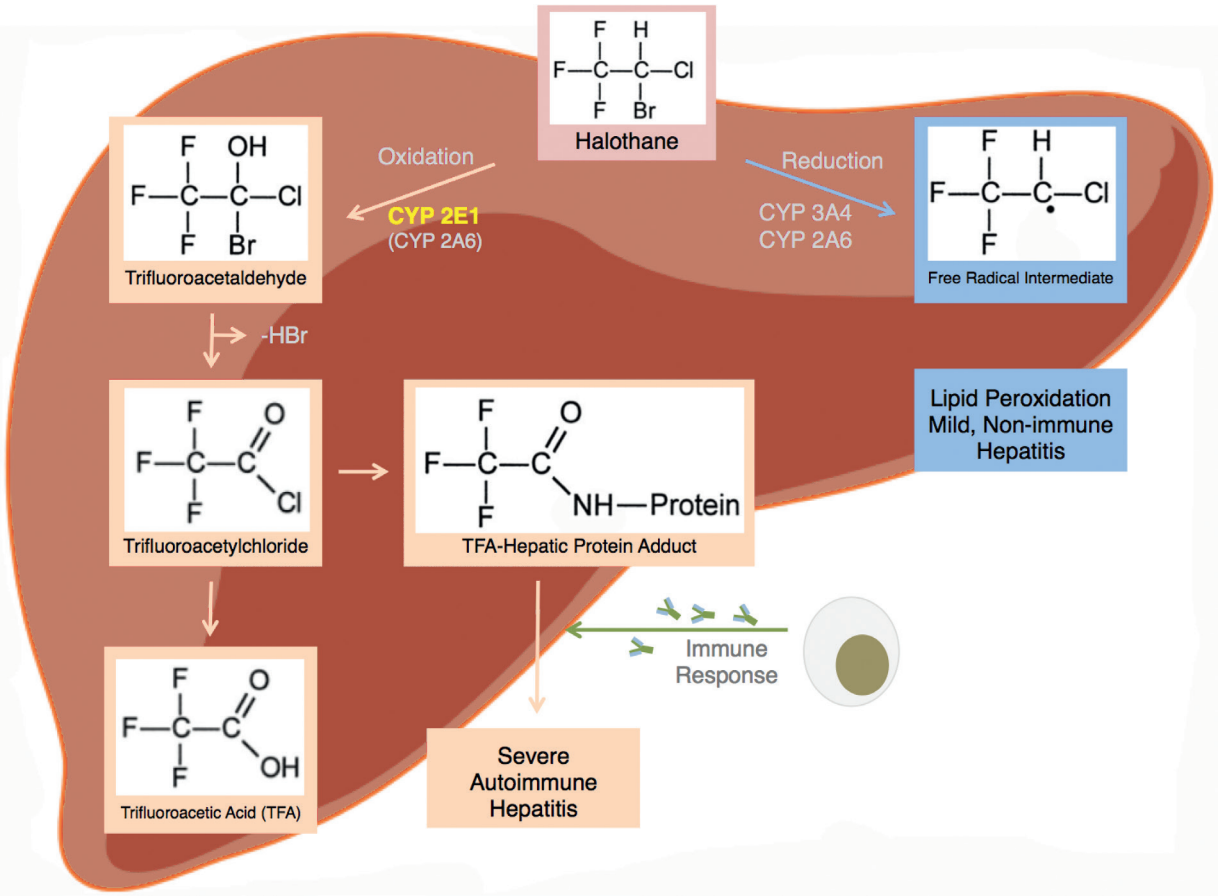
Reports of halothane hepatitis have become rare since the 1980s, but it remains relevant in those countries where halothane is still available for clinical use. The pharmacogenetic link between volatile anesthesia and acute, often fatal, liver injury remains elusive. Up to 20% of administered halothane is metabolized by hepatic CYP 2E1 and 2A6/3A4 via both oxidative and reductive pathways, respectively.[81] Trifluoroacetyl chloride, an oxidative metabolite of halothane, is linked to the development of fulminant hepatocellular damage by covalently binding to hepatic proteins to form trifluoroacetylated neoantigens, which subsequently become a target for autoimmune attack (see Fig. 4.7). Risk factors include hypoxia and HLA tissue types, but there is little information on the pharmacogenetic features that predispose an individual to oxidative, rather than reductive, metabolism of halothane. To date, the single study investigating the CYP profiles of known survivors of halothane hepatitis have not demonstrated differences in activity between survivors and controls across a range of isoenzymes, including 2A6 and 3A4.[82] An important omission, however, is the impact of CYP 2E1 activity in this survivor group.

Pharmacodynamic Alterations

Malignant Hyperthermia

Malignant hyperthermia (MH) is an inherited, multifactorial channelopathy marked by uncontrolled release of calcium ions (Ca^{2+}) from the sarcoplasmic reticulum of skeletal muscle in response to volatile anesthesia and succinylcholine (see Chapter 7). The main channels implicated in the pathogenesis of MH include the ryanodine receptor (encoded by the *RYR1* gene), and the L-type calcium channel within the T-tubules containing the voltage-sensing $Ca_V1.1$ and beta1a subunits (encoded by the CACNA1S and CACNB1 genes, respectively). Many other defects in chromosomal loci not currently associated with genes are associated with MH.[83] Given the complexity of Ca^{2+} homeostasis, it is likely these loci encode for other regulators of Ca^{2+} transport in skeletal muscle whose role in MH is still unknown.

The pharmacogenetics of MH are complex and likely polygenetic. Approximately 50% to 85% of MH cases are linked to mutations in the *RYR1* gene, although this varies depending on geographic population and study design.[84] Inheritance is autosomal dominant, with unknown penetrance, but it is likely highly variable. The



• **Fig. 4.7** Pharmacogenetics of Halothane Hepatitis. Liver injury can occur as a result of oxidative and reductive metabolism of halothane, although it is the oxidative pathway that is most associated with more severe forms of hepatitis. Oxidative metabolism of halothane via CYP 2E1 results in trifluoroacetylated metabolites that covalently bind to liver proteins, resulting in neoantigens that stimulate an autoimmune response. While there are immunologic risk factors that predispose to halothane hepatitis, the role of CYP 2E1 isoforms and the production of trifluoroacetylated proteins has yet to be fully elucidated.

prevalence of genetic variants in *RYR1* predisposing to MH is estimated to be 1:2000,[85] but the incidence of MH is much lower, between 1 and 1.3 per 100,000 anesthetics in the United States, and even lower in ambulatory surgical settings.[86,87] Of the approximately 200 *RYR1* mutations currently known,[88] 66 have been detected in known MH families in the United Kingdom.[83] In approximately 10% to 20% of families, no *RYR1* gene defect could be found. With regard to the *CACNA1S* gene, 6 of more than 50 known variants have been linked to MH,[89] with approximately 1% of MH presentations attributed to defects in *CACNA1S*.

What is increasingly clear from the genotype-phenotype discordance in both laboratory and human clinical studies is that there are additional modulators that influence the manifestation of MH. Post-translational modification of calcium channels by fatty acids[90] and the interaction between these channels and other membrane proteins[91,92] are implicated. When combined, the clinical manifestation of MH is likely a "threshold model" in which the presence of an *RYR1* variant is but one of many other contributors that lead to symptoms.

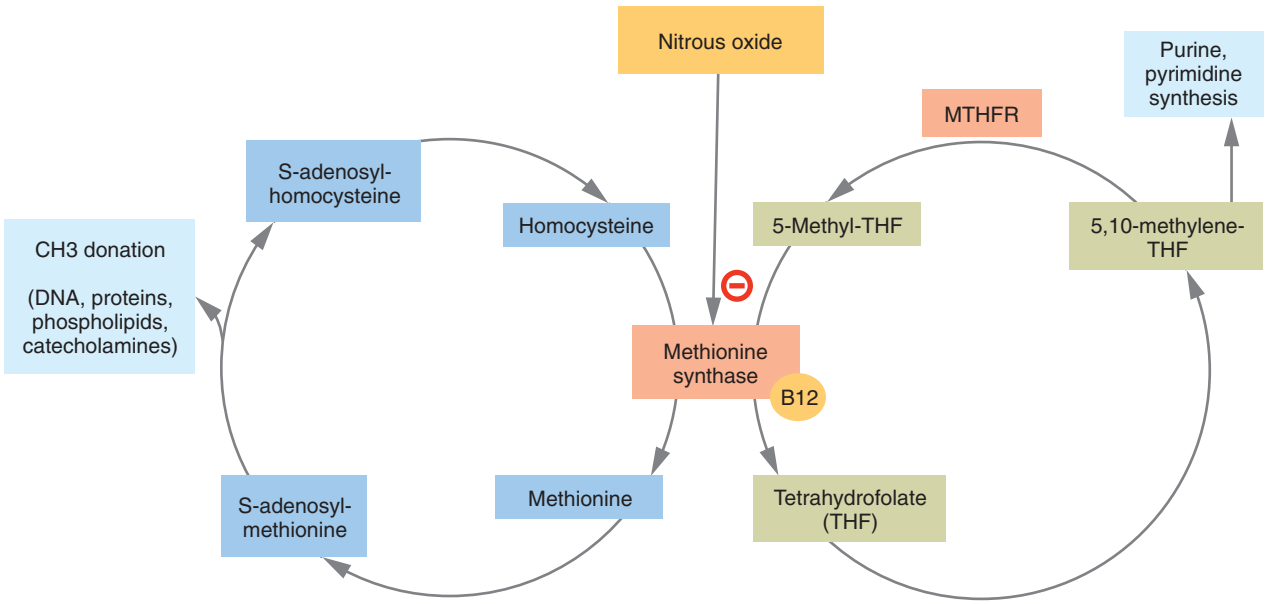
Melanocortin-1 Receptor Gene Variants

Reduced-function variants of the melanocortin-1 receptor *(MC1R)* gene are associated with the red hair phenotype.[93] The red hair trait occurs as a result of an overabundance of pheomelanin (red) pigment relative to eumelanin (dark brown)[93] and is a convenient physical marker for reduced *MC1R* activity. In both knockout mice and humans, reduced-function *MC1Rs* are associated with increased volatile anesthetic and analgesic requirements.[93–95] Whether these *MC1R* variants are directly responsible, or are markers for other determining characteristics common among red-haired individuals, is currently unknown.

MTHFR Gene Variations

Nitrous oxide irreversibly inhibits vitamin B_{12} (cobalamin), which leads downstream effects on enzymes that require vitamin B_{12} as a co-factor. Methionine synthase is one such enzyme, and is central to both the methylation of homocysteine to methionine, and to the conversion of 5-methyl-tetrahydrofolate (THF) to THF. Both metabolic reactions are crucial steps in methylation reactions critical to neurotransmitter, myelin sheath, and nucleic acid synthesis, which particularly affects central nervous system function and rapidly dividing cells such as those in bone marrow (Fig. 4.8). Furthermore, increased plasma homocysteine levels predispose to endothelial cell injury and vascular thrombosis.

Methylenetetrahydrofolate reductase (MTHFR) is an enzyme in the folate cycle that demethylates 5,10-methylene-THF to 5-methyl-THF, the substrate for methionine synthase. MTHFR deficiency occurs as a result of SNPs in the *MTHFR* gene located



• **Fig. 4.8** Nitrous Oxide and MTHFR Deficiency. Nitrous oxide inhibits vitamin B_{12}, which is required by methionine synthase as a cofactor for catalyzing the conversion of 5-methyl-tetrahydrofolate to tetrahydrofolate (THF). Methylene tetrahydrofolate reductase (MTHFR) is an enzyme that converts 5,10-methylene-THF to 5-methyl-THF. In the presence of MTHFR deficiency, the administration of nitrous oxide can result in disorders of purine and pyrimidine synthesis, as well as other downstream reactions that depend on methyl donors from this metabolic cycle.

on chromosome 1. The two common SNPs, 677C>T and 1298A>C, have a cumulative prevalence of approximately 5% to 10% in Western Europe, 20% to 25% in Southern Europe and East Asia, and up to 36% in Mexico.[96,97]

It has been postulated that nitrous oxide imposes a "second hit" to vulnerable patients with preexisting defects in folate or homocysteine-methionine metabolism pathways.[98] Several case reports of repeated nitrous oxide anesthesia administered to patients with *MTHFR* gene mutations describe acute demyelination causing severe neurologic injury and megaloblastic anemia.[98,99] Similar pathology is seen when nitrous oxide is administered to patients with severe vitamin B_{12} deficiency.[100] Although an increase in plasma homocysteine levels is also seen in these patients, there is no correlation with increased risk of perioperative myocardial injury as a result of nitrous oxide anesthesia in these patients.[101] Because of the potentially devastating effects of acute methionine synthase dysfunction, it has been suggested that nitrous oxide be avoided in patients who have a personal or family history of *MTHFR* gene mutation.[102]

Serotonin Receptor Antagonists

Ondansetron and tropisetron are commonly used for the prevention and treatment of postoperative nausea and vomiting (see Chapter 34). Both are transformed into inactive metabolites: ondansetron by multiple CYPs, including 3A4, 1A2, and 2D6, and tropisetron exclusively by 2D6. Populations with the CYP 2D6 ultrarapid metabolizer phenotype can experience failure of antiemetic therapy when ondansetron and tropisetron are used. Within a group of 250 North American women undergoing general anesthesia treated with prophylactic ondansetron, those who were 2D6 ultrarapid metabolizers had a significantly higher incidence of postoperative nausea and vomiting (45%) compared with extensive metabolizers (15%).[103] A similar failure of tropisetron for prevention of chemotherapy-induced nausea and vomiting occurs in 2D6 ultrarapid metabolizers.[104] Interestingly, while poor metabolizers have increased serum drug levels compared with other phenotypes, there is no increase in side effects reported.[103,104] Currently, expert opinion recommends avoidance of 5-HT_3 antagonists primarily metabolized by CYP 2D6 in known ultrarapid metabolizers (ondansetron, tropisetron, dolasetron, palonosetron). Granisetron, an intermediate-acting 5-HT_3 antagonist, is metabolized by CYP 3A4 and 1A1 and is a suitable alternative in these patients. As yet, there are insufficient data to recommend specific changes in practice for poor metabolisers.[105]

Emerging Developments

Precision medicine is an exponentially growing field that is increasingly bridging the gap between laboratory science and clinical application. The term, introduced into common usage in 2011, emphasizes the integration of population genomics with individual clinical and socio-environmental data to guide research and treatment of disease.[106] An example of precision medicine in practice is the use of large-scale genetic databases and multiple patient biomarkers to individualize cancer chemotherapeutic regimens.[107] Another example is point-of-care buccal swab testing for CYP 2C19 polymorphisms, used to predict non-responders to clopidogrel therapy in patients after percutaneous coronary intervention.[108]

It is increasingly recognized that for many drugs, the "one gene, one defect" paradigm is insufficient to fully explain the variability in drug responses between individuals. The use of massive data repositories for systems biology analysis is one approach that better characterizes these complex genome-phenome associations.[109] The creation of robust, intricate biologic models is another approach; one example of this is the use of chimeric mice with "humanized"

livers.[110] Xu and Peltz describe several methods that involve transplanting human liver cells into immunosuppressed transgenic mice, resulting in a biologically active liver that expresses mRNA encoding for human phase I and II enzymes, drug transporters, and other transcription factors.[110] This exciting development expands horizons not only for more accurate prediction of in vivo drug handling, but also the promise of personalized, functional hepatic models through the engraftment of an individual's hepatocytes in these chimeric mice.

In the near future, a fully integrated approach with contributions from the various "omic" bioinformatics branches can bring about virtual models of complex physiologic and disease states that can transform pharmaceutical development, clinical drug trials, and medication prescribing. In an era when guidelines and protocols are pervasive in clinical practice, precision medicine has the potential to be the personalized counterweight that brings about innovations in safety and cost-effectiveness in health care and research in the years to come.

Key Points

- The transporters and enzymes involved with drug metabolism are closely related to ancient defense mechanisms against xenobiotics found across Archaea, bacteria, and eukaryotes.
- Pharmacogenetics is a term that refers to the study of genetic causes of variability in drug response; more recently, a genome-wide approach has been adopted (pharmacogenomics) to more fully understand interindividual differences in drug effect.
- Genomic variants can alter the function of membrane transporters, metabolic enzymes, and target receptors to alter the disposition and effects of many commonly used anesthetic drugs.
- Genetic variants of membrane transporters are an important determinant of differential drug effect between individuals. While these variations alone can cause altered drug behavior, it is increasingly recognized that transporter variants may also alter the function of other enzymes and metabolites to contribute to changes in phenotype.
- Drug metabolism takes place predominantly in the liver, but begins with entry into the body via natural barriers of the gastrointestinal and respiratory tracts, and also occurs in many locations throughout the body.
- Drug metabolism processes can be classified into three phases: drug transport, phase I reactions, and phase II reactions. Phase I reactions alter biologic activity of drugs via alteration of a functional molecular group. Phase II reactions do so by conjugating a water-soluble adjunct to the drug.
- Important metabolic enzymes with variant phenotypes that have an impact on clinical care include CYP 2D6, 2C19, N-acetyltransferase, and butyrylcholinesterase. By overcoming current limitations in bioinformatics, laboratory technology, and study design, it is likely other similar associations will be found.
- The future of pharmacogenomics lies in systems pharmacology, using data from many "omic" fields to model and systems biology to model complex biologic states to guide drug development, test for efficacy, and minimize adverse side effects.

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5

Physiology and Pharmacology of Obesity, Pediatrics, and the Elderly

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CHAPTER OUTLINE

Obese Patients
- Physiologic Changes in Obese Patients
- Anesthetic Pharmacology in Obesity
  - *Sedative-Hypnotics*
  - *Opioids*
  - *Inhaled Anesthetics*
  - *Neuromuscular Blocking Drugs*
  - *Local Anesthetics*

Pediatric Patients
- Physiologic Changes in Pediatric Patients
- Anesthetic Pharmacology in Pediatric Patients
  - *Inhaled Anesthetics*
  - *Propofol*
  - *Midazolam*
  - *Etomidate*
  - *Ketamine*
  - *Opioids*
  - *Neuromuscular Blocking Drugs*
- Anesthetic Toxicity in Neonates and Infants

Elderly Patients
- Physiologic Changes in the Elderly
- Anesthetic Pharmacology in the Elderly
- Postoperative Cognitive Dysfunction

Emerging Developments
- Open Target-Controlled Infusion

Anesthesiologists frequently care for patients at the extremes of age and size. These patient groups have unique features that require special consideration when formulating an anesthetic plan. The purpose of this chapter is to highlight alterations in physiology associated with these special populations, focusing in particular on how the altered physiology influences the behavior of anesthetic drugs as covered in other chapters. To translate this information into the clinical domain, the chapter aims to summarize dosing adjustments that account for body habitus (obese and morbidly obese) and age at both extremes (neonates and elderly).

Obese Patients

Physiologic Changes in Obese Patients

Obesity presents anesthesiologists with numerous challenges that affect their care throughout the perioperative period. Excess body weight affects virtually every system of the body, including the cardiovascular, respiratory, endocrine, digestive, and hematologic systems, among others. In particular, increased chest wall mass, redundant airway tissue, and increased incidence of obstructive sleep apnea make this patient group at increased risk for adverse airway and respiratory events among many other weight-related issues (Table 5.1, Fig. 5.1).

In response to the increasing frequency of obese patients presenting for surgery, the American Society of Anesthesiologists (ASA) updated the ASA's Physical Status Classification System to include obesity as a metric to consider when determining a patient's physical status (Table 5.2).[1] This modification encourages clinicians to acknowledge how obesity-related conditions can lead to adverse events in the perioperative period. Of particular relevance to anesthesiology, obesity can alter the pharmacokinetics and effects of intravenous agents (opioids, sedatives, neuromuscular blockers) and inhalation agents. Increased fat mass, increased blood volume and cardiac output, and reduced tissue perfusion change drug disposition that can lead to changes in the magnitude and time course of drug effect[2,3] (Table 5.3, see Fig. 5.1).

The fact that most anesthetics are highly lipophilic (i.e., as measured by their octanol-water coefficient) raises concerns about accumulation of anesthetics into fatty tissue over the course of an anesthetic. When exploring differences between drugs, however, lipophilicity alone does not reliably predict volume of distribution. Lipophilic drugs can have increased, unchanged, or reduced distribution volumes[4] because drug distribution also depends on other properties, such as protein binding, molecular size, ionization at physiologic pH (pKa), among other factors.

Understanding the relationship between total body weight, lean body weight, and fat weight is also important. As total body weight increases beyond ideal body weight (i.e., as body mass index [BMI] increases), the proportion of lean and fatty tissue begins to diverge (Fig. 5.2). Above a BMI of 30 kg/m^2, lean body weight begins to plateau, and the curve flattens even further as BMI exceeds 40 kg/m^2 as the body has proportionally less lean tissue. Obesity influences the physiology of most organ systems that can alter the pharmacologic behavior of anesthetic drugs. Although drugs from the same class (e.g., opioids) are likely to be influenced by obesity in

Abstract

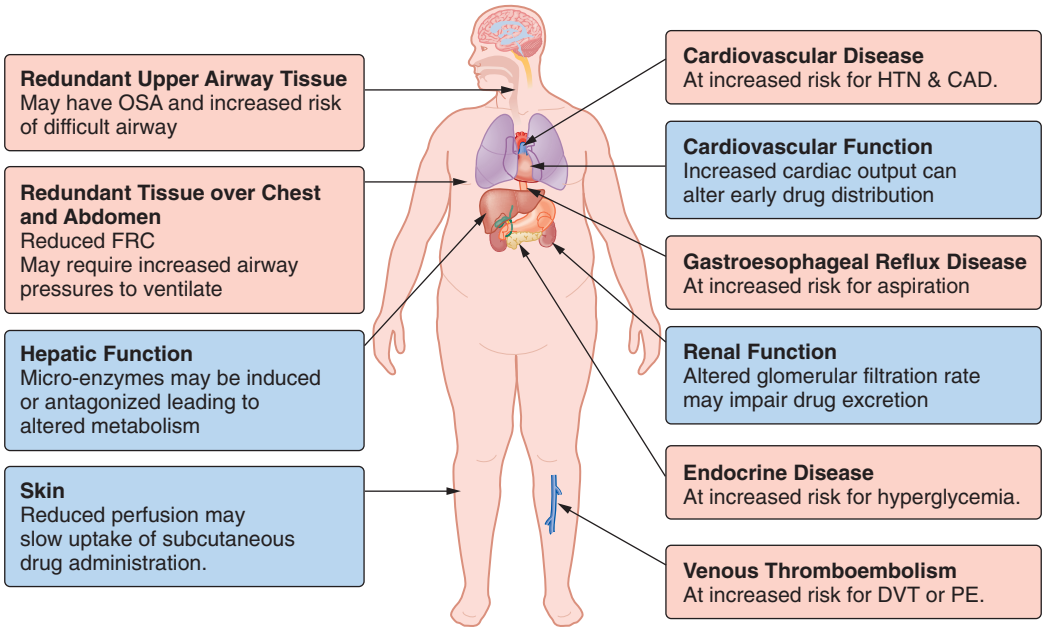
Anesthesiologists are frequently asked to care for patients at the extremes of age and size. These patient groups have unique features that require special consideration when formulating an anesthetic plan. The purpose of this chapter is to highlight alterations in physiology associated with these special populations, focusing in particular on how the altered physiology influences the behavior of anesthetic drugs. To translate this information into the clinical domain, the chapter aims to summarize dosing adjustments that account for body habitus (obese and morbidly obese) and age at both extremes (neonates and elderly).

Keywords

obesity
pharmacokinetics
elderly
neonate
age
size

TABLE 5.1 Anesthetic Considerations and Perioperative Challenges in Obese Patients

Weight-Related Condition	Challenge	Management Considerations
Redundant upper airway tissue	Obstructive sleep apnea Potential difficulty with airway management (more likely in males[107])	Continuous positive airway pressure to stent open the airway when appropriate (procedures requiring sedation, recovery from general anesthesia) Immediate availability of airway adjuncts (e.g., video laryngoscope, supraglottic airways, elastomeric bougie, fiberoptic bronchoscope) and patient positioning
Redundant tissue over chest and abdomen	Reduced functional residual capacity[108] With mechanical ventilation, may require high airway pressures to achieve adequate ventilation,[109] leading to an increased risk of barotrauma	*Induction of anesthesia:* Anticipate rapid drop in oxygen hemoglobin saturation once rendered apneic despite effective preoxygenation *Emergence from anesthesia:* Extubate to continuous positive airway pressure. Place head of bed to 45° to optimize pulmonary mechanics. Maintain plateau airway pressures <30 cmH_20, tidal volumes between 6-8 mL/kg, and judicious titration of positive end-expiratory pressure[110]
Gastroesophageal reflux disease[111]	Increased risk of aspiration	Avoid use of supraglottic airway devices.[112] Consider preoperative administration of a H_2-histamine antagonist[113]
Cardiovascular disease (hypertension,[114] coronary artery disease[115])	Increased likelihood of intraoperative myocardial ischemia and arrhythmias	Maintain mean arterial blood pressure within 10%-20% of preoperative blood pressure. When appropriate, monitor hemoglobin concentration, hemoglobin oxygen saturation, systolic and diastolic blood pressures, and heart rate to maintain adequate coronary artery perfusion, myocardial oxygen delivery, and reduced myocardial afterload.
Venous thromboembolism[116]	Deep vein thrombosis or pulmonary embolism	Prophylactic anticoagulation and intermittent pneumatic leg compression
Hyperglycemia/insulin resistance[117]	Perioperative hyperglycemia[118]	Consider insulin administration to maintain blood sugar concentrations in the 140-180 mg/dL range[119]



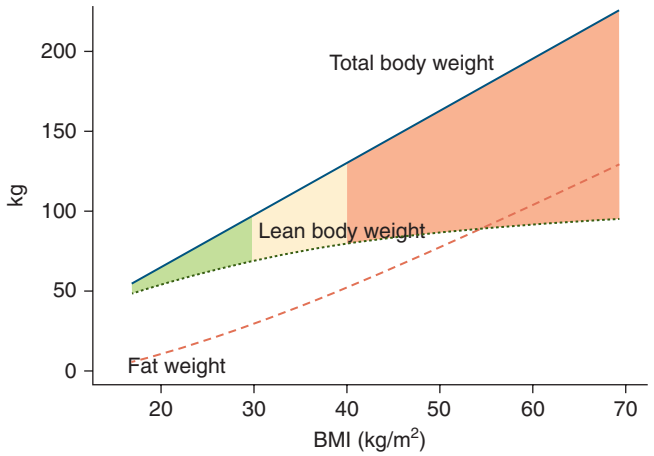
• **Fig. 5.1** Schematic summary of obesity-related physiologic changes that may alter anesthetic drug behavior *(blue)* and anesthetic considerations and perioperative challenges *(red). CAD,* Coronary artery disease; *DVT,* deep vein thrombosis; *FRC,* functional residual capacity; *HTN,* hypertension; *OSA,* obstructive sleep apnea; *PE,* pulmonary embolism

TABLE 5.2 Obesity Considerations for the American Society of Anesthesiologists (ASA) Physical Status Classification System

ASA Physical Status	BMI Range (kg/m^2)
1	≤30
2	31-39
3	≥40

TABLE 5.3 Selected Obesity-Related Physiologic Changes That Alter Anesthetic Drug Behavior

Physiologic Change
Increased cardiac output can alter early drug distribution (e.g., front-end kinetics)[120,121]
Reduced tissue perfusion slowing uptake of subcutaneous injections[2]
Increased or decreased hepatic cytochrome P450 microsomal enzyme function[122,123]
Alterations in hepatic drug biotransformation via uridine diphosphate glucuronosyltransferase[123,124]
Alteration in the glomerular filtration and/or renal tubular-mediated drug excretion[123,125]



• **Fig. 5.2** Relationship of total body weight (TBW), fat weight, and lean body weight (LBW) to body mass index *(BMI)* in a standard height male. The shaded areas mark the differences between LBW and TBW for non-obese and overweight *(green),* the obese *(yellow),* and the very obese *(red).* Note the near plateau of LBW with increasing BMI. (Adapted with permission from Ingrade et al.)

similar ways, it is difficult to generalize obesity-related changes across all classes of anesthetics.

Anesthetic Pharmacology in Obesity

Pharmacology is the study of drug dosing (see Chapters 2 and 3). Anesthetic pharmacology in the morbidly obese is challenging. Although many anesthetic drugs are traditionally dosed according to total body weight (e.g., in milligrams per kilogram or micrograms per kilogram per minute), most weight-based dosing guidelines (i.e., drug labeling in the official "package insert") are founded on data collected in subjects with normal body habitus. For most anesthetic drugs, the guidance that the dose should be altered as body weight increases might never have been tested in a rigorous way. In fact, when formulating an anesthetic regimen for a morbidly obese patient, using total body weight to calculate an appropriate dose is likely to lead to an overdose. This observation is a practical reality that anesthesiologists intuitively understand based on clinical experience. For example, a 120-kg patient does not require twice as much anesthetic as a patient of the same height who weighs 60 kg.

To address this, researchers have explored numerous weight scalars in an effort to minimize the risk of inadequate or excessive dosing in obese patients. The goal is to identify a dose for an obese patient that would behave similar to a conventional dose for a normal-sized patient. Some examples include ideal body weight (IBW), lean body mass (LBW), fat-free mass (FFM), adjusted body weight (ABW), and pharmacokinetic mass (PK mass). Table 5.4 presents the formulas used to calculate selected weight scalars. To provide a clinical context for these weight scalars, Table 5.5 presents examples of scaled weights for an obese and lean individual of the same height and the respective induction doses of commonly used intravenous anesthetics.

Of note from Table 5.5, using the IBW scalar yields doses that are equivalent, regardless of body habitus, the doses would likely be adequate for the lean but insufficient for the obese individual. Using LBW or FFM scalars yields doses that are lower for the lean individual but higher for the obese individual compared with IBW, but both may be inadequate, because LBW or FFM is what remains after fat mass is subtracted from TBW. Using LBW or FFM consistently results in underdosing for both lean and obese patients. Using ABW or PK mass scalars by contrast recommends doses that may be sufficient for induction for both the lean and obese individuals. Lean-scaled weight (LSW) is another weight scalar proposed for use in the operating room for drugs that scale consistent with LBW. It is based on LBW, TBW, and BMI and allows estimation of doses based on a percentage of TBW. LBW has not been validated in vivo.[5]

Identifying the optimal weight scalar has proven to be complex. To add to the complexity, the appropriate weight scalar for a bolus dose can differ from the scalar best suited for continuous infusion. Furthermore, weight scalar choice can vary by drug or drug class. Table 5.6 presents suggested weight scalars for selected anesthetics. Some have been identified through direct experimentation in obese patient populations, whereas others are assumed based on the premise that drugs of a similar class are likely to behave similarly because they often share similar physicochemical characteristics.

For anesthesia clinicians who use target-controlled infusions (TCI), obesity introduces the additional issue of selecting the appropriate pharmacokinetic model to drive the infusion. Although suitable pharmacokinetic models exist for many commonly used sedative-hypnotics, opioids, and neuromuscular blockers, some models are suboptimal when applied to special populations (e.g., extremes of weight or age). Furthermore, recent studies aimed at building new models for these special populations have not yet been incorporated into the software of TCI pumps.[6-8] This problem has forced the clinician to develop creative work-arounds to address the shortcomings of TCI models.[9]

The remainder of this section briefly discusses pharmacokinetic changes associated with obesity for selected sedative-hypnotics, opioids, and potent inhaled agents, reviewing examples of weight scalars and their limitations when used to formulate a rational dosing scheme. A brief review of available pharmacokinetic models used to drive TCI pumps is also provided.

TABLE 5.4 Selected Weight Scalars

Weight Scalar	Comments	Formula[126-128]
Total body weight (TBW)	The total weight of an individual	None
Real body weight (RBW)	The total weight of an individual	None
Ideal body weight[a] (IBW)[127]	The ideal weight associated with maximum life expectancy for a given height. Does not account for total body weight.	$IBW = 0.0022 * Ht^2$
Lean body weight (LBW)[129]	Accounts for total weight, height, and sex. An artifact of this formula is that at extremes of weight, lean body weight becomes increasingly smaller.	$LBW(male) = 1.1 * TBW - 128 * \left(\frac{TBW}{Ht}\right)^2$ $LBW(female) = 1.07 * TBW - 148 * \left(\frac{TBW}{Ht}\right)^2$
Fat-free mass (FFM)[126]	Like LBW, accounts for total weight, height, and sex. The FFM formula has addressed the limitation of the LBW formula at extremes of weight.	$FFM(men) = \frac{9270 * TBW}{6680 + (216 * BMI)}$ $FFM(women) = \frac{9270 * TBW}{8780 + (244 * BMI)}$
Adjusted body weight (ABW)[128]	Accounts for increased lean body mass and likely increased volume of distribution in obese individuals.	$ABW = IBW + 0.4 * (TBW - IBW)$
Pharmacokinetic mass (PK mass)[26,27]	Formulated for fentanyl only. Estimates the apparent pharmocokinetically (PK) active equivalent dosing weight	$PK\ mass = \frac{52}{\left[1 + \frac{196.4 * e^{-0.025 * TBW} - 53.66}{100}\right]}$
Lean-scaled weight (LSW)[5]	Proportional to LBW and normalized for sex, weight, and height.	LSW (men) = 11,432 * TBW/(6,680 + 216 * BMI) LSW (women) = 14,148 * TBW/(8,780 + 244 * BMI)

BMI, Body mass index (kilograms per meter squared); *Ht,* height (in centimeters).
[a]One of many formulas available for IBW.

TABLE 5.5 Scaled Weights and Induction Doses of Common Intravenous Anesthetics for a Lean and Obese Male Individual of the Same Height[a]

	Scaled Weight (kg)		PROPOFOL (2 mg/kg) Total mL of Propofol at 10 mg/mL[b]		FENTANYL (2 mg/kg) Total mL of Fentanyl at 50 µg/mL[b]		ROCURONIUM (0.6 mg/kg) Total mL of Rocuronium at 10 mg/mL[b]	
Dosing Scalar	Lean	Obese	Lean	Obese	Lean	Obese	Lean	Obese
Total body weight	60	120	12	24	2	5	4	7
Ideal body weight	66	66	13	13	3	3	4	4
Lean body weight	51	70	10	14	2	3	3	4
Fat-free mass	51	73	10	15	2	3	3	4
Adjusted body weight	64	88	13	18	3	4	4	5
Pharmacokinetic mass	58	93	12	18	2	4	4	6

[a]Induction doses are shown in milliliters. The lean individual weight 60 kg with body mass index of 20 kg/m^2. The obese individual body mass index is 40 kg/m.^{2} The lean and obese individuals are of the same height (173 cm)
[b]Dosed to the nearest milliliter.

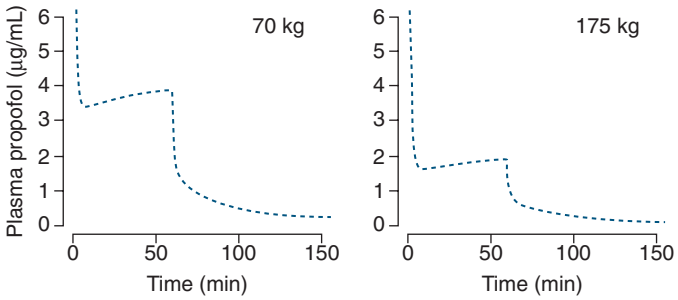
Sedative-Hypnotics

Propofol is the most comprehensively studied sedative-hypnotic in the obese population. TBW has been recommended for calculation of maintenance continuous infusion rates,[10] although recent work suggests using ABW to account for the nonlinear relationship between propofol clearance and TBW.[11] There are also many facets to consider when choosing a scalar for bolus dosing for induction of anesthesia. To avoid medication overdose, LBW has been proposed.[12] As illustrated in Table 5.5, however, use of this scalar might result in underdosing and ABW might be more appropriate.[13] With no established optimal weight scalar, recent work has explored other methods to determine the optimal bolus dose of propofol in obese patients.[14]

TABLE 5.6 Recommended Weight Scalars for Selected Intravenous Anesthetics

Drug	Bolus	Infusion
Sedatives		
Propofol	Loading dose titrated to target processed EEG level[14a]	ABW[11]
Midazolam	TBW[21b]	IBW[b]
Etomidate		IBW[130]
Opioids		
Fentanyl	PK mass	PK mass[26,27]
Remifentanil	FFM	FFM[22]
Sufentanil	TBW[28]	
Hydromorphone	LBW[131,132]	
Morphine	LBW[131,132]	
Neuromuscular Blocking Agents and Reversals		
Succinylcholine	TBW[133]	
Rocuronium	IBW[134]	
Vecuronium	IBW[135]	
Cisatracurium	IBW[136]	
Sugammadex	IBW[137]	

EEG, Electroencephalogram; *FFM,* fat-free mass; *IBW,* ideal body weight; *LBW,* lean body weight; *PK,* pharmacokinetic; *TBW,* total body weight in kg;
Weight scalars in parentheses are assumed based on data from other similar class drugs.
[a]Prior work has explored the use of several weight scalars for propofol. See text for details.
[b]Based on a single pharmacokinetic study.



• **Fig. 5.3** Pharmacokinetic simulation of an identical propofol dose (150-mg bolus injection followed by a 10-mg/min infusion for 60 minutes) administered intravenously to a 70-kg and a 175-kg patient (both 50 years old, 170 cm tall). Note the lower plasma levels in the larger patient. The simulation is based on the pharmacokinetic model of Cortinez et al.[15] (From Cortinez LI, Anderson BJ, Penna A, et al. Influence of obesity on propofol pharmacokinetics: derivation of a pharmacokinetic model. *Br J Anaesth.* 2010;105:448–456.)

One study compared induction of anesthesia with propofol based on LBW versus a loading dose (rapid propofol infusion) titrated to a target processed electroencephalographic (EEG) signal (bispectral index scale [BIS]). Patients induced using the LBW scalar required additional propofol doses to reach the same level of sedation[14] compared with patients titrated to a BIS value of 50. The bolus technique required substantially less time to administer but was not as effective. The loading dose approach led to a more consistent induction of anesthesia and no need for supplemental doses. Thus titrating to a target BIS might be a useful approach in this patient group because of the lack of clear dosing guidelines on a per kilogram basis.

It is clear that significantly obese patients require a moderately higher dose of propofol to achieve the same propofol concentration compared with lean patients. As illustrated in the pharmacokinetic simulation shown in Fig. 5.3, when an exceptionally obese patient receives the same absolute dose of propofol as a lean patient of the same height (i.e., a typical induction and infusion dose for a lean patient), lower propofol blood concentrations are produced. This conclusion is generally consistent with emerging knowledge regarding the impact of extreme obesity on the disposition of most intravenous anesthetic drugs.

With regard to TCI, there are several propofol pharmacokinetic models available to drive TCI pumps.[8,15-18] Data used to build these models included a variety of patient groups (i.e., lean and obese patients, pediatric and elderly patients). When constructing these models, several patient variables (i.e., age, TBW, LBW, and sex) were introduced into selected models to assess whether they improve model performance as determined by how well the model predicted measured plasma propofol concentrations.

When using a TCI pump in an obese patient, two important questions emerge: which pharmacokinetic model is optimal in the obese patient and what weight should be used (i.e., IBW, LBM, TBW)? Cortinez and colleagues studied how well selected propofol pharmacokinetic models predicted plasma propofol concentrations in a morbidly obese patient group[11] in an effort to identify the best model and weight scalar. They found that two models, the Schnider model and the Marsh model, performed best when using ABW. For propofol, using a modified weight scalar with the Schnider or Marsh model may be best suited for TCI in obese and morbidly obese patients. Both of these models are available in many commercial TCI pumps.

Perhaps the most versitile pharmacokinetic model for propofol was recently developed by Eleveld and colleagues.[8] They combined data from 21 propofol pharmacokinetics datasets that included elderly adults, obese adults, children, and normal-sized adult patients and volunteers. From these data they built a propofol pharmacokinetic model incorporating age, sex, and weight as covariates that performs well compared to other propofol models designed for specific-patient populations. This generalizable propofol pharmacokientic model has the abilty to cover a wide range of patient groups. An important caveat to consider when selecting a pharmacokinetic model is that differences in model predictions are likely overshadowed by significant interindividual variability. Many of the available propofol pharmacokinetic models will likely yield similar clinical results if titrated to effect in conjunction with processed EEG monitoring.

Unlike propofol, the influence of obesity of the pharmacokinetic behavior of other sedatives is not as well studied. Weight scalars for thiopental[19,20] and midazolam,[21] but not ketamine and etomidate, have been reported. Work with midazolam in obese patients found that as patient size increases, so does volume of distribution. However, the time to peak plasma concentrations and metabolism were the same regardless of body size. Elimination half-life for midazolam more than doubled compared with normal-sized counterparts, probably because of the large volume of distribution in morbidly obese patients. The clinical implications of this long elimination half-life were not evaluated, but the authors recommended that bolus doses be scaled to TBW and continuous infusion be dosed to IBW.

Opioids

Similar to propofol, remifentanil is perhaps the most well-studied opioid in terms of its pharmacologic behavior in obese patients.

Overall, the disposition of remifentanil in obese and lean patients is similar, but obese patients do indeed require a higher dosage. Researchers have identified that FFM provides a reasonable weight scalar for continuous infusions.[22] With regard to TCI, several pharmacokinetic models[6,22,23] have been devleoped from data collected in a wide range of patient sizes optimizing model predictions using weight, age, and sex as covariates. Many of the model parameters were scaled to LBM (Minto model),[23] modifications of LBM (La Colla model)[22] or an allometric scaling of TBW among other covariates (Kim model).[6] Although the Minto model is the most widely used model for TCI administration of remifentanil, it is known to have serious problems when applied to very obese patients, in part because not many obese patients were included in the dataset from which the model was built (and because of faulty equations for the estimation of LBM).[24] Because of these shortcomings in the Minto model, various work-arounds have been proposed that include entering "fictitious" body weights during initiation of TCI therapy; this approach can be useful but is obviously suboptimal.[22,25] The Kim model addresses the problems associated with the Minto model by including numerous obese subjects into the model dataset and by using updated equations for estimation of body mass indices such as LBM. As the Eleveld model for propofol, the Kim model for remifentanil may prove advantageous in obese patients but has not been clinically validated.

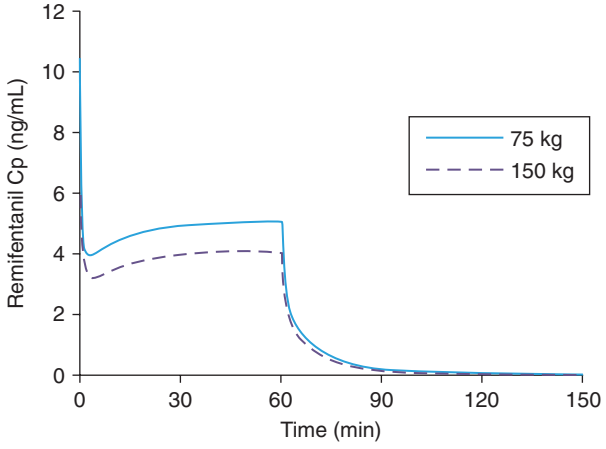
Recent work has combined previously published datasets to refine pharmacokinetic models (see the "Emerging Developments" section). Consider the series of simulations based on the model of Kim and colleagues to visualize the influence of weight on the pharmacologic behavior of remifentanil (see Figs. 5.4 through 5.6). In the first simulation, predicted remifentanil plasma concentrations are plotted over time for an equivalent bolus dose followed by a 60-minute infusion administered to a lean and obese individual of the same age and height (Fig. 5.4). Predicted plasma concentrations were approximately 78% lower in the obese individual. In the second simulation (Fig. 5.5), the authors explore what infusion rate (in micrograms per minute) would be necessary to maintain a target plasma concentration of 5 ng/mL for 30 minutes, a concentration known to provide analgesia across weights of 50 to 200 kg. Infusion rates were nearly doubled to achieve the target concentration over this weight range. Because of remifentanil's rapid clearance, the required infusion rates stabilize after approximately 25 minutes. In a third simulation, the authors predicted the cumulative remifentanil dose for three individuals (lean young individual, lean elderly individual, and obese young individual) to maintain a target plasma concentration of 5 ng/mL for a 5-hour infusion (Fig. 5.6). The cumulative dose for the young obese individual was approximately 125% of the young lean individual. This set of simulations provides a visual illustration of the increased dosing requirements for heavier patients.

Unlike propofol and remifentanil, relatively little work has explored how obesity affects fentanyl pharmacokinetics. Shibutani and colleagues[26,27] characterized a nonlinear relationship between fentanyl clearance and TBW and recommended use of a modified weight, called the *pharmacokinetic mass,* which resulted in effect site concentrations in obese patients that were similar to effect site concentrations in lean patients.

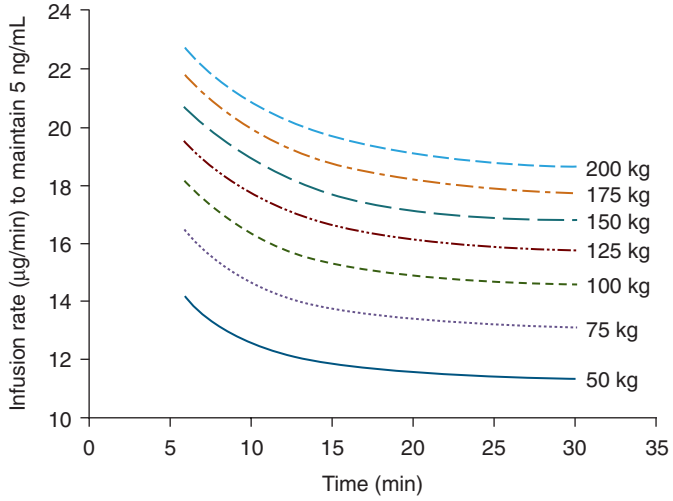
For other opioids, even less information is available. Some work has explored sufentanil pharmacokinetics in obese patients, and similar to midazolam, a linear increase was reported in the volume of distribution with an increase in TBW but similar clearance between lean and obese individuals.[28] The authors suggest that for bolus dosing TBW be used and continuous infusions be judiciously reduced. Use of a sufentanil pharmacokinetic model[29] may be suitable for sufentanil TCIs in morbidly obese patients.[30]

Inhaled Anesthetics

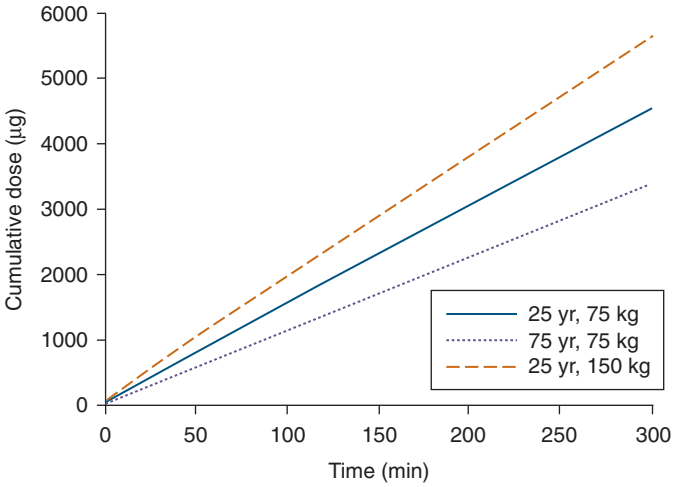
A common perception of potent inhaled agents is that they accumulate in obese more than lean patients and that this prolongs emergence. Research, however, has not confirmed this perception.[31]



• **Fig. 5.4** Computer simulations of plasma concentration *(Cp)* predictions versus time for an identical dose (not weight-adjusted) administered intravenously to 75- and 150-kg subjects (both 25 years of age and height 175 cm) using the Kim model. The simulated dosing regimens consisted of a 50- µg bolus injection followed by a 15-µg/min continuous infusion for 60 minutes. (Reprinted with permission from Kim KT, Obara S, Egan TD, et al. Disposition of remifentanil in obesity: a new pharmacokinetic model incorporating the influence of body mass. *Anesthesiology.* 2017;126:1019–1032.)



• **Fig. 5.5** Simulation of infusion rate (in micrograms per minutes) requirements to achieve a target plasma concentration of 5 ng/mL over 30 minutes for a range of body weights assuming an age of 50 years and height of 175 cm. (Reprinted with permission from Kim TK, Obara S, Egan TD, et al. Disposition of remifentanil in obesity: a new pharmacokinetic model incorporating the influence of body mass. *Anesthesiology.* 2017; 126:1019–1032.)



• **Fig. 5.6** Simulation of the cumulative remifentanil doses (in micrograms) required to achieve and maintain a plasma concentration of 5 ng/mL over time when administered by target-controlled infusion for a 25-year-old, 75-kg subject *(solid line)*; a 75-year-old, 75-kg subject *(dotted line);* and a 25-year-old, 150-kg subject *(dashed line).* All subjects for these simulations are assumed to be 175 cm tall. (Reprinted with permission from Kim TK, Obara S, Egan TD, et al. Disposition of remifentanil in obesity: a new pharmacokinetic model incorporating the influence of body mass. *Anesthesiology.* 2017; 126:1019–1032.)

Two pharmacokinetic factors contribute to this observation. First, the time required for adipose tissue to equilibrate with the inspired volatile anesthetic concentration is long; the times required to achieve 63% of the final equilibrium in adipose tissue for desflurane and isoflurane exceed 22 and 35 hours, respectively.[32,33] Second, blood flow to adipose tissue *decreases* with increasing obesity,[34] reducing the overall delivery of drug to this tissue bed.

Based on their pharmacokinetic profiles, there could be some advantage to choosing one potent inhaled agent over others. Desflurane has a faster washout and improved recovery compared with sevoflurane in obese individuals when no premedication is used.[35] With a quicker recovery,[36] desflurane might be well suited for use in this patient group to minimize adverse effects related to slow emergence in patients with limited oxygen reserves as a result of a reduced functional residual capacity. Given the pronounced interaction between volatile anesthetics and opioids or sedatives, addition of midazolam or fentanyl will likely reduce desflurane's advantages over sevoflurane.[37]

Neuromuscular Blocking Drugs

Formulating a rational dosage scheme for neuromuscular blockade in obese patients can be challenging given the increased likelihood of difficult intubation, the need for excellent intubating conditions on the first attempt, and the need to provide mask ventilation should intubation be unsuccessful. Prior work suggests that TBW is appropriate for succinylcholine and IBW is appropriate for nondepolarizing agents (see Table 5.6). As a rule of thumb, clinicians sacrifice onset time with a lower total dose but gain a faster recovery (see Chapter 22).

Succinylcholine was studied in 45 morbidly obese patients (BMI > 40 kg/m^2) comparing a dose of 1 mg/kg using three different weight scalars: IBW, LBW, and TBW. Across groups, there was no difference in onset time. Longer recovery time correlated with the larger overall dose (e.g., 1 mg/kg using TBW being the largest), although recovery times were relatively short compared with other longer-acting neuromuscular blocking drugs. Intubating conditions were adequate in all groups, but laryngoscopic view was better in the group dosed to TBW. The authors recommended dosing succinylcholine based on TBW,[38] prioritizing the laryngoscopic view over duration of blockade.

Studies comparing TBW and IBW as the basis for dosage calculation for rocuronium in morbidly obese patients found that at a dose of 0.6 mg/kg using TBW led to a prolonged duration of action but did not improve intubating conditions compared to IBW.[39,40] Similar results have been observed with vecuronium.[41-43] Thus the consensus is to dose rocuronium and vecuronium to IBW to achieve a shorter duration of blockade without compromising intubating conditions.

For neuromuscular blockade reversal with sugammadex, weight scalar recommendations vary. Some authors recommend using IBW and others suggest using ABW,[44,45] whereas a pooled analysis of 1418 adult obese patients led to a recommendation that sugammadex be dosed according to TBW.[46] Given the favorable sugammadex safety profile, dosing to TBW is a reasonable approach. Reversal doses are a function of blockade depth. Use of a peripheral nerve stimulator capable of quantitative train-of-four monitoring allows accurate determination of blockade depth and the appropriate sugammadex dose. In brief, profound (no train-of-four, no posttetanic twitch), deep (no train-of-four, one or more posttetanic twitches), moderate (one to three train-of-four count), shallow (train-of-four ratio 0.1-0.4), and minimal (train-of-four ratio > 0.4) blockade are reversed with 16, 4 to 8, 2, 2, and 2 mg/kg of sugammadex, respectively.

An interesting feature of sugammadex reversal is that it can be used to provide rapid reversal after administration of high-dose rocuronium (e.g., 1.2 mg/kg) following a rapid sequence induction. In an emergency setting of "can't intubate and can't oxygenate," deep blockade by rocuronium can be completely reversed faster than spontaneous recovery from an intubating dose of succinylcholine (1 mg/kg).[47] Although sugammadex reversal is fast regardless of blockade depth, a simulation study concluded that residual effects from induction doses of sedatives and opioids may persist after blockade reversal.[47] Thus, although they are no longer paralyzed, patients can remain unresponsive or have significant respiratory depression. If both unresponsiveness and respiratory depression exist, patients might not be able to self-rescue from a "can't intubate–can't oxygenate" scenario. Given that obese patients have reduced functional residual capacity and a shortened time to oxygen-hemoglobin desaturation when rendered apneic despite adequate preoxygenation, they are at increased risk for hypoxia.[47] Another important consideration when administering a large sugammadex dose (e.g., 16 mg/kg) is that the dose might not be immediately available at the point of care without proper preoperative planning and preparation.

Local Anesthetics

The safe dose of local anesthetics varies with the route of administration, the properties of the local anesthetic, and the addition of epinephrine. Plasma concentrations are the highest after intercostal nerve block and decrease as follows: intercostal > caudal > epidural > brachial plexus > sciatic/femoral.[48] Plasma concentrations of local anesthetics do not correlate well with body weight or BMI in adults but correlate better with weight in children.[49-51] Local anesthetic toxic doses have not been well studied in obese patients. The widely recommended axiom of the smallest effective dose is appropriate in this patient population.

Pediatric Patients

When formulating an anesthetic dosing regimen for a pediatric patient, an important consideration is that children are not miniature adults. Anatomic and physiologic changes that occur between the newborn period and adult life have important pharmacologic implications. In part because the early drug development process is focused on adult volunteers and patients, these developmental changes are often not well accounted for in available dosing guidelines. Ideally, dosing recommendations should be based on research in children along all phases of development and maturation to characterize drug pharmacokinetics and pharmacodynamics properly. Unfortunately, detailed information along these lines is not available for most anesthetics.

Given the cost of drug development, pharmaceutical companies often seek approval from regulatory agencies for adults, but not children. As such, many anesthetics are administered "off-label" using adult doses scaled to pediatric patients. In response, the United States National Institute of Childhood Health and Human Development formed the Pediatric Pharmacology Research Unit Network in 1994, and in 1997, the U.S. Food and Drug Administration (FDA) developed the Modernization Act[52] to incentivize drug research in pediatric patients by extending the duration of market exclusivity for approved drugs.

One challenge is to account for changes in body composition, metabolic capacity, and body surface area that occur with age. Several approaches have been explored (e.g., dosing based on body surface area or allometric scaling), but the most common approach is to use weight-normalized dosing according to age (e.g., where available milligrams per kilograms for neonates up to 44 weeks' postconception in age), infants (1-12 months of age), and children (up to 12 years of age).

Physiologic Changes in Pediatric Patients

Neonates, infants, and children present anesthesiologists with challenges throughout the perioperative period. Selected physiologic changes such as differences in airway anatomy, chest wall and respiratory system function, and cardiovascular function place this patient group at increased risk for adverse airway and respiratory events as well as other pediatric issues (Table 5.7, Fig. 5.7). For many of these physiologic changes, inherent variability is associated with maturation and interpatient and intrapatient differences that influence anesthetic drug behavior and alter dosing considerations.

For example, neonates and infants have greater total body water than their adult counterparts, resulting in a larger volume of distribution with water-soluble drugs such as succinylcholine and many antibiotics. With a larger volume of distribution, a higher initial loading dose is required to achieve therapeutic plasma concentrations. Neonates also have lower serum albumin and total protein concentrations, resulting in higher free plasma levels of highly protein-bound drugs, such as bupivacaine, opioids, sedatives, and antibiotics. The kidneys and liver of neonates are immature compared with those of adults. The developmental physiology of the liver is complex, but in general hepatic enzymatic drug metabolism is decreased in neonates, and the neonatal liver receives disproportionately less cardiac output than an older child or adult. The neonatal kidney is less efficient, prolonging the half-life of drugs primarily excreted through the kidneys. Neonates also have a decreased proportion of body mass as fat and muscle, which can prolong drug effects depending on redistribution into those tissues.

Anesthetic Pharmacology in Pediatric Patients

In general, anesthesiologists can expect significant variability in anesthetic dosing of pediatric patients.[53] Thus only general dosing guidelines are possible for most anesthetic drug classes. A brief discussion of dosing recommendations for selected anesthetics is provided in the following text and summarized in Table 5.8.

Inhaled Anesthetics

Potent inhaled agents are frequently used in pediatric anesthesiology because of their utility for mask induction. The minimum alveolar concentration (MAC) varies with age (see Table 5.8): neonates have a MAC 20% less than that of infants,[54] and premature infants have an even lower MAC.[55] MAC increases through infancy until age 3 to 5 and then declines steadily with age.[56,57] In general, the MAC of an infant is 1.6 to 1.8 times the MAC of a 40-year-old adult, and the MAC of a premature infant is 1.2 to 1.6 times lower than that of an infant. With significant interpatient variability, anesthesiologists titrate the dose of inhaled agents and administer intravenous adjuncts (e.g., opioids, nonsteroidal antiinflammatory drugs) to meet anesthetic requirements (e.g., minimize patient movement, maintain blood pressure, blunt or block the response to a painful stimuli).

Propofol

Comparison to other anesthetics, propofol has been well characterized in neonates and children. Prior work has established that dosing by TBW is best and that children can require up to 50% to 100% more propofol than in adults.[58] For example, neonates required a 3-mg/kg bolus to tolerate chest tube removal. Of note, propofol is metabolized more slowly in neonates compared with children until about 3 months of postnatal life or 54 weeks' postgestational age.[59]

A serious concern with propofol when administered to pediatric patients for sedation during mechanical ventilation is propofol infusion syndrome. Development of the syndrome is more likely when propofol is administered at rates above 67 μg/kg per minute (4 mg/kg per hour) for more than 48 hours. Presenting signs include hyperlipidemia, rhabdomyolysis, refractory bradycardia leading to asystole, and/or lactic acidosis.[60] The syndrome is often lethal; treatment consists of discontinuing propofol and supportive care. Early diagnosis of propofol infusion syndrome is key to achieving a good outcome. The mechanism of propofol infusion syndrome is unclear, but one hypothesis is that propofol disrupts mitochondrial fatty acid metabolism to cause an accumulation of fatty acids that can induce life-threatening ventricular arrhythmias.[61] Another hypothesis suggests that propofol impairs mitochondrial function, disrupting electron transport and oxidative phosphorylation, causing metabolic acidosis and cellular hypoxia.[62]

Midazolam

Midazolam is a useful adjunct and premedication to minimize separation anxiety and fear and can be administered by multiple routes (intranasal, intravenous, rectal, oral, intramuscular, or sublingual, see Table 5.8). When administered as an intravenous bolus, its anxiolytic effect begins within 1 to 2 minutes, giving the impression that it is a fast-acting drug. Although it has a rapid onset of anxiolytic effect, it requires 6 to 9 minutes to reach peak effect and has a long decrement time. When administered by mouth, midazolam has a slower onset of effect (20-30 minutes). Suggested oral doses of 0.5 to 0.75 mg/kg should be administered

TABLE 5.7 Anesthetic Considerations and Perioperative Challenges in Neonates and Infants[138]

Neonate-/Infant-Related Condition	Challenge	Management Considerations
Airway anatomy • Large head with prominent occiput • Large tongue • Preferential nose breather—breathing difficult with excessive secretions • Glottic opening at level of C3-C4 • Long epiglottis—can flop posteriorly • Narrowest segment of the airway is subglottic	Airway obstruction Difficult laryngoscopy	Position head and neck to maintain in a neutral position Where feasible, maintain patent nasal passages Consider small endotracheal tube to minimize postextubation stridor Position endotracheal tube to avoid inadvertent extubation or endobronchial intubation with head movement (target 1 cm above the carina)
Chest wall anatomy and pulmonary physiology • Compliant chest wall • Ventilation is primarily from the diaphragm • Ventilation is rate dependent • Closing volume is larger than the functional residual capacity (until age 6 years) • Work of breathing may exceed 15% of oxygen delivery • Thick-walled alveoli • Fewer alveoli (10% of adult) • Frequent postoperative apneas in premature infants	Limited respiratory reserve Reduced functional residual capacity that is further reduced with apnea and anesthesia Airway closure at expiration and rapid respiratory muscle fatigue Apneas longer than 15 seconds or associated with hypoxia and bradycardia	*Induction of anesthesia:* Anticipate rapid drop in oxygen hemoglobin saturation once rendered apneic despite effective preoxygenation Consider decompressing stomach if abdominal pressure is limiting diaphragm movement. Caution with aggressive bag mask ventilation Consider using positive end-expiration pressure, continuous positive airway pressure, or intermittent positive-pressure ventilation to stent open airway and reduce work of breathing Vigilant postoperative respiratory monitoring in high-risk neonates and infants Consider caffeine 10-20 mg/kg oral or intravenously
Cardiovascular system • Fixed stroke volume • Cardiac output is heart rate dependent • High vagal tone	Prone to bradycardia and low cardiac output	Treat neonates with heart rate <100 beats/min with restoration of oxygenation and epinephrine 10 μg/kg
Volume status • Immature renal function • Large surface area relative to weight • Larger extracellular volume	Dehydration	Maintain urine output 1-2 mL/kg
Hepatic function	Decreased opioid metabolism	Prolonged opioid effect
Metabolism • Limited glycogen reserves • Immature thermoregulation	Hypoglycemia Hypothermia	Glucose infusion in neonates at risk Consider techniques to increase core body temperature (ambient temperatures of 32°C-34°C for neonates and premature infants)
Central nervous system • Immature blood brain barrier • Opioids and antibiotics easily cross the blood-brain barrier	Prolonged and variable duration of action	Consider judicious dosing of opioids

30 minutes before parental separation to achieve anxiolysis and sedation for children between the ages of 1 and 10 years.[63]

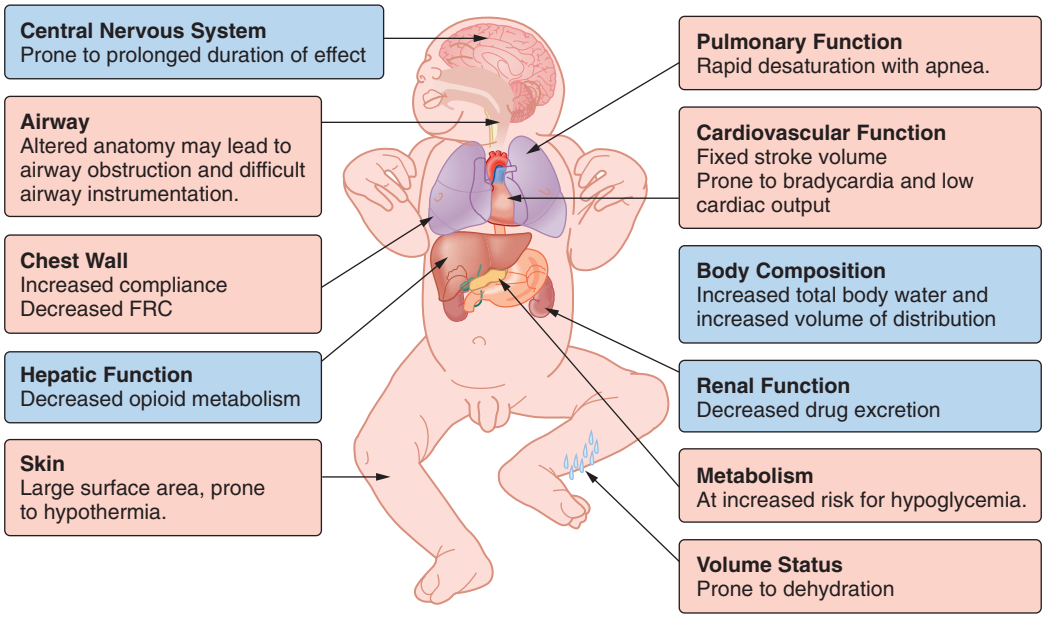
When considering use of midazolam as an anxiolytic, a few features of its pharmacologic profile merit consideration. Midazolam is metabolized primarily by the hepatic microsomal enzyme cytochrome P 450 (CYP) 3A4 and has an active metabolite, α-hydroxy-midazolam. Patients with impaired hepatic function can have an altered response. Although the pharmacokinetics of midazolam have been well characterized, the pharmacokinetics of α-hydroxy-midazolam are not well known. This active metabolite may be responsible for an unexpectedly long duration of midazolam's effect, although this is largely speculative.

Etomidate

Pharmacokinetic information on etomidate in pediatric patients is limited. A study of the pharmacokinetics of etomidate in 49 children older than 6 months of age concluded that younger children have greater clearance and an increased central compartment volume and thus require a larger bolus dose than older children. The authors recommend an age-based dose rather than weight-based.[64] In a study of neonates and infants with cardiac disease, a significantly lower clearance of etomidate was observed than in the previous study, as well as a high degree of variability in etomidate pharmacokinetics.[65]

Ketamine

Similar to midazolam, ketamine can be administered as a premedication via several routes (intravenous, transmucosal, oral, or intramuscular; see Table 5.8). Ketamine can provide sedation and analgesia with minimal respiratory or cardiovascular depression but does have adverse side effects such as dysphoria and excessive salivation. To minimize salivation, ketamine can be combined with



• **Fig. 5.7** Schematic summary of anesthetic considerations *(blue)* and perioperative challenges *(red)* in neonates and infants. *FRC,* Functional residual capacity.

TABLE 5.8 Dosing Considerations of Selected Anesthetics in Pediatric Patients

Drug	Route of Administration	Dose
Sedatives		
Propofol[139,140]	IV: Induction (age >3 yr)	2.5-3.5 mg/kg
	IV: Sedation (infusion)	125-150 µg/kg/min
Midazolam[140-143]	PO: Premedication	0.25-0.5 mg/kg (maximum 20 mg)
	Intranasal: Premedication	0.2-0.3 mg/kg
	IV: Premedication	0.05 mg/kg
	Intranasal: Sedation	0.2-0.3 mg/kg (maximum 10 mg per dose)
	IM: Sedation	0.1-0.15 mg/kg
	IV: Sedation (age 6 mo to 5 yr)	0.05-0.1 mg/kg (maximum 6 mg)
	PR: Sedation	1 mg/kg
	SL: Sedation	0.5-0.75 mg/kg
	IV infusion: Sedation (neonates <32 wk)	0.03 mg/kg per hour
	IV infusion: Sedation (neonates >32 wk)	0.06-0.12 mg/kg per hour; titrate to effect
Etomidate[65,140,144,145]	IV: Induction	0.3 mg/kg (0.2-0.6 mg/kg)
	IV: Sedation	0.1-0.3 mg/kg; repeat as needed
Ketamine[140,146-148]	PO: Premedication	6-10 mg/kg
	IM: Premedication	3-7 mg/kg
	IV: Sedation	0.5-2 mg/kg per dose
	IV: Induction	1-2 mg/kg
	IV: Analgesic	0.1 mg/kg
	IV: Analgesic (infusion)	0.1-0.3 mg/kg per hour

TABLE 5.8 Dosing Considerations of Selected Anesthetics in Pediatric Patients—cont'd

Drug	Route of Administration	Dose
Opioids		
Fentanyl[149-151]	IV bolus: Analgesic	1-2 μg/kg
	IV bolus: Loading dose	5-10 μg/kg
	IV: Infusion	1-3 μg/kg per hour
	Intranasal	1-2 μg/kg
	Oral transmucosal fentanyl	5-15 μg/kg
Remifentanil[149,152,153]	IV: Bolus	1 μg/kg
	IV: Infusion	0.25-3.0 μg/kg per minute
Sufentanil[154-156]	IV bolus: Loading dose	1-2 μg/kg
	IV: Infusion	0.1-0.2 μg/kg per hour
	Intranasal	2 μg/kg
Hydromorphone[149,157]	PO (children)	0.05 mg/kg q4-6h
	PO: (adolescents)	1-4 mg-dose q4-6h
	IV: Bolus	5-10 μg/kg q4-6h
	IV: Continuous	3-5 μg/kg per hour
	Caudal	10 μg/kg
Morphine[158-160]	PO: Immediate release	0.3 mg/kg per dose q4-6h
	PO: Continuous release	0.3-0.6 mg/kg per dose q12h
	IV: Infusion (neonates)	0.01-0.02 mg/kg per hour
	IV: Infusion (children)	0.01-0.04 mg/kg per hour
	Caudal	30-50 μg/kg
	Intrathecal	5-7.5 μg/kg
Neuromuscular Blocking Agents and Reversal		
Succinylcholine[161-163]	IV: Fast onset	1.5-2 mg/kg
	IM	4 mg/kg
Rocuronium[164,165]	IV: Intubation	0.3-1.0 mg/kg
	IV: Maintenance	0.1 mg/kg
Vecuronium[166,167]	IV: Intubation	0.05-0.1 mg/kg
	IV: Maintenance	0.02 mg/kg
Cisatracurium[168,169]	IV: Intubation	0.1-0.2
	IV: Maintenance	0.02-0.05
Sugammadex[170,171]	IV (train of four 1-2/4)	2-4 mg/kg
	IV (profound paralysis)	16 mg/kg

Inhaled Anesthetics

Drug	Indication	MAC
Isoflurane	Preterm (<32 wk)	1.28[172]
	Preterm (32-37 wk)	1.41[172]
	7-30 mo	1.69[173]
	Effect of N_2O	MAC = 1.69 − 1.45 × N_2O fraction[173]
	4-10 yr	1.69[174]
	Effect of temperature	1.47 (34°C), 1.22 (31°C)[174]
	4-9 yr	1.27 (MAC_{EXT})[175]
Sevoflurane	Neonates	3.3[176]
	1-6 mo	3.2[176]
	6-12 mo	2.5[176]
	1-3 yr	2.6[176]
	2-12 yr	2.3-2.5,[176,177] 2.90 (MAC_{INT}),[178] 1.60-1.70 (MAC_{EXT})[179,180]
	1-3 yr with N_2O 60%	2[56]
	2-6 yr	1.45 (MAC_{BAR})[181]
		0.57 (with fentanyl 2 μg/kg) (MAC_{BAR})[181]
		0.35 (with fentanyl 4 μg/kg) (MAC_{BAR})[181]
Desflurane	Neonates	9.16[182]
	1-6 mo	9.42[182]
	6-12 mo	9.92[182]
	1-3 yr	8.72[182]
	3-5 yr	8.62[182]
	5-12 yr	7.98,[182] 7.7 (MAC_{EXT})[179]

IM, intramuscular; *IV,* intravenous; *MAC,* minimum alveolar concentration; MAC_{BAR}, MAC for abolition of sympathetic response to incision; MAC_{EXT}, MAC for deep extubation; MAC_{INT}, MAC for intubation; N_2O, nitrous oxide; *PO,* oral; *PR,* rectal administration.

an antisialogogue, and to minimize dysphoria it can be combined with a benzodiazepine.

Like midazolam, ketamine is also metabolized primarily by the hepatic microsomal enzyme enzymes CYP 3A4 and to a lesser extent 2B6 and 2C9. Ketamine has two active metabolites: norketamine and dehydronorketamine. When administered intranasally, S-ketamine achieves peak effect in approximately 18 minutes, but there is significant interpatient variability in plasma concentrations and absorption times.[66]

For intramuscular injection, the time to peak concentration is shorter (15 minutes). For this route of administration, ketamine bypasses the portal circulation. As such, ketamine concentrations are much higher than norketamine concentrations, and without the first-pass effect, norketamine concentrations peak at 1 to 2 hours. By way of comparison, equianalgesic plasma concentrations for orally administered versus intramuscularly administered ketamine are 40 and 150 ng/mL. These discrepancies are likely a function of differences in norketamine concentrations.[67]

Opioids

Although morphine pharmacokinetics in neonates are well established, the efficacy of morphine at clinically used doses is more ambiguous. A study of 140 preterm neonates randomly assigned to receive an intravenous loading dose of morphine 100 μg/kg or saline solution placebo during endotracheal suctioning revealed only a mild analgesic benefit (as determined by multiple validated pain measurement instruments).[68] A study of 20 children aged 3 days to 6 years given 0.15 mg/kg morphine intravenously after congenital cardiac surgery showed an increased dose per kilogram needed in children 1 to 6 months of age but a high degree of variability in morphine disposition.[69]

Clinical experience suggests that younger patients, particularly infants, are quite sensitive to the effects of opioids such that opioids typically produce more profound and longer duration of effect in younger children. Because the enzymatic metabolism of remifentanil is largely mature in children, some experts have asserted that remifentanil is well suited for use as an intraoperative opioid in children.[70]

Neuromuscular Blocking Drugs

Intravenous rocuronium 0.6 mg/kg generally produces intubating conditions 1 to 4 minutes after administration in children, and 1.2 mg/kg decreases the time to less than 1 minute to 3 minutes. Succinylcholine 2 mg/kg IV bolus produces 100% block in less than 1 minute after administration.[71]

Anesthetic Toxicity in Neonates and Infants

A major emphasis of anesthetic clinical pharmacology research in recent years has been the exploration of anesthetic toxicity in neonates and infants. There is concern that exposure to anesthetics early in life, especially repeated exposure, may be associated with decreased cognitive performance later in life. Major sources of evidence include in vitro toxicity studies, clinical studies in animal models, and retrospective, hypothesis-generating data-mining studies in humans. This effort has gained worldwide attention and has prompted regulatory agencies to issue practice advisories regarding the use of common anesthetics in pediatric patients. Prospective, longitudinal studies are ongoing.

Research exploring formation of neuronal networks and synaptic contacts (developmental synaptogenesis) indicates that this process primarily occurs during the last trimester in utero and the first few years of life, with the first several months of neonatal life being the most intense period as the brain increases in size and neuronal connections.[72,73] The neurotransmitters gamma-aminobutyric acid and glutamate play an important role in developing these neuronal connections. Central nervous system depression by anesthetics alters the balance of excitatory and inhibitory synaptic transmission. Although transient, this imbalance can cause apoptosis of developing neurons and glia.

The neurodegenerative effect of anesthetics on infants has been confirmed across several mammalian species, resulting in neurotoxicity and both short- and long-term behavioral changes. The relationship between the duration of synaptogenesis and the length and number of anesthetic exposures is complex, but even a single exposure during active synaptogenesis can produce neurodegeneration. In rodents, timing seems more critical than duration as a determinant of damage. In higher mammalian brains, both a single long exposure and multiple shorter exposures impair neurocognitive development. Although behavioral studies suggest cognitive and emotional deficits in addition to morphologic changes, causality between the observed morphologic changes and behavioral problems has not been demonstrated. Although this has implications not only in providing general anesthesia for procedures in pregnant women and children but also in children requiring sedation in the intensive care unit, there are limitations to the animal data, including the difference between anesthetizing healthy animals in contrast to children with comorbidities requiring anesthesia and attention in the intensive care unit. Furthermore, there are questions about the generalizability of daily anesthetic exposures in animals.[74,75]

Retrospective clinical studies have explored potential connections between early anesthetic exposure and cognitive changes in humans to include failure to reach developmental potential, an increase in hyperactive disorders, learning disabilities, and other cognitive and behavioral impairments.[76] Age at exposure and duration and number of exposures appear to be important factors in the development of these deficits. Given that this body of work is retrospective, it does not control for confounders that might influence interpretation of the findings. Thus, as there is insufficient evidence that anesthetic exposure up to age 3 years of age in humans is associated with cognitive deficits, it remains controversial as to whether findings in animal studies can be applied to humans.

Several clinical studies are investigating the relationship between exposure to anesthesia and neurocognitive deficits. Some of these include the Pediatric Anesthesia and Neurodevelopment Assessment (PANDA), the Mayo Anesthesia Safety in Kids (MASK) study, and the General Anaesthesia compared to Spinal anaesthesia (GAS) study. PANDA, a multicenter study, explored the long-term cognitive effects of anesthesia between two groups: those who receive an anesthetic for an inguinal hernia repair up to 3 years of age and their siblings who have not had an exposure to an anesthetic before age 3 years. The neurocognitive effects were evaluated from ages 8 to15 years and no difference was found between the groups. The GAS study compared awake-spinal anesthesia to sevoflurane-based general anesthesia in children younger than 60 weeks but born at more than 26 weeks' gestational age who required inguinal hernia repair. Interim findings from the GAS study showed that sevoflurane anesthesia less than 1 hour in duration did not increase the risk of adverse neurodevelopmental outcome at age 2 years compared to awake-regional anesthesia, with further assessment at 5 years.[77] Thus far, the PANDA study has not shown any difference in mean scores of the secondary assessments.[78] The MASK study compared results from neurocognitive tests in children younger than the age of 3 years who have received one or more anesthetics with age-matched children with no exposure to anesthesia. Results

from the MASK study showed no significant difference in intelligence quotient as adolescents between singly and multiply exposed children, although processing speed and fine motor skills were reduced in children who had multiple exposures.[78a]

Although informative, these observational studies are not able to account for inherent differences between children who require procedures with exposure to anesthesia and children who do not. Children who require surgery and anesthesia at a young age may be predisposed to neurodevelopment delays related to the severity of an illness and/or the surgical procedure and not the anesthetic exposure itself.[79] Some have voiced concern that the FDA warning might cause unnecessary delays in procedures that require an anesthetic, leading to poor patient outcomes.[80] Multiple European societies also recently published a consensus statement in response to the FDA warning stating that although anesthesiologists should provide adequate information and try to avoid unnecessary risks, there is no compelling evidence to change anesthetic practice.[81]

Given that the PANDA and GAS studies provide some clinical evidence that a single, relatively brief exposure to general anesthesia in otherwise healthy children is unlikely to cause clinically detectable deficits in global cognitive function or serious behavioral disorders, the FDA acknowledges that anesthetic drugs are at times needed for young children and pregnant women who require painful procedures. As such they recommend that patients in their third trimester of pregnancy or young children proceed with medically necessary procedures. However, they recommend giving strong consideration to delaying elective procedures in these patient groups until the individuals at risk are older than 3 years of age.[82]

Further research is warranted to explore possible subtle behavioral effects, vulnerable ages of exposure, gender differences, and variability among specific anesthetic drugs. Specifically, studies that explore the use of protocols that minimize anesthetic exposure through the use of short-acting drugs, adjuvants, multimodal pain therapy, and/or local or regional techniques might provide important insights into optimizing care for this patient group.

Elderly Patients

Anesthesiologists recognize that elderly patients require reduced anesthetic doses to produce a desired effect and avoid unwanted adverse effects. Although the mechanisms underlying this increase in anesthetic drug sensitivity are incompletely understood, the dose of most anesthetics can by reduced by 25% to 75% to achieve a near-equivalent effect compared with young healthy adults. We briefly discuss physiologic changes that influence anesthetic drug behavior (Table 5.9, Fig. 5.8) and considerations of dosing of common anesthetics (Table 5.10) in the elderly.

Physiologic Changes in the Elderly

Several important age-related physiologic changes likely influence how elderly patients respond to anesthetics. Physiologic changes include a loss of important anatomic units, such as neurons, nephrons, and alveoli, and a deterioration of metabolic regulatory processes at a molecular level,[83] among many others. In general, healthy elderly people maintain reasonable basal physiologic organ function. However, under the stress of anesthesia and surgery, their physiologic reserves are tested and can be substantially diminished. Although age is an independent risk factor for poor outcomes, it does not provide a consistent predictor of how anesthetic drugs behave. In fact, genetics, socioeconomic status, and environmental conditions (among many others) are likely to influence organ function in this patient group. Furthermore, comorbidities, such as preexisting neurologic, hepatic, or renal disease, can increase patient sensitivity to anesthetics.[84] Chronologic age does not consistently correlate with physiologic age, and there can be substantial variability in organ function across individuals of the same age.[85] Healthy elderly patients without significant coexisting disease and with normal body habitus and good exercise tolerance might not require a reduction in anesthetic dose.[86,87]

Anesthetic Pharmacology in the Elderly

In general, anesthetic agents work by reducing neuronal activity and disrupting network connectivity by either reducing excitatory currents (such as by N-methyl-D-aspartate receptor) or increasing inhibitory currents (such as by gamma-aminobutyric acid receptors) in the brain.[88,89] There are several possibilities for how aging might influence anesthetic effect. Reduced cardiac output in the elderly is known to reduce drug mixing[90] such that anesthetic drugs develop higher than expected peak drug concentrations.[90,91] Reduced cardiac output also diminishes perfusion to metabolic organs, thereby slowing drug clearance, as observed with propofol and etomidate. Reduced cardiac output can also reduce the volume of distribution.[18,92-94]

Although there is a relative paucity of detailed information describing how age influences anesthetic drugs, for selected modern anesthetics (e.g., propofol and remifentanil) pharmacologic models have been developed that account for age.[18,95-97] Using these models, simulations can compare the time course of drug concentration and effect over a wide range of doses and ages with the goal of understanding how the dosage scheme should be modified for these various age groups. For example, numerous previously published remifentanil pharmacokinetic datasets have been combined to build a pharmacokinetic model that predicts plasma remifentanil concentration for any intravenous dosage scheme using age as a covariate.[23] For example, simulations suggest that at steady-state the infusion rates necessary for a 50- or 75-year-old individual of normal body habitus are 87% or 74%, respectively, of what is required in a healthy 25-year-old individual (Figs. 5.9 and 5.10).

Similar model-building studies have been conducted for propofol, examining the influence of advanced age on its pharmacokinetic and pharmacodynamic behavior. As shown in Fig. 5.11A, a given infusion rate yields a modestly higher plasma propofol concentration in the elderly, although the steady-state concentration is reached slightly faster and blood concentrations decline slightly faster in the elderly patient once the infusion is terminated.[18] A subsequent study confirmed that the concentration-effect relationship is substantially shifted to the left in the elderly (i.e., the concentration producing 50% of maximal effect is much lower in the older patient) as shown in Fig. 5.11B Thus propofol doses in the typical elderly patient must be adjusted significantly lower compared with younger patients, although considerable variability is to be expected.

Postoperative Cognitive Dysfunction

Postoperative cognitive dysfunction (POCD) is a heterogeneous disorder of mental processing and executive functioning that has been frequently described in older adults, particularly those undergoing cardiac surgery. A systematic review found that 22%

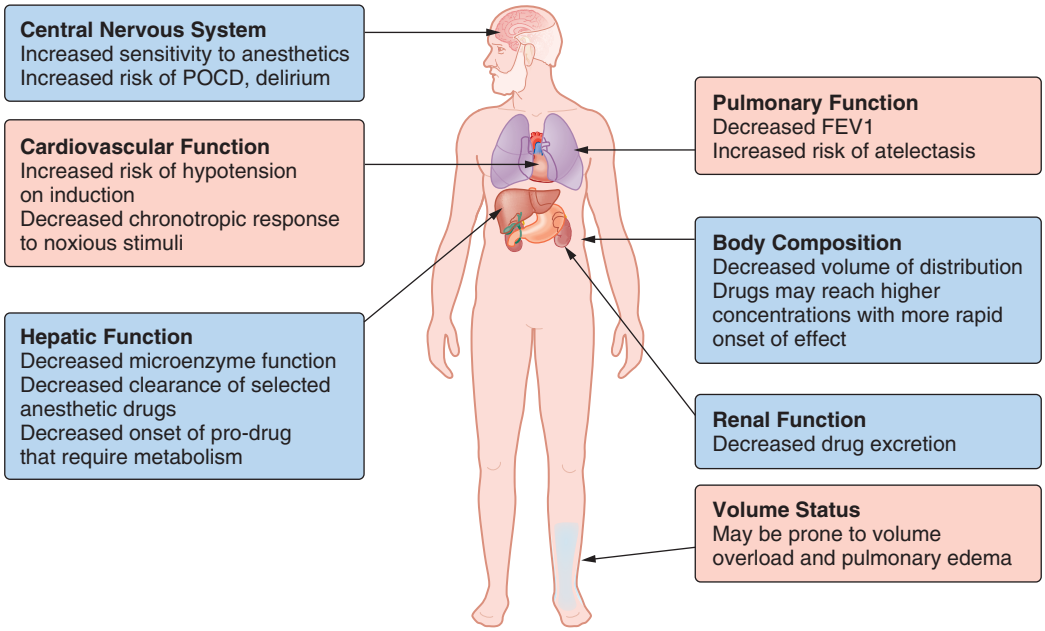
TABLE 5.9 Physiologic Changes in the Elderly and Potential Perioperative Consequences[183]

Organ System	Physiologic Changes	Perioperative Consequences
Neurologic System	• Increased neuronal degradation from increased enzymatic activity • Decreased brain mass • Decreased neurotransmitter synthesis • Ill-defined changes in receptor function • Decreased functional connectivity between neurons	• Increased sensitivity to anesthetic drugs[184] • Decreased hypoxic drive, hypercarbic ventilatory drive • Increased likelihood for postoperative delirium and cognitive dysfunction. especially in the presence of infections, blood loss, fever, opioids, anticholinergics, opioids, anticholinergics, preexisting cognitive impairment, or renal failure
Cardiovascular System	• Alterations in blood pressure, pulse pressure, and sinoatrial node conduction • Reduced left ventricular compliance, increased wall thickness and size • Increased myocardial oxygen demand • Reduced aortic and great vessel compliance[185] • Decreased baroreceptor sensitivity, decreased responsiveness to β-adrenoreceptors and renin-angiotensin-aldosterone system[34]	• Increased risk of hypotension on induction and greater lability during anesthesia[89,186] • More sensitive to the cardiovascular depression from propofol[187] • Hemodynamic lability is associated with more adverse outcomes during surgery[188,189] • Decreased chronotropic response to noxious stimuli. Decreased ability to increase in cardiac output • Reduced response to β_1-agonism[185]
Pulmonary System	• Physiologic shunt, ventilation-perfusion mismatch, closing capacity, and work of breathing are increased • Chest wall compliance, minute ventilation, respiratory muscle strength, and vital capacity are decreased	• Decreased forced expiratory volume in 1 second • Increased likelihood of atelectasis and hypoxia • Decreased reserves in presence of adverse respiratory events from decreased gas exchange and pulmonary mechanics
Hepatic System	• 10% decrease in hepatic blood flow per decade of life • 20%-40% decrease in liver mass in elderly patients[185]	• Anesthetic drugs metabolized by hepatic microsomal enzymes have reduced metabolism (up to 40% by age 80 yr) • Clearance of drugs where metabolism is limited by flow to the liver may be reduced by 30%-40%. Drugs that are highly extracted by the liver or highly protein bound (e.g., midazolam, fentanyl, lidocaine, and propofol) are likely to be more affected[190] • Decreased: onset/effectiveness of prodrugs (e.g., angiotensin-converting enzyme inhibitors)
Renal System	• Decreased renal mass and number of nephrons • Reduced renal blood flow (30%-50% by age 70 yr) and glomerular filtration rate[191,192] • Reduced concentrating ability	• High urine volume is required to excrete waste • May be prone to volume overload and pulmonary edema • Less able to respond to changes in sodium load • Less able to conserve water under conditions of water deprivation. More prone to hyponatremia
Body Composition	• 10%-15% decrease in total body water[193] • 20%-40% increase in body fat increases with decrease in muscle mass[190] • Decreased blood albumin concentration	• A decrease in initial distribution volume can lead to higher anesthetic drug plasma concentrations after intravenous bolus administration[185] • Lipid-soluble anesthetic drugs may have a larger distribution that can prolong effect • Increase in the unbound fraction of selected drugs (e.g., warfarin, phenytoin). Of note, other drugs are primarily bound to α_1-acid glycoproteins (e.g., lidocaine)[194]

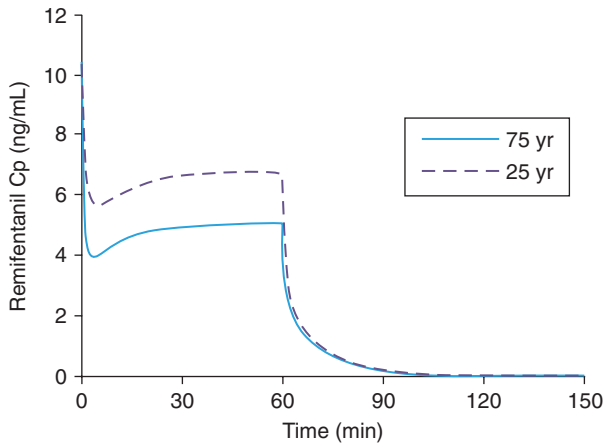
of patients undergoing coronary artery bypass graft operations experience statistically significant cognitive decline, although it may be as high as 53% of patients at discharge.[98,99] In this area, statistical significance may not equate to clinical significance, and most patients do not experience any functional decline.[99] However, some patients experience such intellectual or memory decline that they are unable to return to employment. Most patients who incur POCD return to their baseline within weeks or months, but a small subset of patients never fully recovers.[99,100]

Patients at high risk for POCD after cardiac surgery include those of increased age, those with chronic disabling neurologic disease or peripheral vascular disease, those living alone, and those with postoperative complication(s). Protective factors include greater number of years of education and shorter cardiopulmonary bypass time.[101] POCD can only be objectively assessed when a battery of tests of mental status and multiple cognitive domains has been performed before surgery and anesthesia as a baseline. This is done for research purposes but is rarely done in clinical practice. Further complicating the matter is the lack of agreement on which tests should be performed, the learning effect that confounds results, and what level of decline constitutes POCD.[98,102]

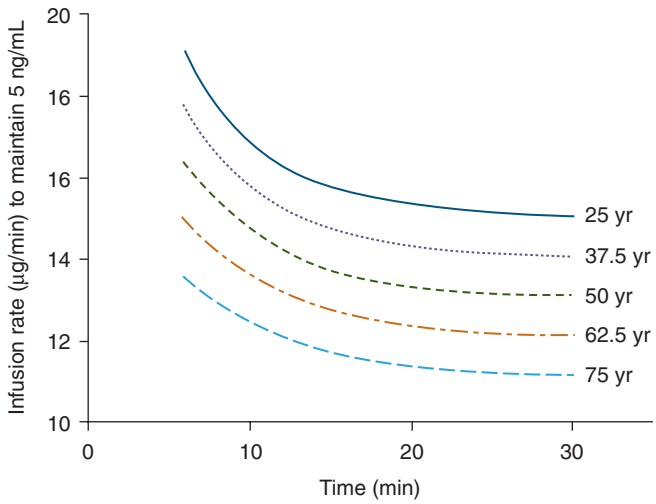
In a large, prospective study after noncardiac surgery, POCD was common at hospital discharge (30% to 41%, depending on the age group) and decreased over time. Independent risk factors



• **Fig. 5.8** Schematic summary of anesthetic considerations *(blue)* and perioperative challenges *(red)* in the elderly. *FEV_1,* Forced expiratory volume in 1 second; *POCD,* postoperative cognitive dysfunction.



• **Fig. 5.9** Computer simulations of plasma concentration *(Cp)* predictions versus time for an identical dose (i.e., not weight-adjusted) administered intravenously to 25-year-old and 75-year-old subjects (both weighing 75 kg, height 175 cm) using the Kim model. The simulated dosing regimens consisted of a 50-µg bolus injection followed by a 15-µg/min continuous infusion for 60 minutes. (Reprinted with permission from Kim TK, Obara S, Egan TD, et al. Disposition of remifentanil in obesity: a new pharmacokinetic model incorporating the influence of body mass. *Anesthesiology.* 2017; 126:1019–1032.)



• **Fig. 5.10** Simulation of infusion rate (in micrograms per minute) requirements to achieve a target plasma concentration of 5 ng/mL over 30 minutes for a range of ages assuming a body weight of 75 kg and height of 175 cm. (Reprinted with permission from Kim TK, Obara S, Egan TD, et al. Disposition of remifentanil in obesity: a new pharmacokinetic model incorporating the influence of body mass. *Anesthesiology.* 2017; 126:1019–1032.)

for POCD in noncardiac patients were similar to those described in cardiac patients: increased age, lower educational level, and history of stroke. The elderly are at greater risk of long-term problems related to POCD, and patients with POCD are more likely to die in the first year after surgery.[102]

Delirium is defined as a transient syndrome with complete return to function. However, patients with delirium seem to be at increased risk of long-term cognitive and functional decline, and the relationship between postoperative delirium (POD) and POCD is an area of active research.[98] The two disorders share some risk factors (older age, peripheral vascular disease, cerebrovascular disease, and low level of education), leading some to postulate that they are manifestations of the same disorder.[100,103] One study found that delirium developed in 46% of patients after cardiac surgery but that patients with POD returned to baseline on cognitive tests within 6 months after surgery. However, patients with POD were less likely to return to preoperative functional levels than patients without delirium.[103] Another recent study showed a similar pattern of POD increasing the risk for early cognitive decline, with a general return to function by 1 year. This

TABLE 5.10 Dosing Considerations of Selected Anesthetics in the Elderly

Sedatives

General considerations
- For induction of anesthesia, consider small incremental bolus doses.[195,196]
- Pharmacokinetics: reduced clearance and distribution volume.
- Pharmacodynamics: left shift in the concentration-effect relationship increasing sensitivity.[197]

Propofol
- Pronounced hypotension with bolus dosing.[195] Consider 20% or more reduction in bolus dosing.
- Less propofol is required for moderate sedation and to maintain general anesthesia. The effect site concentration necessary to achieve loss of responsiveness in a 75-year-old may be 50% of the concentration necessary in a 20-year-old.[197]
- With equivalent doses, older patients develop more profound changes in the electroencephalogram, require more time to reach deeper states of anesthesia, and require more time to regain responsiveness.[198]
- Pharmacokinetic changes may be more pronounced in women than men.[199]

Etomidate
- Well-suited for elderly population owing to less hemodynamic instability when compared with propofol.
- Consider potential adverse effects from adrenal suppression, even after a single induction dose.

Midazolam
- Can have prolonged duration of effect and contribute to postoperative delirium. Consider risks and benefits before administering.[200]
- May lead to pronounced ventilatory depression even with anxiolytic doses. May be worrisome in an unmonitored setting.
- Reduce dose by up to 75% in elderly patients.[196]

Opioids

General considerations
- Respiratory depression is a primary concern, which increases with age[201] and in the presence of other sedating drugs.
- Impaired hepatic and renal function might influence opioid choice to minimize prolonged analgesia or adverse side effects.
- Pharmacokinetics: reduced clearance and distribution volume.
- Pharmacodynamics: left shift in the concentration effect relationship, increasing sensitivity.

Fentanyl
- Pharmacokinetics are not well described in elderly, but have limited change with age. To account for increased sensitivity,[202] reduce bolus dosing and titrate to effect.

Remifentanil
- Reduce bolus doses by 50% and infusion rates by 33%.[95] Can have slower onset of effect with bolus administration: 2-3 min versus 90 sec in young adults.
- Appropriate for elderly as it has a short duration of action and does not depend on renal or liver function to be cleared.

Meperidine
- Not recommended because of increased risk of postoperative delirium.[203] With high concentrations, associated with agitation, seizures, anticholinergic effects (e.g., dementia-like effects), and negative inotropic properties.

Neuromuscular Blocking Agents

- Pharmacodynamics are not significantly altered (e.g., elderly have the same 50% effective dose as younger individuals).
- Onset to maximal effect may be delayed 30 to 60 sec owing to decreased cardiac output.
- Recovery time may be prolonged by 50%.[204] This might be a function of age-related impairment of liver metabolism and/or renal excretion.
- Consider cisatracurium as it is not dependent on renal or hepatic funciton.[204]

Inhaled Anesthetics

- Minimum alveolar concentration decreases with age: for potent inhaled agents, 6% per decade of age after 40; for nitrous oxide, 7.7% per decade of age.

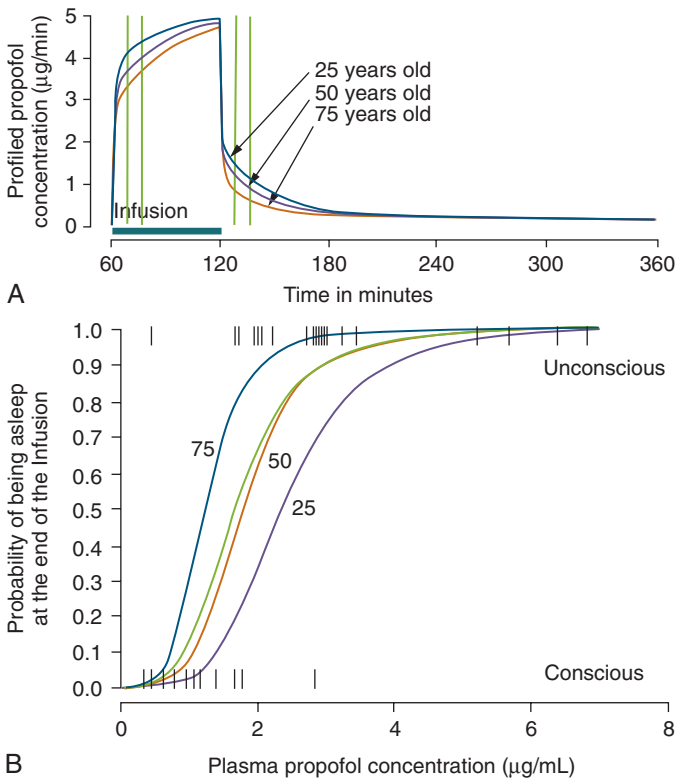
study demonstrated that worse performance in attention-requiring tasks predicted POD, which might help clinicians prevent POD.[100]

The development of POCD is a multifactorial process and involves factors including circulating hormone levels, microembolic events, maintenance of cerebral perfusion, and direct effects of anesthetics on the brain. The last factor has led to studies comparing POCD after regional anesthesia or general anesthesia, with interesting results. Despite the logical conclusion that anesthetics acting on the brain affect cognition in the elderly and the widespread concern about neurotoxicity of anesthetics on the developing brain, neuraxial techniques have not been shown to better preserve cognitive function than general anesthesia.[104-106]

Emerging Developments

Open Target-Controlled Infusion

A key shortcoming of pharmacokinetic/pharmacodynamic modeling studies is that they often include a small number of patients. These smaller datasets are suboptimal in investigating the influence of



• **Fig. 5.11** A, Pharmacokinetic model of propofol comparing plasma concentrations produced by a given infusion over a range of ages in adults. B, Pharmacodynamic model of propofol demonstrating effect of a given infusion over a range of ages in adults. (From Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology*. 1998;88:1170–1182. Used with permission.)

various "special populations," such as age, body weight, and sex. In response to this limitation, clinical pharmacology enthusiasts worldwide combined efforts to create a data warehouse called Open Target-Controlled Infusion (TCI*) and invited investigators to contribute their data. The goal of the Open TCI project is to provide investigators with larger datasets that can be exploited to refine and perfect the pharmacokinetic/pharmacodynamic models used for target-controlled infusions.

Recent work has taken advantage of Open TCI to build more comprehensive pharmacokinetic/pharmacodynamic models, particularly as TCI relates to determining the influence of special populations, such age and body weight, on selected intravenous anesthetic behavior. For example, a propofol pharmacokinetic model was constructed from 21 previously published datasets with data from elderly, children, adults, and obese individuals of both sexes.[8] The data spanned an age range of 0.25 to 88 years, a weight range of 5.2 to 160 kg, and contained nearly 11,000 drug concentration measurements from 660 individuals. A remifentanil model has also been constructed from nine previously published datasets including lean, obese, and morbidly obese adults.[6] The data spanned an age range of 20 to 85 years, a weight range of 40 to 220 kg, and contained nearly 4500 blood concentration measurements from 229 individuals. These new "super" pharmacokinetic models show promise as useful tools in driving TCIs and real-time pharmacologic drug displays but they will require prospective validation to ensure efficacy and safety in clinical practice among these various patient subgroups.

[a]Available at www.opentci.org.

Key Points

- Obesity and extremes of age modify physiology such that anesthetists must make dosage adjustments to optimize therapy.
- Obesity alters the pharmacokinetic behavior of anesthetic agents. These changes are not uniform across all drug classes.
- Various scalars (total body weight, lean body mass, ideal body weight, and so on) have been proposed as the basis for calculating anesthetic dosing in obese patients. Pharmacologic modeling efforts have attempted to determine which scalar is most appropriate for specific drugs.
- In general, obese patients require higher drug dosages but not nearly as high as would be suggested by total body weight. A heuristic rule of thumb is that dosage calculations should account for approximately 30% of body weight in excess of ideal body weight.
- Anatomic and physiologic changes that occur between the newborn period and adult life have important pharmacologic implications. These ontogenetic-related changes (in circulatory physiology, drug metabolic capacity, body tissue composition, and so on) mandate that clinicians apply age-specific knowledge to the formulation of dosing schemes in pediatric patients.
- Anesthetic toxicity in neonates and infants is a topic of major concern and controversy in contemporary anesthesiology. Evidence from in vitro studies, in vivo animal models and retrospective data-mining studies in humans suggest that repeated anesthetic exposure in the young might decrease cognitive function in adult life. Ongoing, longitudinal, prospective, human studies will perhaps help clarify this controversy in the future.
- Physiologic changes in elderly patients generally result in a reduced dosage requirement based on both pharmacokinetic and pharmacodynamic mechanisms. For many drugs, the reduced dosage requirement is substantial (e.g., by 50%-75% for remifentanil).

Key References

Cortinez LI, De la Fuente N, Eleveld DJ, et al. Performance of propofol target-controlled infusion models in the obese: pharmacokinetic and pharmacodynamic analysis. *Anesth Analg*. 2014;119:302–310. This article used five of the available pharmacokinetic models for propofol in morbidly obese patients to characterize the bispectral index response (BIS) in this population. Propofol concentration was underestimated in all of the models. Using adjusted body weight improved the performance of two of the models, and there was no apparent effect of obesity on the time profile of BIS response or the propofol concentration-BIS relationship. (Ref. 11).

Davidson AJ, Disma N, de Graaff JC, et al. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. *Lancet*. 2016;387:239–250. The secondary outcomes reported in this ongoing study helped abate concerns over the impact of a single anesthetic on the developing brain by showing that 1 hour of sevoflurane anesthesia in infancy does not increase the risk of adverse neurodevelopment at outcome at 2 years of age compared to awake-regional anesthesia. (Ref. 77).

Minto CF, Schnider TW, Egan TD, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology*. 1997;86:10–23. This landmark study clearly demonstrated the influence of advancing age on both the dispostion and effects of remifentanil. The age effect is substantial, translating into a 50% to 80% decrease in dose requirement for elderly patients. (Ref. 23).

Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. *Anesthesiology*. 1999;90:1502–1516. This article determined the effects of age on propofol pharmacodynamics, including characterization of the relation between plasma concentration and the time course of drug effect. Propofol had a faster onset in older patients and older patients were more sensitive to the hypnotic and electroencephalographic effects of propofol than were younger patients. (Ref. 97).

Shibutani K, Inchiosa MA Jr, Sawada K, et al. Pharmacokinetic mass of fentanyl for postoperative analgesia in lean and obese patients. *Br J Anaesth*. 2005;95:377–383. The authors suggest an innovative dosing scalar for obese patients, pharmacokinetic mass, which was created using plasma concentrations and observed opioid effects in obese and lean patients. (Ref. 27).

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6

Pharmacodynamic Drug Interactions

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CHAPTER OUTLINE

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History

Pharmacology is characterized by detailed descriptions of the actions of individual drugs. In the case of anesthesia, no single drug has been found to be universally satisfactory and indeed general anesthesia is now regarded as a set of desirable clinical endpoints rather than a discrete phenomenon of its own. Useful endpoints include lack of awareness and a pleasant induction and recovery; lack of movement, adequate muscle relaxation, reasonable blood pressure control; and maintenance of homeostasis by suppressing autonomic reflexes while balancing the narrow therapeutic index of many of the drugs to ensure positive outcomes. Consequently, multiple drugs are used for all but the simplest of procedures.

This concept of multiple drug use was first described by Lundy in 1926, who used the term *balanced anesthesia*.[1] His concept included the liberal use of local or regional anesthesia as well as hypnotics, volatile anesthetics, and opioids. At the time, use of volatile agents as a sole anesthetic was common, but unacceptable cardiovascular and respiratory depression frequently accompanied the high doses required to suppress movement to noxious stimuli—a finding still true of the volatile anesthetics in use today.[2]

The theory behind balanced anesthesia is that using desirable drug combinations reduces dose requirements of individual drugs, minimizing the incidence of unwanted side effects in those with a narrow therapeutic index and so improving the quality of anesthesia. A review of the contribution of anesthesia to perioperative mortality found evidence to support this notion with the relative risk of dying within 7 days of surgery being 2.9 times greater if one or two anesthetic drugs were used, compared with the use of three or more.[3] Today, balanced anesthesia is the standard approach to general anesthesia.

Many drugs used in anesthesia have overlapping actions and, when given in combination, can be used to produce effects distinct from those they create individually. To maximize the clinical utility of any drug, it is important to understand its effects when used alone and in combination. The interaction between propofol and fentanyl is a notable example. Propofol alone is effective at causing unconsciousness without intolerable adverse effects. The much larger doses required to prevent movement in response to surgical pain also suppress respiration and can unacceptably reduce blood pressure. On the other hand, fentanyl is incapable of reliably causing unconsciousness and even in very high doses does not reliably suppress movement to pain. When these two drugs are used in combination, there is only a modest reduction in the dose of propofol required to cause unconsciousness, but a dramatic reduction in the dose required to suppress movement to pain with less reduction in blood pressure. The relative dosage of the combination of propofol and opioids also allows a degree of independent control of two critical variables—unconsciousness and lack of movement in response to pain.

Early studies of drug interactions include that by Fraser in 1872,[4] who described pharmacologic antagonism between physostigmine and atropine, and by Frei in 1913,[5] who used isobolographic analysis to demonstrate increased effectiveness of combinations of disinfectants for killing bacteria compared with individual agents. The response surface method, which is now used to describe the entire dose response relationship of two drugs, was first proposed by Loewe in 1928,[6] who described synergy as an "inflated sail" and additivity as a "tense sail." The concept was introduced into modern anesthetic clinical pharmacology analysis by Minto et al. in 2000.[7] The seemingly daunting task of describing an entire response surface for the interaction between two drugs was found to be tractable and as few as 20 intensively studied subjects are needed to adequately describe the interaction between two drugs.[8] The tedious calculations are easily performed on a modern computer,

Abstract

Modern balanced anesthesia consists of the use of a number of drugs to achieve the desired clinical endpoints, such as no awareness, no movement, muscle relaxation, control of blood pressure and control of heart rate in the face of the noxious surgical stimulus. Understanding the methodology used for the study of drug interactions and knowing the interactions that occur between commonly used anesthetic drugs is important for using them effectively and safely.

Keywords

drug interactions
synergy
additivity
response surface methodology
propofol
opioids
volatile anesthetics

something Loewe clearly lacked. Response surface methodology is now the basis of many studies of commonly used drug combinations. Although outwardly complex, the models can be used to increase the accuracy of anesthetic doses and improve prediction of expected effects in patients. They have been incorporated into some anesthetic monitors for real-time display and can be used to optimize drug titration, promoting outcomes such as reduced wake-up times or increased cardiovascular stability without increasing hypnotic depth.

This chapter introduces terminology used to describe drug interactions, the methodology used to study drug interactions, and the important interactions between commonly used anesthetic drugs. Some of these interactions are covered in other chapters of this text in more detail (see Chapters 2, 10, 11, and 17). Interactions among combinations of analgesics or antiemetics as used postoperatively are not reviewed in this chapter; however, similar methodologies and rules can be applied when considering their use in combination.

Study of Drug Interactions

Terminology

Drug interactions are usually considered in the dose or concentration domain. A simple experiment that illustrates interactions between two drugs takes half the *dose* of each that alone causes a certain level of effect. Assume that level of effect is equal to 1. If the drugs are additive, one would expect these two half doses given together to produce the same effect as giving the whole dose of either drug alone (i.e., 0.5 + 0.5 = 1). This expected effect for a dose combination becomes the null hypothesis against which one can assess the presence (or absence) of a positive or negative interaction. If the observed effect is greater than expected (<0.5 + <0.5 = 1), synergy exists. A commonly used drug combination in which this occurs is propofol and midazolam. Together, the individual doses are reduced to about one third so that 0.33 + 0.33 ≡ 1. If the observed effect was less than expected (>0.5 + >0.5 = 1), infra-additivity exists (Fig. 6.1). If instead one combines half the *effect* of two drugs, the answer would be very different. This is because the sigmoid log-dose effect relationship is highly nonlinear, meaning drug *effects* cannot be simply added.

The term *infra-additive* is used when less effect than that expected from simple additivity is observed. The combination of midazolam and ketamine exemplifies the effect of infra-additivity. Midazolam has only a moderate effect on the ketamine dose required to suppress response to verbal command and no effect on the ketamine dose required to suppress movement to a noxious stimulus.

The term *antagonism* is reserved for interactions in which there is an absolute reduction in the effect of one drug in the presence of the other. For instance, the analgesic effect of fentanyl is reduced in the presence of naloxone. In this example, naloxone is incapable of causing analgesia when given alone. An underlying assumption of this definition of additivity is that a drug cannot interact with itself, so two half doses of the same drug must be additive.

$$\text{Interaction Index} = \frac{da}{DA} + \frac{db}{DB}$$

• **Fig. 6.1** General equation for additivity as defined by Loewe. D_A and D_B are the doses of drugs *A* and *B*, respectively, that create a given effect alone, while *da* and *db* are the doses of drugs *A* and *B*, respectively, that create that same effect when given in combination. The median effect dose or median effective concentration are the most commonly used values for D_A and D_B. An interaction index of 1 = additivity, <1 = synergy, and >1 = infra-additivity. (Reprinted with permission from Loewe S. The problem of synergism and antagonism of combined drugs. *Arzneimittelforschung.* 1953;3:285–290.)

Shift in Dose-Response Curve

The dose-response relationship for most anesthetic drugs can be described using the standard *sigmoid* E_{max} model. Its characteristics include (1) a threshold drug concentration that must be surpassed before any effect is seen, (2) an increase in effect proportional to logarithmic increases in drug concentration, and (3) saturation after which additional increases in drug concentration no longer produce an increase in effect (Fig. 6.2).

When a second drug is introduced, the simplest model of an interaction describes its influence, at a single fixed dose, on the dose-response relationship of the first drug. Using the previous example, intravenous fentanyl 1 μg/kg, administered immediately before intravenous propofol, shifts the propofol dose-response curve for unconsciousness to the left. This equates to a 20% reduction in dose for that endpoint. Likewise, the curve for suppression of movement to a noxious stimulus shifts to the left by 50%. This model demonstrates that fentanyl affects the noxious endpoint more than the hypnotic endpoint, which is expected from our knowledge of the individual drugs.

This approach to studying interactions accounts for the dose requirements for the two drugs when given together, but describes the interaction at only one dose of fentanyl. It does not describe whether the interaction with the second drug is additive or synergistic or whether there is a therapeutic advantage to using the combination. To quantitate the interaction, and to decide whether synergy exists, a description is needed of the drug's effects when given individually, as well as when given together, and for a range of doses. Use of isobolograms is an alternative approach to interaction analysis that partly addresses these limitations.

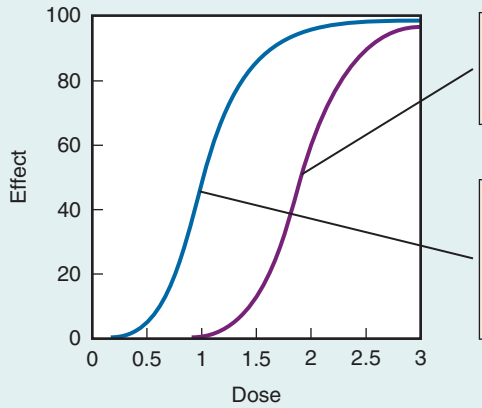
Isobolograms

The traditional approach to quantitating a drug interaction for two drugs is to construct graphs of the dose pairs that together produce a single level of effect. These isoeffect lines are called *isoboles*. Comparison of an isobole with a line of additivity signals the interaction type: a straight line indicates additivity; inward bowing indicates synergy; outward bowing indicates infra-additivity or antagonism (see Fig. 6.2).

Isobolograms are easy to construct and analyze when both drugs are individually capable of producing the endpoint in question. Numerous studies in the literature use this methodology and their conclusions are comparable to those of studies using more complex methodologies. Typically a departure from additivity of less than 10% has been regarded as additive on the basis that even if statistically significant, it is clinically irrelevant. When one drug cannot achieve the endpoint in question, it is still possible to determine whether synergy exists, but the exact degree of departure from additivity cannot be accurately determined.[9] A limitation of using isobolograms is that the result is only applicable to the effect level investigated. To gain a full understanding of the interaction between two drugs for all effect levels, it is possible to overlay a series of isoboles ranging from minimal effects to the maximal effect attainable (E_{max}).[10]

Analysis of isobolograms involves determining the dose-response relationship for each drug individually and then exploring the

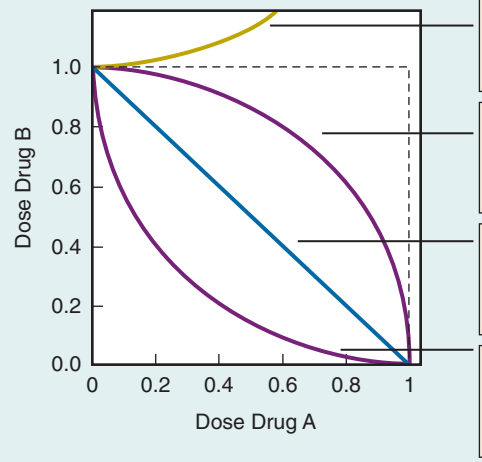
Shift in dose-response curve
The standard dose response curve for a single drug is shifted to the left along the horizontal axis by the presence of a second drug.



Drug A alone, for example: ED_{50} Drug A = 1.9
This is a standard *sigmoid* E_{max} dose-response curve.
(e.g., Propofol for immobility)

Drug A + Drug B e.g., ED_{50} Drug A = 1.0
in presence of drug B
In the presence of Drug B, dose requirements of Drug A are reduced.
(e.g., Propofol in the presence of fentanyl 1 μ/kg at an endpoint of immobility)

The isobologram
An isobologram is an iso-effect line whereby all the combinations of each drug along the line give the same observed effect. Multiple isobolograms can be drawn for different effect levels such as ED_{50} or ED_{95}. The doses required of each drug individually are on the X and Y axes respectively.



Antagonistic
Drug A increases dose of drug B to achieve the same effect
(e.g., Naloxone and fentanyl for analgesia)

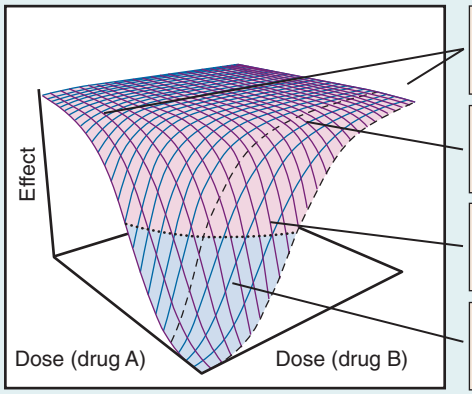
Infra-additive e.g., >0.5 + >0.5 = 1
Together the individual doses of each drug are slightly reduced to achieve the same effect
(e.g., Ketamine and midazolam for sedation)

Additive e.g., 0.5 + 0.5 = 1
Together, half the dose of each drug will achieve the same effect
(e.g., Isoflurane and nitrous oxide for immobility)

Synergistic e.g., <0.5 + <0.5 = 1
Together, less than half the expected dose of each drug is required to achieve the same effect
(e.g., Propofol and midazolam for hypnosis)

The response surface
The response surface is a three dimensional graph with drugs A and B on the horizontal axes and effect on the vertical axis. The concept embraces shift in dose-response curves and the isobologram, and describes effects for the complete set of doses for the endpoint in question. Responses may be either continuous such as bispectral index and blood pressure, or quantal such as a sedation scale, awake/sleep and movement/immobility.

The response surface



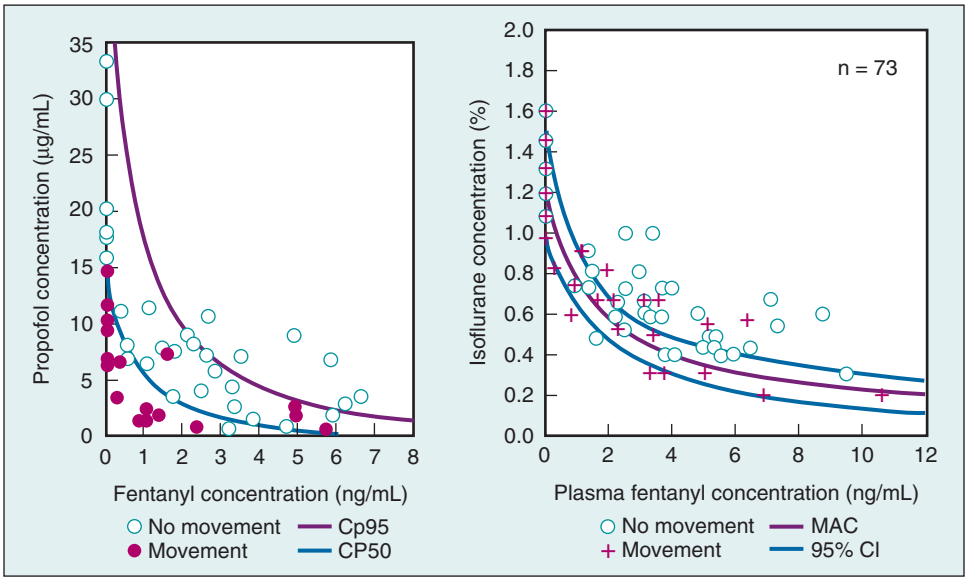
Dose-response curve
Drug A alone is on one axis and drug B in the other axis

Shift in dose response
Drug B in the presence of a constant concentration of Drug A

Isobologram
The 50% effect isobole is shown.
Outward bowing of the surface indicates synergy

Response surface
All doses of drug A and B and their responses are shown
(e.g., Sevoflurane and remifentanil for immobility)

• **Fig. 6.2** Common methods for studying drug interactions using shift in dose response-curve *(top panel),* isobolograms *(middle panel),* and response surfaces *(bottom panel). ED_{50},* median effective dose. *ED95,* dose which attains 95% of maximum effect. E_{max}, maximal effect attainable.



• **Fig. 6.3** Isobolograms for propofol-remifentanil interaction and isoflurane-remifentanil interaction for an endpoint of no movement to surgical incision. Note that not all patients can be immobilized with fentanyl alone even in high doses. Fentanyl 1 ng/mL is equivalent to the peak effect of a bolus of fentanyl 3 µg/kg in a young adult. *Cp50,* Plasma concentration at which a drug exerts its function in 50% of the cases; *Cp95,* plasma concentration at which a drug exerts its function in 95% of cases; *MAC,* minimum alveolar concentration. (Modified from Smith C, McEwan AI, Jhaveri R, et al. The interaction of fentanyl on the Cp50 of propofol for loss of consciousness and skin incision. *Anesthesiology.* 1993;78:864–869; and McEwan AI, Smith C, Dyar O, et al. Isoflurane minimum alveolar concentration reduction by fentanyl. *Anesthesiology.* 1994;81:820–828.)

dose-response relationship of the drugs in combination. Simple experiments investigate dose pairs that maintain a fixed dose ratio of the individual drugs. It is also possible to combine any number of dose combinations and responses and to calculate an isoeffect line using nonlinear regression—this is now the preferred method[11,12] (Fig. 6.3). The standard isobologram assumes that the potency ratio of the two drugs remains constant for all dose pairs. In some instances this assumption does not hold true, such as when individual dose-response curves reach different levels of maximum effect. These cases require special consideration in that the line of additivity may in fact be curved.[13] Consequently this can lead to false identification of synergistic relationships. Although isobolographic methodology is appropriate for studying interactions of these types, they are better described by more sophisticated analyses.

Response Surface Models

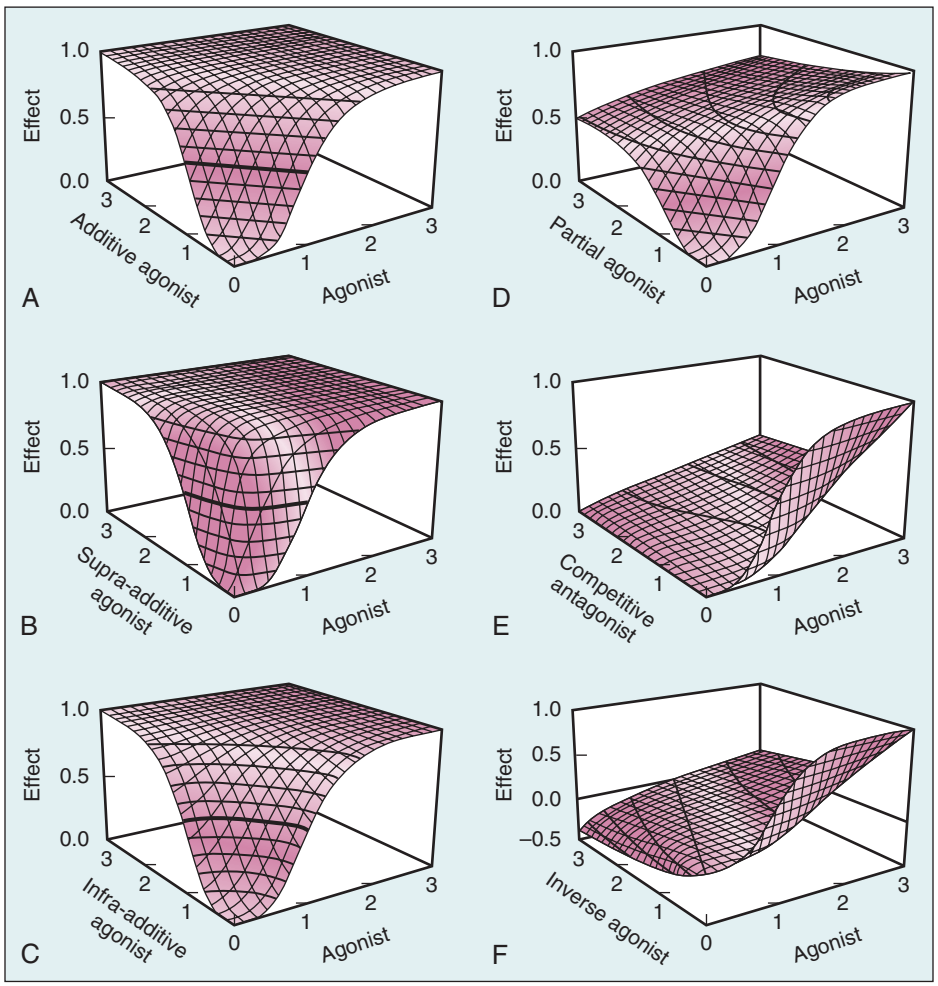
Response surface methodology allows one to create a complete description of the dose-response relationship between two drugs for all levels of effect for a given endpoint. That response surfaces characterize the entire spectrum of drug effect is an important advantage of this approach in anesthesia clinical pharmacology. Anesthesia practice is unique in that anesthetists must target profound drug effects during an operation and then reverse the effect rapidly when the operation is finished. Thus to study anesthetic clinical pharmacology fully, it is necessary to understand the entire concentration-effect relationship and how to transition from full effect to recovery efficiently.

These models all assume that the interaction is constant over time (i.e., stationary). In creating response surfaces, it is also assumed that the surface is smooth and that individuals in the study population show a similar degree of drug interaction. The latter is important because it is not practical to study more than a small part of the entire dose-response surface in each patient. Response surface models are typically built in carefully controlled volunteer studies in which multiple measurements can be made; the resulting models are then validated in patients. The concept embraces previous approaches to drug interaction analysis, including the shift in the dose-response curve and the isobologram. It also provides a strong visual representation of the interaction that is easy to remember given the complexity of the mathematics involved. Response surfaces give a mathematical description of the magnitude of an interaction for all dose pairs of two drugs, which enables these models to be used in real time to predict the likely response of patients to the drugs used. They also allow identification of optimal drug dose combinations. For example, remifentanil 0.8 ng/mL:propofol 2 to 3 µg/mL was the optimal concentration pairing to prevent movement and blood pressure changes in response to esophageal instrumentation without causing intolerable ventilatory depression.[14] The study is significant because it identifies the optimal dose ratio for a useful clinical endpoint while minimizing the risk of an unwanted side effect.

Response surface methodology is suitable for studying all the common types of drug interactions among agonists, partial agonists, antagonists, and inverse agonists (Fig. 6.4).

Trial Design

The basic steps to deriving a response surface are described in Fig. 6.5. Three different mathematical approaches have been chosen—Greco, Minto, and Bouillon et al.—but the basic principles underlying them are similar. There are also other valid approaches.[7,10,15–19] Although each model draws a slightly different



• **Fig. 6.4** Response surfaces for a variety of drug interactions. All drugs have an initial effect = 0. A is an additive interaction between two agonists; B is a synergistic interaction between two agonists; C is an infra-additive interaction between two agonists; D is the interaction between a partial agonist and a full agonist; E is the interaction between an agonist and antagonist; F is the interaction between an inverse agonist and a full agonist. (Reprinted with permission from Minto CF, Schnider TW, Short TG, et al. Response surface model for anesthetic drug interactions. *Anesthesiology.* 2000;92:1603–1616.)

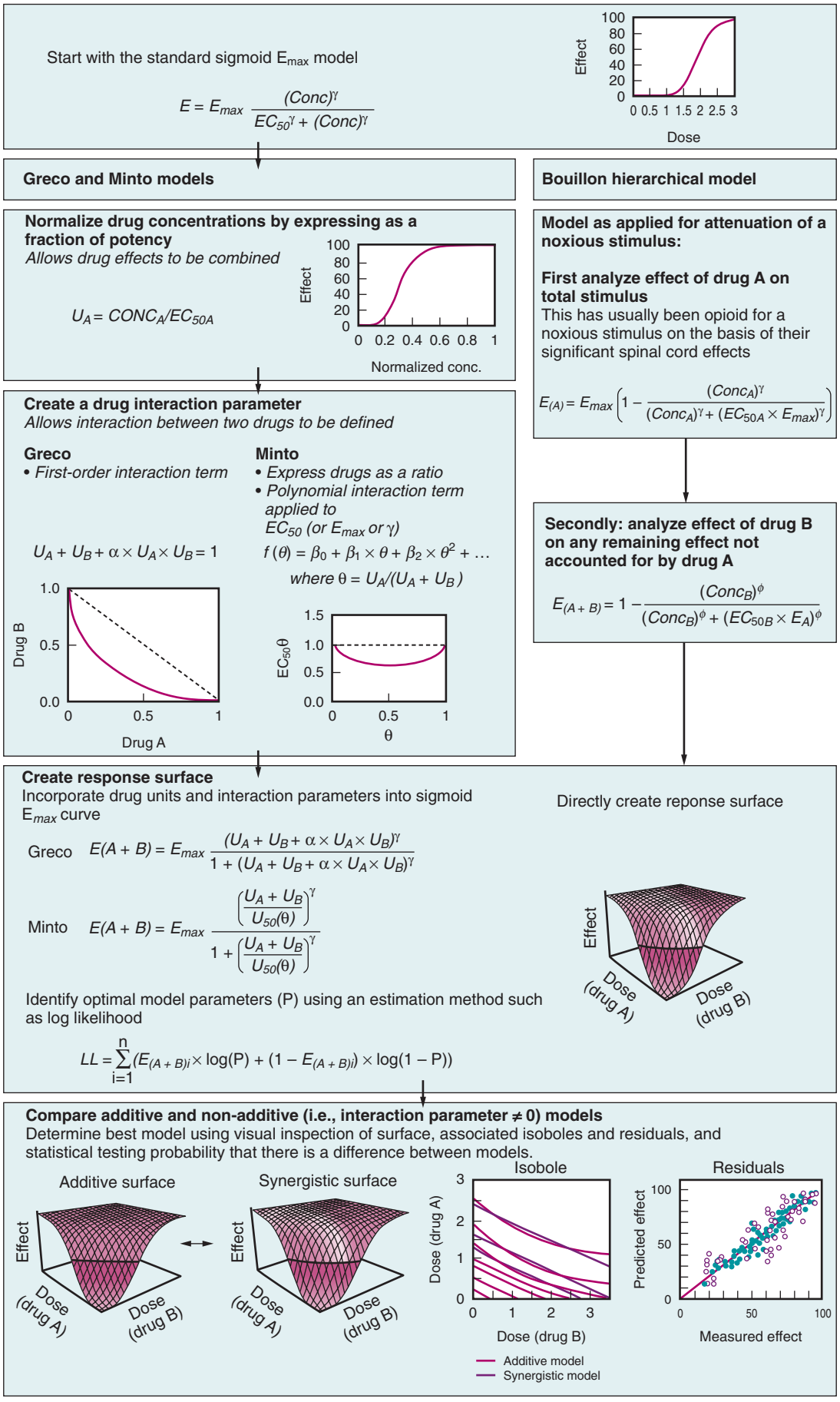
shape for the surface, the differences are not large. The three approaches are empirical in that they make no assumption about the nature of the underlying interaction.

The Greco model is simple to apply and uses a single interaction parameter.[10] In doing so, it assumes the interaction is constant for all drug pairs and gives the surface a symmetric shape. This is an advantage when coverage of the surface is uneven but may lead to forcing the data to fit a shape that the data do not actually possess. (This model is used in Fig. 6.11 and 6.12.)

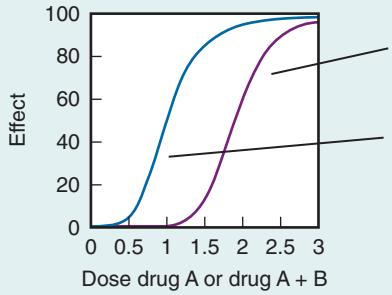
The Minto model is capable of capturing virtually any shape across the response surface.[7] It preserves the sigmoid shape of the dose-response curve for all drug combinations and is suitable for describing all commonly encountered drug interactions in anesthesia, including those between a pharmacologic agonist-antagonist combination (see Fig. 6.4). Interactions can be applied to each of the variables in the sigmoid E_{max} equation individually. This facilitates describing interactions between those drugs whose individual response curves are diverse in terms of curve shape, slope, and maxima, and allows the investigator to determine the required level of model complexity, although the model has been criticized for having too many parameters. (This model is used in Fig. 6.7.)

The model of Bouillon et al., also known as the hierarchical model, sequentially processes drug effects for one drug, then the other drug.[19] It is simple to implement but has the quirk that parameter estimates will vary depending on their order of introduction into the model. Although the order by which drugs should be introduced into the model might appear logical, there are no formal criteria established and the order of analysis that results in the best fit to the data can vary for different endpoints within the same dataset. The model makes the assumption that the relationship follows a sigmoid dose-response curve but does not make a mathematical assumption about the shape of the combined surface. There is no interaction parameter, but instead goodness-of-fit can be assessed against other models describing the data. (This model is used in Fig. 6.9.) This model has also been extended to describe the effects of three or more drugs.[20]

Generic trial designs for the three methods for studying drug interactions are summarized in Fig. 6.6. Suitable methodology and power analysis for response surface trial design have been determined by simulation analysis. It is essential that trials cover most of the surface for robust models to be derived.[8] Endpoints can be either continuous (e.g., blood pressure or bispectral index)

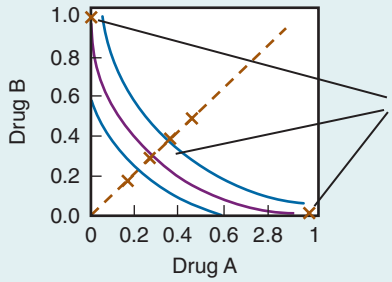


• **Fig. 6.5** Three mathematical approaches to creating a response surface model for a pair of anesthetic drugs. *Conc.,* Concentration; E_{max}, maximal effect attainable; EC_{50}, median effective concentration. (Modified from Minto CF, Schnider TW, Short TG, et al. Response surface model for anesthetic drug interactions. *Anesthesiology.* 2000;92:1603–1616; Greco WR, Bravo G, Parsons JC. The search for synergy: a critical review from a response surface perspective. *Pharmacol Rev.* 1995;47:331–385; and Bouillon TW, Bruhn J, Radulescu L, et al. Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. *Anesthesiology.* 2004;100:1353–1372.)

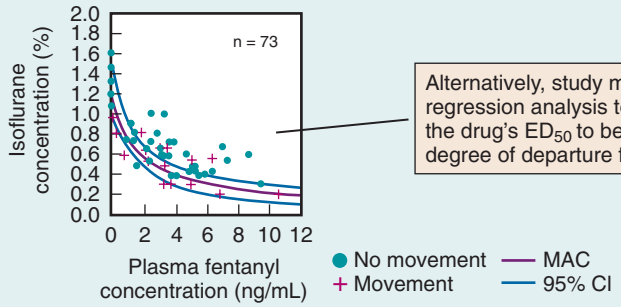


Shift in dose-response curve
The standard population dose-response curve for a drug is determined

Drug A *in presence of drug B*
This is then repeated in the presence of a second drug. The approach is suitable for either quantal data where patients are given a range of fixed doses, or continuous data where the entire dose-response curve can be described in each patient (e.g., propofol ED_{50} alone and in the presence of fentanyl 1 μg/kg at an endpoint of immobility).[11] In this example, drug B has reduced dose requirements of drug A by 50%.

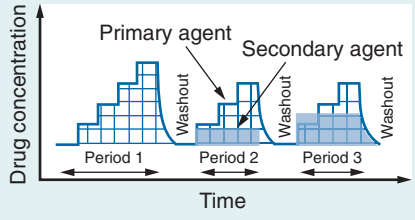


An isobologram
1. Study each drug individually to obtain individual ED_{50}s.
2. Study fixed ratios of the two drugs to find the combined ED_{50}.
3. Iso-effect lines for ED_{50}, ED_5, and ED_{95} are interpolated. There is a 33% reduction in expected dose using the combination. This degree of synergy is found when propofol and midazolam are given together for hypnosis.[43]

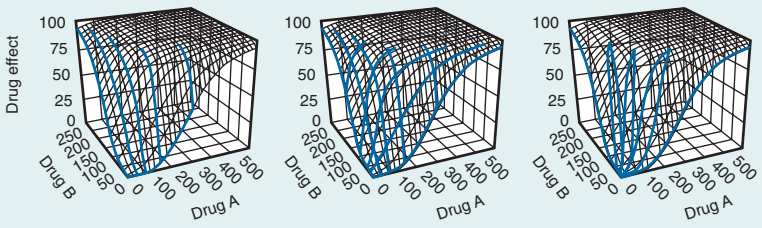


Alternatively, study multiple dose pairings of the drug and perform a nonlinear regression analysis to find the isobologram.[12] Note that it is not essential for each of the drug's ED_{50} to be known to demonstrate synergy with the combination, but the degree of departure from additivity cannot be precisely estimated.

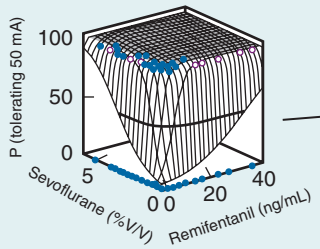
A response surface
These can be created for quantal or continuous data. Studying just 20 patients has been found adequate to characterize response surfaces using a continuous measure such as bispectral index. It is essential to cover most of the surface. The optimal design criss-crosses the surface giving the most robust result.



Study plan for individual patients[15]
1. Use stepped infusions of first drug, wait for steady state, make effect measurements such as bispectral index, movement to pain, blood pressure, etc.
2. Repeat using fixed concentrations of second drug.

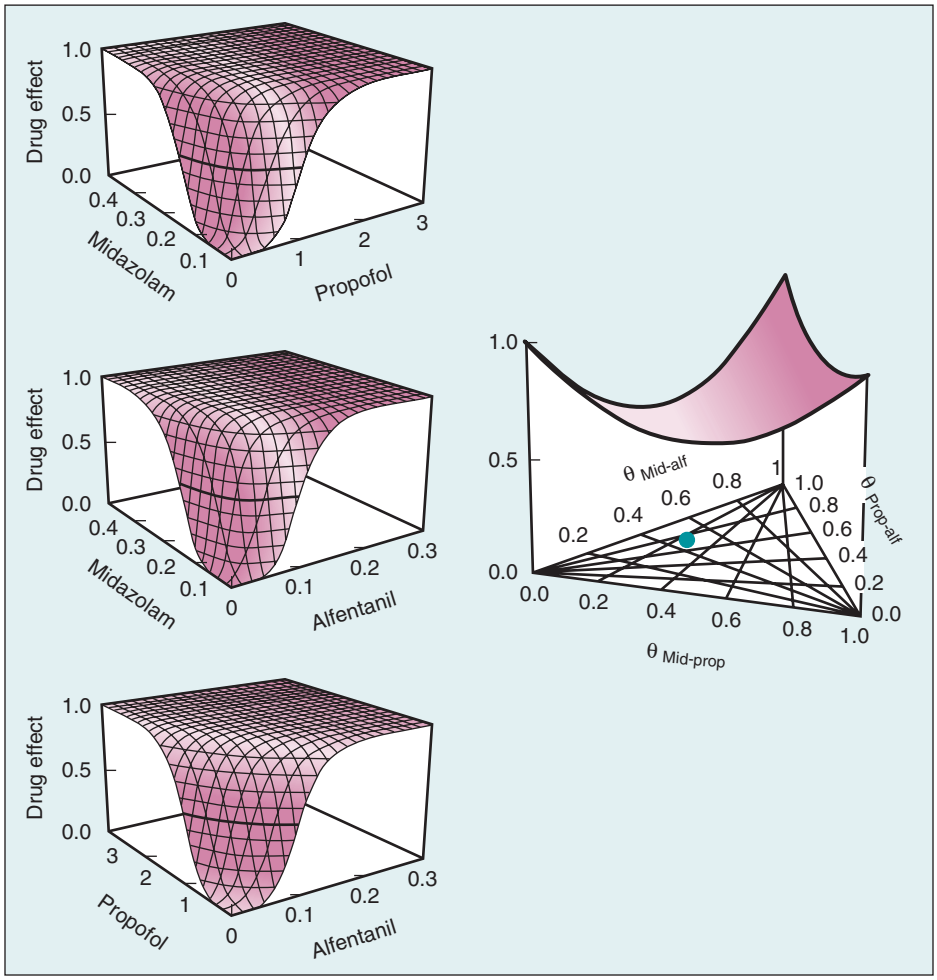


Three designs for covering the surface using continuous data[8]
The criss-crossed design (center) requires fewer patients to capture the interaction than do the alternative designs (using fixed concentrations of one drug with varying concentrations of the second drug, or varying both drug concentrations together in a fixed dosing ratio).



For quantal data
The effect is either 0 or 100%.
The figure shows the interaction between remifentanil and sevoflurane for a noxious stimulus.[15]

• **Fig. 6.6** Trial design for studying drug interactions. *ED_{50},* Median effect dose; *ED_{95},* effective dose, 95% response; *MAC,* minimum alveolar concentration.



• **Fig. 6.7** Response surfaces for paired interactions between propofol, midazolam, and alfentanil for an endpoint of loss of response to verbal command; the paired combinations all showed synergy. The figure on the right shows the ED_{50} isoboles for each of the paired interactions. The three-drug combination caused no more synergy than expected from the paired interactions but would appear as a deeper hollow in the parameter surface if it existed. The *blue dot* on the "floor" of the graph indicates the nadir of the three-drug combination surface. $^{\theta}$*Mid-alf,* midazolam and alfentanil; $^{\theta}$*Mid-prop,* midazolam and propofol. (Modified from Minto CF, Schnider TW, Short TG, et al. Response surface model for anesthetic drug interactions. *Anesthesiology.* 2000;92:1603–1616.)

or quantal (e.g., response to verbal command or surgical incision). The type of interaction is identified by comparing an additive model, where the interaction parameter is excluded or is made to equal zero, with one that has an active interaction parameter. The choice of the best model is made by visual inspection of the surface, comparison of residual plots, and statistical testing of the reduction in log likelihood between related models.[7,8] The response surface method can be extended to three or more drugs, although clear visualization becomes impractical beyond three drug interactions (Fig. 6.7).

Pharmacologic Basis of Drug Interactions

The interactions described in this chapter are based on observational data rather than being derived from an understanding of underlying pharmacologic mechanisms. They are important because the degree of synergy is often large and cannot usually be inferred from knowledge of the individual drug actions. Synergy may also be present for undesirable side effects such as hypotension or respiratory depression. Drugs with known effects at gamma-aminobutyric acid $(GABA)_A$ and opioid receptors usually show additivity or synergy when given together.[9] It is thought that this synergy is mostly a result of drugs with separate mechanisms acting to produce the same effect. However, drugs with known primary actions at N-methyl-D-aspartate (NMDA) receptors such as ketamine or nitrous oxide do not interact synergistically with GABAergic drugs. Evidence supports both pharmacokinetic and pharmacodynamic explanations for drug synergy.

The most extensive research into the mechanisms for synergy is for propofol and midazolam. In the presence of propofol, midazolam concentrations are increased by 25%; the reverse also holds true for propofol in the presence of midazolam.[21,22] This pharmacokinetic effect is not large enough to explain all of the observed interactions. Observations of sedative and hemodynamic endpoints found synergy for sedation and additivity for hemodynamic effects. In vitro studies of $GABA_A$ receptors have also shown

a similar degree of pharmacodynamic interaction, with midazolam markedly reducing propofol requirements to hyperpolarize the postsynaptic membrane potential.[23] The interaction occurred only when GABA concentrations were low, disappearing at high GABA concentrations. The extensive study of this drug combination using a variety of methods and the consistency of the finding of synergy also indicates that the various methods used to study interactions are robust. In vitro testing of propofol and sevoflurane in combination has also found additivity at $GABA_A$ receptors.[24]

When intravenous propofol was used for induction, a small dose of propofol given 2 minutes before a subsequent dose reduced total propofol requirement by 30% compared with a single bolus dose of propofol.[25] The study introduces the concept of temporal relationships in drug interactions, which can be clinically important at anesthetic induction. It is unknown whether this effect was due to pharmacokinetic or pharmacodynamic causes.

Understanding Drug Interactions Among Commonly Used Anesthetic Drugs

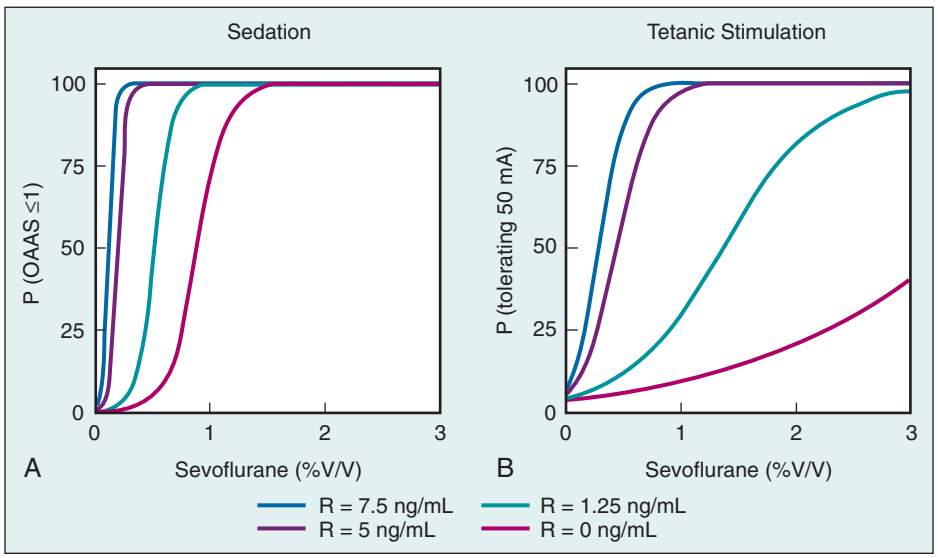
Inhaled Anesthetics and Opioids

Inhaled anesthetics and opioids are the most commonly used drug combination for anesthesia maintenance. As stated, at a hypnotic endpoint, low concentrations of fentanyl 1 to 2 ng/mL have a minor effect on volatile anesthetic dose.[12] At larger doses of fentanyl, there is increasing sedation and a ceiling effect becomes apparent, after which no further increases in effect are seen despite increasing concentration. As even high doses of opioids alone cannot guarantee unconsciousness, supplementation with 0.1 to 0.2 minimum alveolar concentration (MAC) of volatile anesthetic is required to ensure that this endpoint is achieved.[12,26–29] Similarly, on emergence, small doses of opioid have little effect on waking concentrations of volatile anesthetic.[30]

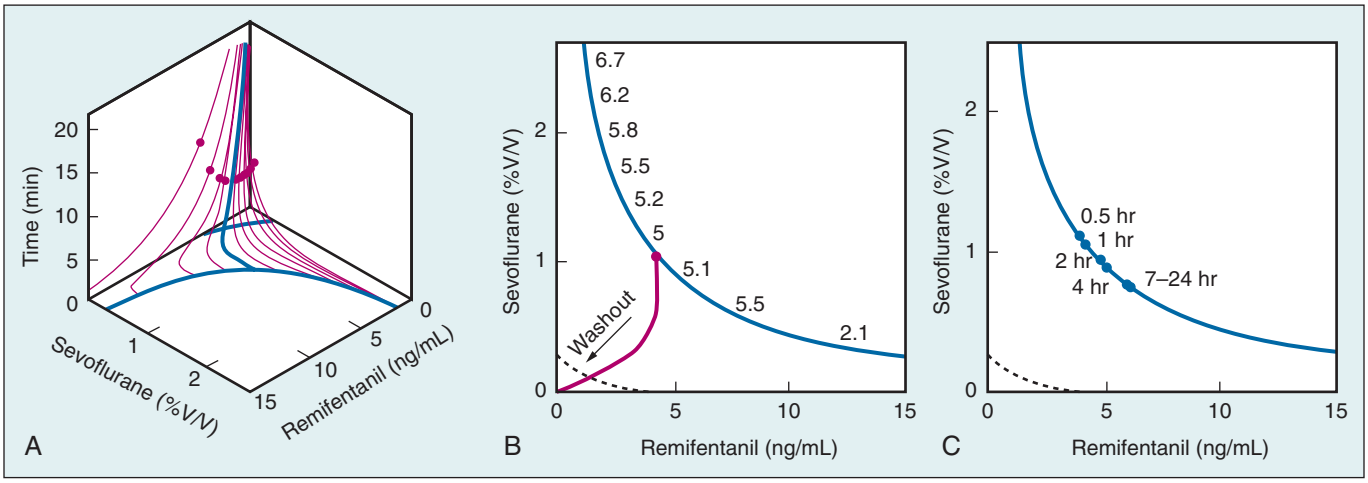
For noxious endpoints there is marked synergy. This is usually expressed as opioid infusion requirements to reduce MAC by 50%. This value is equivalent to the MAC suppression produced by 60% to 70% nitrous oxide and provides a useful reference point for comparing the relative analgesic effects of opioids.[31] Again there is a ceiling to the opioid effect with even very large doses of opioid not guaranteeing a lack of movement to noxious stimulus when given as a sole agent.[12,26,27] Isoflurane has been the most frequently studied drug, but similar results have been found for sevoflurane-fentanyl and desflurane-fentanyl combinations.

Models for a variety of volatile anesthetic-opioid combinations have been created that can be implemented in real time for any dose combination and to make predictions of optimal dose pairings. There are therapeutic benefits to the combination in terms of reduced volatile anesthetic use, more rapid emergence, and improved hemodynamic stability in response to surgery without excessive cardiac depression or unnecessarily deep anesthesia.

Sevoflurane and remifentanil are synergistic in preventing movement to pain with remifentanil at 1.25 ng/mL more than halving sevoflurane requirements when given alone (Fig. 6.8).[32] Remifentanil also decreases variability in sevoflurane requirements with increasing concentrations of remifentanil, reflected by much steeper population dose-response curves. These results can be generalized within drug classes, allowing isoflurane and fentanyl to be substituted for sevoflurane and remifentanil without affecting the model's ability to predict the effects of the combination.[33] The model can be used to make predictions of recovery times after anesthesia (Fig. 6.9). Although the spread in actual recovery times was 6 to 15 minutes, 50% of patients woke within 2 minutes of predicted recovery time. Using a pharmacodynamic model of



• **Fig. 6.8** Dose-response curves for sevoflurane-remifentanil combinations for a sedative endpoint (A) and a noxious endpoint (B). Remifentanil markedly reduces dose requirements and also steepens the dose-response curve, making dosage more predictable. *OASS,* Observer assessment of alertness-sedation; *P,* probability; 1 = no response to moderate prodding or shaking; 50 mA is a tetanic stimulus of 50 mA applied for 5 seconds, a noxious stimulus similar to surgical incision. *R,* remifentanil. (Reprinted with permission from Manyam SC, Gupta DK, Johnson KB, et al. Opioid-volatile synergy: a response surface model with remifentanil and sevoflurane as prototypes. *Anesthesiology.* 2006;105:267–278.)



• **Fig. 6.9** Modeling of sevoflurane-remifentanil combinations that suppress response to a noxious stimulus in 95% of patients with most rapid emergence after a 1-hour procedure. Graph A shows the predicted decline in effect site and alveolar concentrations for remifentanil and sevoflurane after stopping drug administration regimens targeted to reach the EC_{95} isobole for tetanic stimulation for 1 hour. The EC_{95} isobole is on the "floor" of the cube; the vertical axis represents time elapsed since stopping the administration of the drugs. The isobole representing an 80% probability of the return of responsiveness (Observer's Assessment of Alertness/Sedation score >4) is shown by dots superimposed on the concentration decay curves. The *highlighted curve* is the sevoflurane and remifentanil target concentration pair that resulted in the fastest return of responsiveness. In graph B, the numbers on the isobole are wake-up times (in minutes) for a variety of dose pairs; the minimum wake-up time in 50% of patients was 5 minutes. The effect of increasing duration of infusion is shown in graph C, where a small increase in the ratio of remifentanil to sevoflurane is required for earliest wake-up owing to greater accumulation of sevoflurane after prolonged use. (Reprinted with permission from Manyam SC, Gupta DK, Johnson KB, et al. Opioid-volatile synergy: a response surface model with remifentanil and sevoflurane as prototypes. *Anesthesiology.* 2006;105:267–278.)

sevoflurane concentration rather than relying on end-tidal anesthetic concentrations has further improved the model.[34] End-tidal concentrations do not allow forward prediction of effects caused by volatile anesthetic accumulation over time.

Inhaled Anesthetics and Other Agents

Benzodiazepines reduce volatile anesthetic requirements. Premedication with midazolam 0.05 mg/kg reduces desflurane MAC by 20% during brief procedures. The nature of the interaction has not been determined.[35] Ketamine has been formally studied only in animals, wherein marked synergy was demonstrated in the MAC of isoflurane in dogs.[36] The α_2-adrenergic agonists clonidine and dexmedetomidine decrease dose requirements of isoflurane and sevoflurane in clinical studies.[37–40] Oral clonidine 5 μg/kg reduced isoflurane MAC by 20%. A dexmedetomidine infusion of 0.6 ng/mL reduced sevoflurane MAC by 20%. The nature of the interaction has not been determined. Studies of nitrous oxide combined with volatile anesthetics have found mild infra-additivity for an endpoint of MAC, but additivity in processed electroencephalogram (median power).[41,42]

Propofol

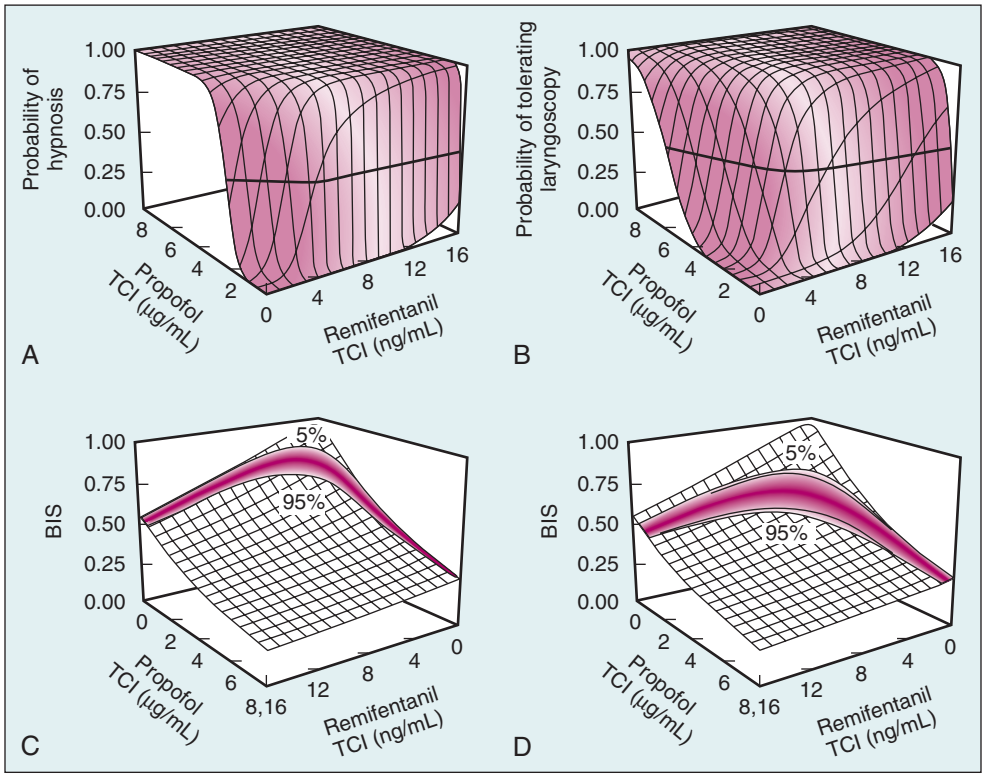
Propofol drug interactions with midazolam, opioids, and volatiles have been extensively studied at a variety of endpoints, including light sedation, lack of movement to a noxious stimulus, and change in blood pressure.

Propofol and Midazolam

This combination acts synergistically at an endpoint of hypnosis, causing a 37% decrease in expected dose at anesthesia induction (see Fig. 6.7).[43] The effect is present both following bolus doses and during infusions and does not depend on the order of administration of the drugs.[20,21] A response surface was constructed using infusion of the combination and found the optimal ratio for hypnotic synergy to be propofol 4.7 ng/mL:midazolam 1 ng/mL.[22] The hemodynamic effects of the combination were additive, with propofol depressing blood pressure 3.1 times more than an "equihypnotic" dose of midazolam. Because of the hypnotic synergy, this meant that the combination caused less hemodynamic depression than propofol did as a sole agent, indicating a therapeutic benefit from use of the combination. Hemodynamic responses after a noxious stimulus were not studied. Midazolam also markedly decreases the amount of propofol required to produce immobility to a noxious stimulus, while lacking the ability to produce immobility when given as a sole agent, even at the high dose of 1 mg/kg.[43] This interaction can be used to reduce total propofol dose during prolonged procedures and might also provide a cost benefit.

Propofol and Opioids

This is the most commonly used drug combination for intravenous induction of anesthesia and total intravenous anesthesia; it is also used in low doses for procedural sedation. At anesthesia induction, small doses of opioids, such as fentanyl 1 μg/kg, have a small effect



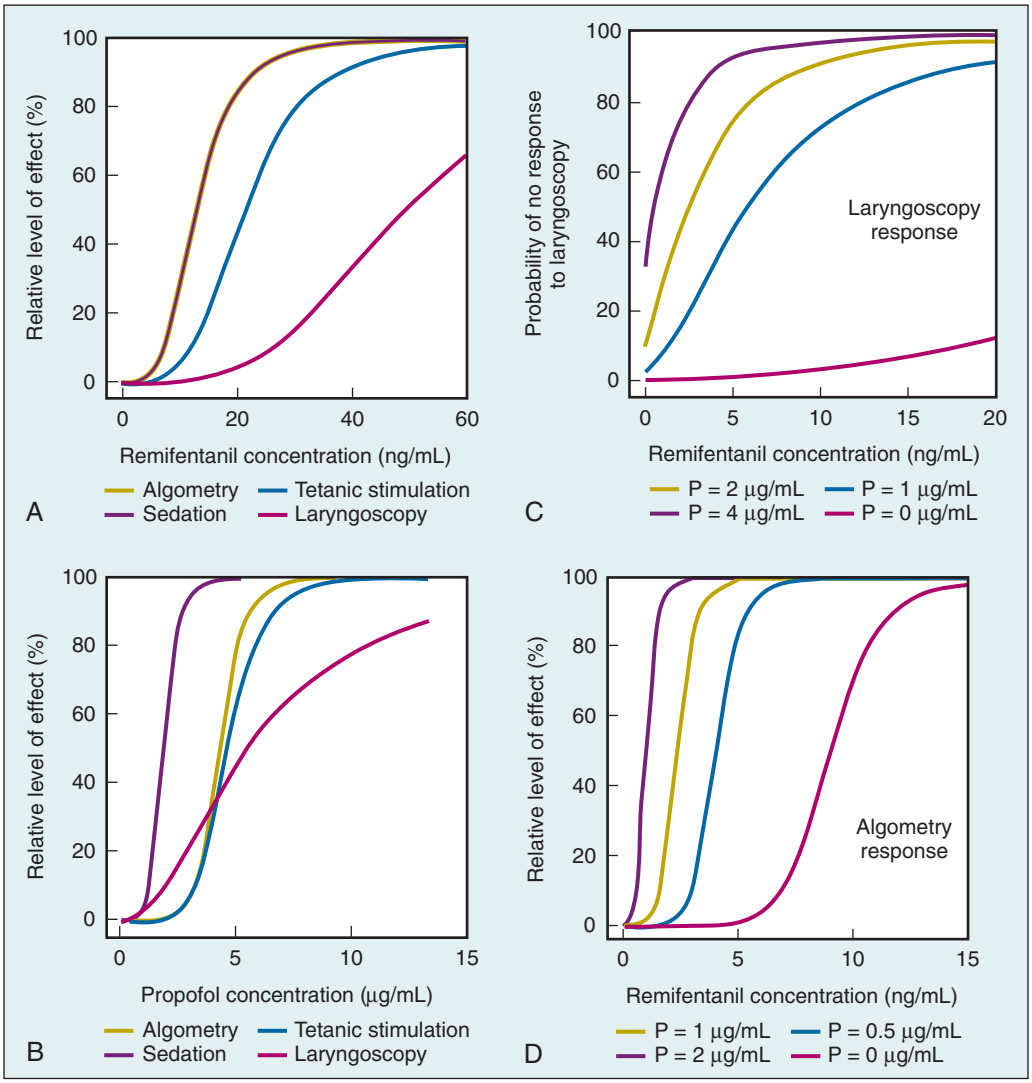
• **Fig. 6.10** Response surfaces for propofol-remifentanil interaction at an endpoint of hypnosis (A) defined as no response to shouting and shaking, and response to a noxious endpoint (B) defined as no response to laryngoscopy. The isoboles for the two endpoints have been superimposed on the bispectral index *(BIS)* response surface in C and D, respectively. The authors have reversed the orientation of the response surface in C and D, with maximum dose at the back and maximum effect at the bottom of the graph. The study shows a high degree of synergy at both endpoints and the inability of remifentanil when given as a sole agent to reliably achieve either endpoint, even at high doses. The synergy seen in the hypnotic and noxious endpoints does not extend to the BIS, where the interaction is additive. This is possibly due to remifentanil having little effect on the electroencephalogram in the clinical dose range used. Overlaying these two clinical endpoints on the BIS surface demonstrates the difference between synergy at the noxious endpoint and additivity in the BIS. *TCI,* Target Controlled Infusion. (Reprinted with permission from Bouillon TW, Bruhn J, Radulescu L, et al. Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. *Anesthesiology.* 2004;100:1353–1372.)

on the hypnotic dose of propofol, reducing dose requirements by 20%, but a large effect on propofol dose to suppress movement to pain, reducing dose requirements by 50%. There have been five detailed studies of combined propofol and remifentanil infusion using response surface models.[19,44–47] The combination is synergistic at all clinical endpoints and is strongest at concentrations of remifentanil up to 4 ng/mL (equivalent to the effect of a steady-state infusion rate of approximately 0.15 μg/kg per minute in a young adult), where there is a 66% reduction in expected dose with little further synergy shown by higher doses of remifentanil. The bispectral index is additive in this concentration range, presumably because remifentanil causes little sedation when used as a sole agent in low doses; studies using very high concentrations of remifentanil have shown synergy (Figs. 6.10 and 6.11).[45]

Response surface models have been used to optimize drug-dose ratios for useful clinical endpoints.[46] Optimal combinations for early wake-up times show that using relatively more remifentanil to propofol is advantageous when compared with using fentanyl with propofol. Equipotent optimal dose ratios were approximately propofol 2 μg/mL:remifentanil 5 ng/mL compared with propofol 3.5 μg/mL:fentanyl 1.5 ng/mL (Fig. 6.12). A study of respiratory effects showed marked synergy for this undesirable side effect and that it is not possible to reliably suppress response to noxious stimuli with the combination without inducing significant respiratory depression in most patients (Fig. 6.13). Note that blood pressure changes in response to sustained noxious stimuli such as surgical incision have not been studied. These recommendations might also need to be modified depending on the degree of hemodynamic suppression allowed. For clinical purposes, equivalent doses of the phenylpiperidine opioids fentanyl, alfentanil, sufentanil, and remifentanil can be used interchangeably as the degree of interaction with propofol is thought to be the same.[46]

Propofol and Inhaled Anesthetics

This combination is used at non–steady state at the beginning of all anesthetics where intravenous induction is followed by volatile maintenance. Sevoflurane and propofol have been studied at a

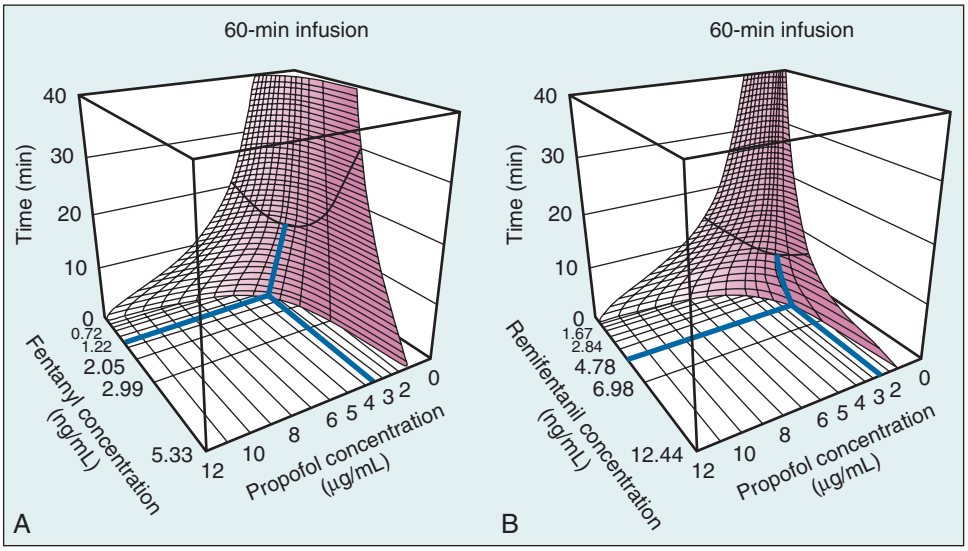


• **Fig. 6.11** Change in propofol requirement with increasing doses of remifentanil. The concentration-effect relationships for remifentanil and propofol alone for various endpoints are shown in A and B (these represent the far right and far left axes of response surface plots for each endpoint). Plots C and D are concentration-response curves derived from response surfaces (i.e., these graphs are "cuts" through the surfaces at various propofol concentrations); this representation allows simplified interpretation. Note the very high concentration of remifentanil in graph A compared with graphs C and D; in the standard clinical range up to 10 ng/mL target concentration, remifentanil is only mildly sedative, whereas propofol potently suppresses all but the most painful stimuli. In combination, remifentanil potently decreases the amount of propofol required to suppress noxious stimuli such as laryngoscopy, but there was little additional synergy gained by increasing remifentanil concentrations above 4 ng/mL as illustrated in the study in Fig. 6.11. *P,* Steady-state propofol concentration. (Reprinted with permission from Kern SE, Xie G, White JL, et al. A response surface analysis of propofol-remifentanil pharmacodynamic interaction in volunteers. *Anesthesiology.* 2004;100:1373–1381.)

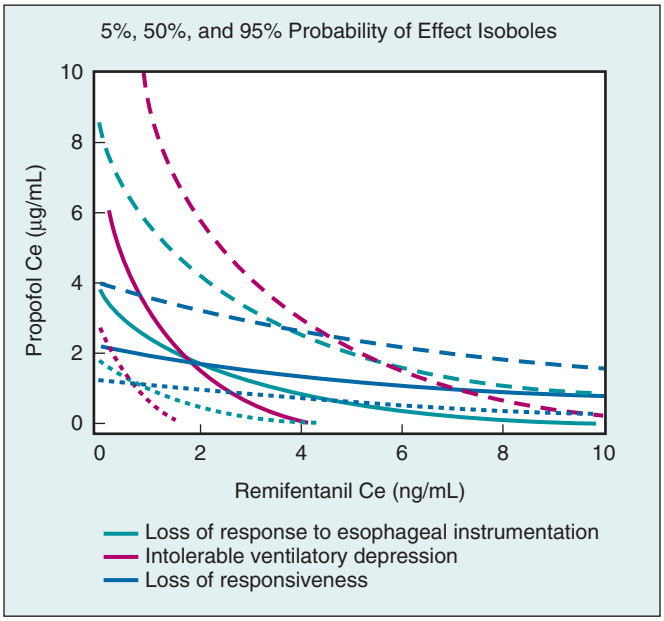
variety of endpoints ranging from response to shaking and shouting to response to surgical incision.[48–50] The combination is additive at all endpoints. Additivity was also shown for the bispectral index and other processed electroencephalogram indices such as spectral entropy and response entropy, both in volunteer studies and in the clinical setting. It is thought that other volatile agents such as desflurane and isoflurane behave similarly, but they have not been formally studied. Nitrous oxide 67% decreases propofol requirements by 25% to 35% for the endpoint of surgical incision. Two studies of target controlled infusions of propofol in the presence of nitrous oxide 67% have found the median effect dose (ED_{50}) of propofol to be 4.5 and 4.9 µg/mL, respectively. This is an example of an infra-additive drug interaction.[51,52] The three-drug combination of propofol, remifentanil, and sevoflurane has also been studied and found to be additive.[53]

Midazolam and Opioids

This combination has not been studied in detail using response surface methodology. Basic studies using isobolographic analysis



• **Fig. 6.12** Optimization of propofol-opioid total intravenous anesthesia for fentanyl (A) and remifentanil (B). The optimal dose ratios to provide 95% probability of no movement to surgical stimulus with earliest wakeup times were propofol 3.4 µg/mL: fentanyl 1.3 ng/mL and propofol 2.5 µg/mL:remifentanil 4.8 ng/mL. The superimposed *blue lines* indicate these optimal doses. The estimated time to 50% of patients being awake is 12 minutes for propofol-fentanyl and 6 minutes for propofol-remifentanil. The rapid offset of remifentanil compared with fentanyl means a higher ratio of opioid to propofol results in earlier wake-up times. Data are only displayed for a 1-hour infusion, with the differences smaller after brief infusions and greater with prolonged infusions. (Reprinted with permission from Vuyk J, Mertens MJ, Olofsen E, et al. Propofol anesthesia and rational opioid selection: determination of optimal EC50-EC95 propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. *Anesthesiology.* 1997;87:1549–1562.)



• **Fig. 6.13** Adequate suppression of response to shaking and shouting *(blue)* and to a noxious stimulus (esophageal instrumentation, *red*) without unacceptable respiratory depression. The latter is defined as a respiratory rate less than 5 breaths/min *(green).* Note that the spread of concentration targets is very wide with the ED_{95} being double the ED_{50}, and the ED_5 being less than half the ED_{50}. The *solid lines* are for ED_{50}, the *dotted lines* ED_5, and the *dashed lines* ED_{95}. *ED_5,* Effective dose, 5% response *ED_{50},* median effect dose; *ED_{95},* effective dose, 95% response. (Reprinted with permission from LaPierre CD, Johnson KB, Randall BR, et al. An exploration of remifentanil-propofol combinations that lead to loss of response to esophageal instrumentation, a loss of responsiveness, and/or onset of intolerable ventilatory depression. *Anesth Analg.* 2011;113(3):490–499.)

have shown midazolam and fentanyl or alfentanil to act synergistically to produce hypnosis.[54–56] Midazolam also potently suppresses opioid requirements to reduce movement to a noxious stimulus. The triple combination of propofol, alfentanil, and midazolam has been studied for an endpoint of hypnosis.[7,54,55] The triple combination caused no more effect than expected from the individual drugs and their paired interactions, which all showed synergy (see Fig. 6.7). Note that although the data are shown here as a response surface, the coverage of the surface is not good; only a single fixed dose ratio has been studied using each combination.

Ketamine and Midazolam or Propofol

Ketamine and propofol are known to have distinctly different modes of action. Midazolam is often used to suppress emergence phenomena related to ketamine and can also be used in combination for sedation or induction of anesthesia. Midazolam has an infra-additive effect on ketamine hypnosis and no effect on the ketamine dose required to suppress movement to a noxious stimulus.[57] The combination of propofol and ketamine has an additive effect for an endpoint of sedation, and propofol has only a small influence on ketamine doses required to block movement to a noxious stimulus (i.e., infra-additive).[58] The drugs have opposing effects on hemodynamic variables. At an optimal propofol:ketamine dose ratio of 3:1 there is minimal change in both heart rate and blood pressure when used for anesthesia induction in healthy patients.

Other Drugs and Applications

The use of response surface models to describe pharmacodynamic interactions is spreading beyond investigating anesthetic drug pairs

and into other drug combinations. Recently response surface methodology was used to quantify synergy for rocuronium- and cisatracurium-induced muscle relaxation using train-of-four as the effect signal.[59] In pediatrics, response surface models have been used to suggest optimal propofol-ketamine combinations for light sedation requiring analgesia and to predict wake-up times,[60] and have been integrated with other information such as study attrition and models of baseline pain to interpret combined analgesic data in children following tonsillectomy.[61] There are currently no studies that test whether adult interaction studies also apply to children.

Emerging Developments

Drug Interaction Displays on Monitors

Manufacturers have incorporated response surface models of drug action into new anesthesia monitor displays (Navigator Applications Suite, GE Healthcare, Helsinki, Finland; SmartPilot View, Intelligent Display, Dräger Medical AG & Co. KG, Lübeck, Germany). These systems display probabilities of hypnosis and movement to pain based on population models for the drugs used (Fig. 6.14). The models contain adjustments for age, weight, height, and sex and

• **Fig. 6.14** Real-time displays of predicted anesthetic drug effects. The top screen shows the interaction between propofol and sevoflurane in a patient induced with propofol for endpoints of sedation and analgesia. Notice the gap in our knowledge soon after induction, because the three-drug interaction among propofol, remifentanil, and sevoflurane has not been studied. The lower display shows propofol-remifentanil anesthesia. The isobologram on the left has shaded scales showing the population ED_{50} for light anesthesia and deep anesthesia and the ED_{95} for deep anesthesia. The line on the isobologram shows the effect course the patient has taken, including a prediction of the future effect course given the current dosage. *ED_{50}*, Median effect dose; *ED_{95}*, effective dose, 95% response. (Navigator Applications Suite, GE Healthcare, Helsinki, Finland; and SmartPilot View, Intelligent Display, Dräger Medical AG & Co. KG, Lübeck, Germany.)

display the influence of opioids on MAC of the volatile anesthetic used and the interaction between propofol and opioid to make predictions of anesthetic effect and time to waking. As well as providing a probability of response, they also display the variation in response expected in a typical patient population with ED_{50} and ED_{95} displayed. The calculations are done in real time with adjustments in dosage continuously incorporated into the model to predict likely effects. This real-time modeling greatly increases the dosing information available to anesthetists and is an improvement on current displays, which are often limited to a single number for MAC that is not adjusted for age. These prediction modules are intended to bring the detailed knowledge about anesthetic drug behavior found in textbooks and the modeling literature to the clinical domain by applying the models in real time in a user-friendly display.

Such information can be used to guide a more accurate titration of volatile and opioid dose. The population modeling of the drug interactions also allows prediction of a probability of movement, something that current depth monitors such as the bispectral index cannot do.[19,32] The displays provide information at both sedative and noxious endpoints and also provide predictions of recovery time. The inclusion of probabilities of movement and time to waking might appear overly detailed, but they give a more accurate appraisal of the sedative effects of the drugs given and their likely time course than was previously available. They also reduce task load in the operating room.[62] The library of drugs incorporated into these displays is currently limited to commonly used opioids, volatile anesthetics, and propofol. It has been shown that isoflurane can be substituted for sevoflurane and fentanyl for remifentanil without loss of fidelity of the model, providing further evidence that phenylpiperidine-based opioids behave similarly and can be used interchangeably.

Pharmacodynamic-Based Target Control and Closed-loop Infusions

Pharmacodynamic model, target-controlled infusion of propofol and remifentanil has been studied in trials experimentally using a response surface model to control the concentrations of the two drugs to produce a predicted level of effect (bispectral index) rather than a predicted blood concentration.[63] The concept allows drug titration to alter reflex suppression with an opioid without altering anesthetic depth. Analogous to this, a dual closed-loop controller that achieves the same objective by titrating propofol and remifentanil in response to both bispectral index and arterial pressure targets.[64] These devices both carry the promise of improved accuracy in the titration of anesthetic drugs to patient need.

Key Points

- Current anesthetic practice is based on the use of drug combinations, a concept termed *balanced anesthesia* by Lundy in 1926. Study of the pharmacology of common combinations of drugs has greatly increased our knowledge of clinical anesthetic pharmacology.
- Drug interactions can be described by (1) shifts in dose-response curves, where one drug influences the dose-response curve for a second drug; (2) isobolograms, which are isoeffect lines for two drugs both capable of influencing the endpoint in question; and (3) response surfaces, which create models of all possible combinations of two or more drugs for a given effect.
- Drug interaction studies can be used to define optimal dose ratios for desired outcomes such as maximum synergy (or lowest total dose), most rapid emergence, and least respiratory or hemodynamic depression.
- The combinations of propofol with an opioid, and a volatile agent with an opioid, show a small additive effect at hypnotic endpoints and a large degree of synergy in suppression of response to a noxious stimulus. The combination of propofol with a volatile anesthetic such as sevoflurane is additive.
- Response surface models can be used in real time to create predictions of likely anesthetic effect in the operating room. These models have been incorporated into a new generation of monitor displays and are a sophisticated advance on the simple display of a predicted MAC value on most current anesthesia monitors.

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Schumacher PM, Dossche J, Mortier EP, et al. Response surface modeling of the interaction between propofol and sevoflurane. *Anesthesiology*. 2009;111:790–804. This study provides a description of the propofol-volatile anesthetic interaction that is commonly used but often ignored by anesthetists. It includes a detailed description of the methodology and analysis of a clinical drug interaction study. (Ref. 49)

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7

Adverse Drug Reactions

ABHINAV KANT, JONATHAN BILMEN, AND PHILIP M. HOPKINS

CHAPTER OUTLINE

Definition

Drug Administration Errors

Types of Adverse Drug Reactions
- Type A Reactions: Augmented (Dose-Related)
- Type B Reactions: Bizarre (Drug Idiosyncrasy, Non–Dose-Related)
  - *Acetylator Status*
  - *Cytochrome P450 Variants*
  - *Plasma Cholinesterase Variants*
  - *Glucose-6-Phosphate Dehydrogenase Deficiency*
  - *The Porphyrias*
  - *Malignant Hyperthermia*
  - *Allergic Drug Reactions*
- Type C Reactions: Chronic (Direct Organ Damage, Dose-Related, and Time-Related)
- Type D Reactions: Delayed (Time-Related)
  - *Type E Reaction: End of Use (Withdrawal)*
  - *Type F Reactions: Drug Failure*

Emerging Developments
- "Swiss Cheese" Model in Adverse Drug Reactions
- New Technology to Decrease Drug Errors in Anesthesia

Definition

No medicine is risk free, yet the definition of an adverse drug reaction may not be straightforward. The World Health Organization (1972 Technical Report No. 498) defines an adverse drug reaction as "A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function." One particular problem with this vague definition is that it assumes that all individuals are the same and hence the "normal dose" of a drug is to be comparable within a population. It does not consider differences in pathophysiology within individuals that can alter the way a drug behaves in terms of its pharmacokinetics or pharmacodynamics. Another problem is that it can be difficult to distinguish an adverse drug reaction from what is commonly known as a "side effect." A side effect can occur within or outside the normal dose of a medication. One particular aspect of a side effect, which may differ from an adverse drug reaction, is that the effect can be beneficial. An example in anesthetic practice is the use of lidocaine as an antiarrhythmic.[1] This drug was originally licensed for its use as a local anesthetic, yet its inhibitory effects on cardiac sodium channels can be used to dampen cardiac conduction. Further confusion with the definition of an adverse drug reaction is when a drug is being researched or is under surveillance after its initial commercial release. The European Medicines Agency good clinical practice guidelines state that "In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions."

The majority of adverse drug reactions can be attributed to a drug interacting with another or several other drugs. The practice of anesthesia involves the coadministration of several drugs alongside any drugs a patient may already be taking. The potential for drug interaction is therefore very high and this topic is covered elsewhere in this book (see Chapter 6).

With regard to anesthetic adverse drug reactions, a large analysis of more than 11,000 adverse drug reactions in more than 6600 patients in the United Kingdom showed a mortality of 9% with the largest proportion (>40% of deaths) associated with inhalation anesthetics and the smallest proportion (8% of deaths) from local anesthetics.[2] The most frequently reported adverse drug reactions were associated with the use of intravenous induction agents.

Historically, adverse drug reactions were classified into two distinct categories; type A and type B.[3] Type A reactions were classed as "dose-related" and included pharmocokinetic and pharmacodynamic variations within populations as well as drug interaction. Type B described reactions that were not dose related but idiosyncratic or allergic and often in genetically susceptible individuals. Type A reactions are more common than type B reactions and count for more than 80% of all reactions. This classification has evolved into one described neatly by Edwards and Aronson[4] and a modification is shown in Table 7.1. This chapter focuses on the general principles of the mechanisms of adverse drug reactions that can be applied to a wide range of drugs used in the practice of anesthesia. For ease, the layout of the chapter reflects the classification as described in Table 7.1.

Drug Administration Errors

Adverse drug reactions can occur if the drug is incorrectly administered to a patient. Note that this does not fall into the classification described previously. Over the past 2 decades, NHS England (and formally the National Patient Safety Agency [NPSA]) and the Institute of Medicine in the United States have both compiled massive data highlighting that this is a serious and widespread

Abstract

In the 16th century, Paracelsus recognised that any medicinal substance has the potential to do harm, defining the dose as the determinant of whether the substance is a remedy or a poison. Despite this prescient and succinct observation, the intervening 450 years have failed to yield an agreed definition of an adverse drug reaction, although they all encompass the notion that intended therapeutic use of a medicine has resulted in unintended harm. We now know that not all adverse drug reactions are dose-related and the distinction between dose-related and non-dose-related reactions is commonly used in classification systems. Dose-related adverse drug reactions reflect inter-individual pharmacokinetic and pharmacodynamic variability. The risks of such reactions occurring with a particular drug depend on the difference between the effective therapeutic dose and the toxic dose, often described as the therapeutic index or certain safety factor. Although dose-related adverse drug reactions are more common during anaesthetic management than non-dose-related reactions, the latter can be the most dangerous, for example malignant hyperthermia or anaphylaxis. Across all branches hospital practice the greatest incidence of adverse drug reactions (total incidence and fatal outcomes) arises from drug administration errors. In anesthetic practice there have extensive analyses of the causes of drug errors and proposals to mitigate the human factors responsible: these include several technological innovations.

Keywords

adverse drug reactions
anesthetics
medication errors
malignant hyperthermia
butyrylcholinesterase
anaphylaxis

TABLE 7.1 Classification of Adverse Drug Reactions

Mnemonic	Type of Reaction	Features
A: Augmented	Dose-related	Common Related to pharmacologic action of the drug Predictable Low mortality
B: Bizzare	Drug idiosyncrasy, non–dose-related	Uncommon Not related to pharmacologic action of the drug Unpredictable High mortality
C: Chronic	Dose-related, time-related, direct organ damage	Uncommon Usually dose-related
D: Delayed	Time-related	Uncommon Usually dose-related Becomes apparent sometime after the administration of the drug
E: End of use	Withdrawal	Uncommon Occurs soon after withdrawal of the drug
F: Failure	Unexpected failure of therapy	Common Dose-related Often caused by drug interactions

Modified from Edwards R, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet.* 2000;356:1255–1259.

issue in hospitals and drug administration errors are the single most preventable cause of patient harm. Although the majority of these reported errors lead to minimal or no harm, in anesthesia they have the potential to cause devastating effects. A U.K. study of 12,606 reported incidents showed medication errors occurred in 1,120 patients.[5] Of these, only 15 (1.3%) resulted in severe harm or even death. A further 6-month analysis of reports to the NPSA regarding drug errors in intensive care showed of the 2428 incidents reported, 355 different drugs were involved, with morphine, gentamicin, and norepinephrine the most common.[6] A review of anesthetic drug errors states that an error can happen as frequently as every 133 anesthetics.[7] Much work is being done to prevent administration errors and recent evidence suggests that double-checking of drugs with a second person may reduce errors.[8,9]

Drug errors need not be as late as the administration phase but can occur during the prescription. Illegible handwriting, inaccurate medication history, confusion with the drug name, inappropriate use of decimal points, use of abbreviations, and use of verbal orders have all been implicated in prescribing errors.[10]

For some drugs, inaccurate knowledge of dosing information among prescribers can lead to erroneous dosing.[11] A drug developed in a nonanesthetic context could have its dosing regimen inappropriately applied to the perioperative situation. This applies to some drugs that were introduced into clinical practice at a time when licensing legislation was less vigorous. A good example of this is morphine, for which the traditional quoted dose for severe postoperative pain is 0.15 mg/kg given intramuscularly. This dose was deemed the effective dose for battlefield casualties. However, one can now accept that battlefield casualties are an inappropriate model for postoperative pain as the pain tolerance of those injured in battle is high as a result of the psychological and neurohumoral response to the situation.[12]

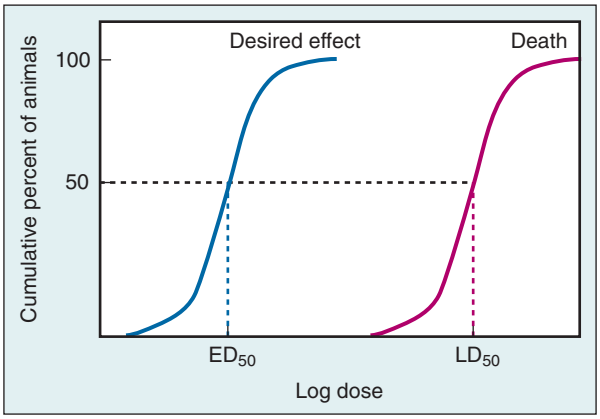
Another example is antiemetic medication. None of the currently available antiemetics was developed primarily for perioperative use. Many were first introduced as treatments for motion sickness, vestibular disorders, migraine, or for the treatment of side effects of radiation therapy or cytotoxic chemotherapy. The butyrephenone droperidol was introduced into anesthetic practice as a neuroleptic agent in a dose of approximately 0.1 mg/kg.[13] Neuroleptanesthesia as a technique is now rarely performed; however, it does still demonstrate the antiemetic efficacy of droperidol. This efficacy is maintained at doses 10 times lower than those used for the neuroleptic effect. It may well be that more commonly used antiemetics such as phenothiazines and antihistamines (see Chapter 34) are also being used in inappropriately high doses in the perioperative setting with potentially avoidable side effects.

Types of Adverse Drug Reactions

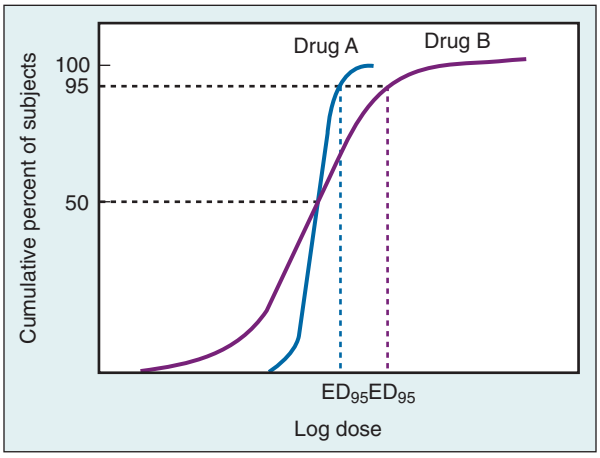
Type A Reactions: Augmented (Dose-Related)

Paracelsus (1493-1541) once noted "All substances are poisons: there is none which is not a poison. The right dose differentiates a poison and a remedy." Despite the administration of a drug in its intended therapeutic dose range, some patients exhibit an adverse effect. This may occur as a result of variation of an individual's drug response within a unimodal population variation in response.[14] This phenomenon is termed *drug intolerance.* The causes of drug intolerance are multifactorial with environmental and genetic factors involved. The intolerance of the drug is invariably related to the dose administered and there are numerous examples of these in anesthesia. One example is the intrathecal administration of a local anesthetic that can result in either a desired, low, or high block level dependent on patient characteristics.[15-17] The most common dose-related reactions seen with anesthetic agents (inhalation or intravenous) are dampening of the normal cardiovascular and respiratory functions, and indeed these reactions are sometimes used for clinical benefit.[18,19] This relationship between desired effect and unwanted effect remains at the forefront of toxicology.

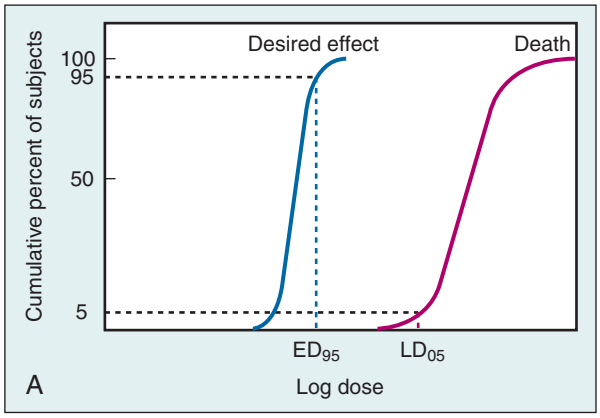
Conventionally we measure the propensity for adverse effects of drugs by the therapeutic index. In the preclinical testing of new drugs, the *therapeutic index* provides a ratio of the LD_{50} (the dose that causes death in 50% of animals) to the ED_{50} (the dose that produces the desired effect in 50% of animals). The LD_{50} and ED_{50} are calculated from cumulative quantal dose-response curves as illustrated in Fig. 7.1. Although widely established within toxicology, the therapeutic index does have its limitations. Consider two drugs A and B with the same ED_{50} value. If the population variability on response to drug B is greater than drug A (Fig. 7.2), then there will be a larger ED_{95} (dose that produces the desired effect in 95% of subjects) value in drug B. Clinically the ED_{95} or even the ED_{99} is far more useful than the ED_{50} as we would want as many patients as possible being treated with a beneficial effective dose, yet the dose must not reach levels that produce important unwanted effects. It also becomes clear that the ED_{50} is not an ideal dose for clinical purposes as one would not want to produce an unwanted/lack of effect in 50% of patients. Figs. 7.3 and 7.4

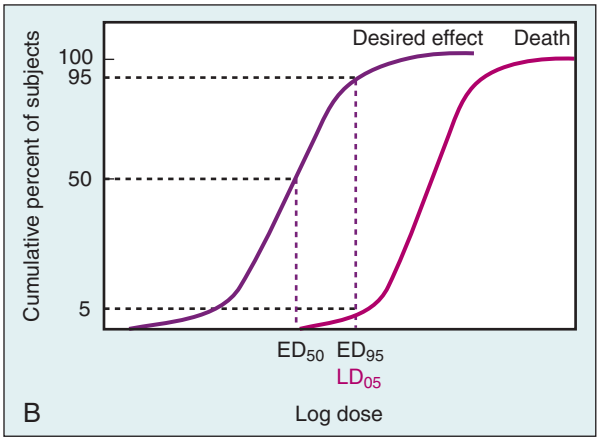


• **Fig. 7.1** Quantal dose-response curves to illustrate derivation of the therapeutic index from the ratio of the LD_{50} (dose that causes death of 50% of animals) to the ED_{50} (the dose that produces the desired effect in 50% of animals).



• **Fig. 7.2** Quantal dose response curve of two drugs with identical ED_{50} but different ED_{95} doses. This results from the greater population variability in response to drug B compared with drug A and illustrates how therapeutic effectiveness can vary between two drugs with similar potency, when potency is defined on the basis of the ED_{50}. *ED_{50}*, Dose that produces the desired effect in 50% of subjects; *ED_{95}*, dose that produces the desired effect in 95% of subjects.





• **Fig. 7.3** Illustration of the principle of the certain safety factor in animal studies. Each panel shows the quantal dose response curves for two effects of the same drug, the desirable therapeutic effect and an unwanted effect, in this case death. For the drug in panel A, there is good separation between the ED_{95} and LD_{05}. The drug in panel B, however, has a reduced certain safety factor because the ED_{95} is identical to the LD_{05}. *ED_{50}*, Dose that produces the desired effect in 50% of animals; *ED_{95}*, dose that produces the desired effect in 95% of animals; *LD_{05}*, dose that is lethal in 5% of animals.

further illustrate this principle. A more useful pharmacologic concept revolves around the *certain safety factor*. This is the ratio of the dose to produce an unwanted effect in a defined proportion of the population (usually 1%) to the dose to produce a desired effect in a proportion 100 minus that defined. In other words, the certain safety factor is most commonly described as TD_{01}/ED_{99}, where TD is the toxic dose. The certain safety factor can be adjusted if the unwanted effect of the drug is particularly serious; hence $TD_{0.1}/ED_{99.9}$ or $TD_{0.01}/LD_{99.99}$, and so on could be used.

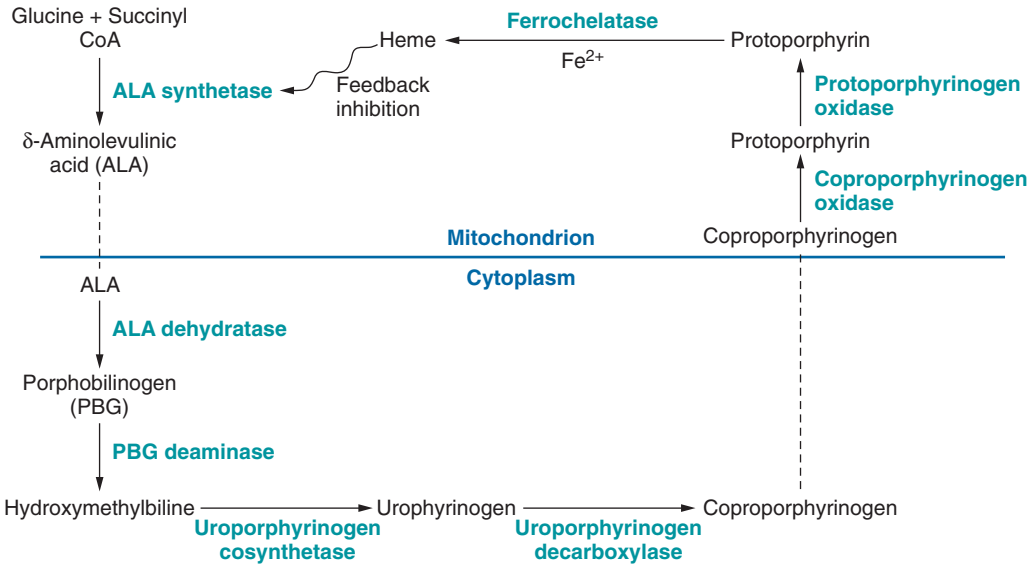
The doses used in the calculation of the certain safety factor also define the limits of the therapeutic window. Dose-response relationships remain a popular area for anesthetic research.[20,21] Newer drugs, combinations of drugs, and techniques to administer them are slowly being introduced in all areas of anesthetic practice and each will undoubtedly have the ability to cause harm.

Type B Reactions: Bizarre (Drug Idiosyncrasy, Non–Dose-Related)

Some adverse drug reactions are not dose related and occur within individuals with genetic susceptibility. Pharmacogenetic variation has been identified in drug metabolism (acetylation, cytochrome P450 variants, plasma cholinesterase variants), inability to compensate for drug effects (glucose 6-phosphate dehydrogenase deficiency, acute porphyrias) in drug effects themselves (malignant hyperthermia), or even immune mediated responses (allergies). Each of these examples is discussed separately (also see Chapter 4).

Acetylator Status

Drugs such as isoniazid, hydralazine, procainamide, some sulfonamides, sulfasalazine, nitrazepam, and caffeine undergo acetylation, which is a phase 2 nonmicrosomal conjugation reaction. The enzyme group responsible are the N-acetyltransferases. There are two different isozymes in humans, encoded by the genes *NAT1* and *NAT2*. *NAT1* is ubiquitously expressed and has 28 polymorphisms described to date, most of which have a similar acetylation rate as the reference gene. Currently there are 88 polymorphisms of *NAT2* recognized. *NAT2* is expressed in the liver, small intestine,



• **Fig. 7.4** The metabolic pathway for heme synthesis. A block in any of the enzymes in the pathway will result in accumulation of porphyrin precursors, especially following metabolic stress or hemorrhage. Fe^{2+}, Ferrous ion.

and colon and is thus regarded as the enzyme responsible for processing xenobiotics. These polymorphisms are responsible for the observed enzyme processing behavior, which defines human individuals as fast, intermediate, or slow acetylators. The prevalence of slow acetylation can be as high as 60% in Caucasians and 10% to 20% in Asians.[22] Slow acetylation, resulting in a prolonged half-life of the drug, can predispose individuals to a greater risk of side effects such as peripheral neuropathy (isoniazid), lupus syndrome (hydralazine and procainamaide), allergic reactions and hemolysis (sulfonamides), and gastrointestinal effects (sulfasalazine).

Cytochrome P450 Variants

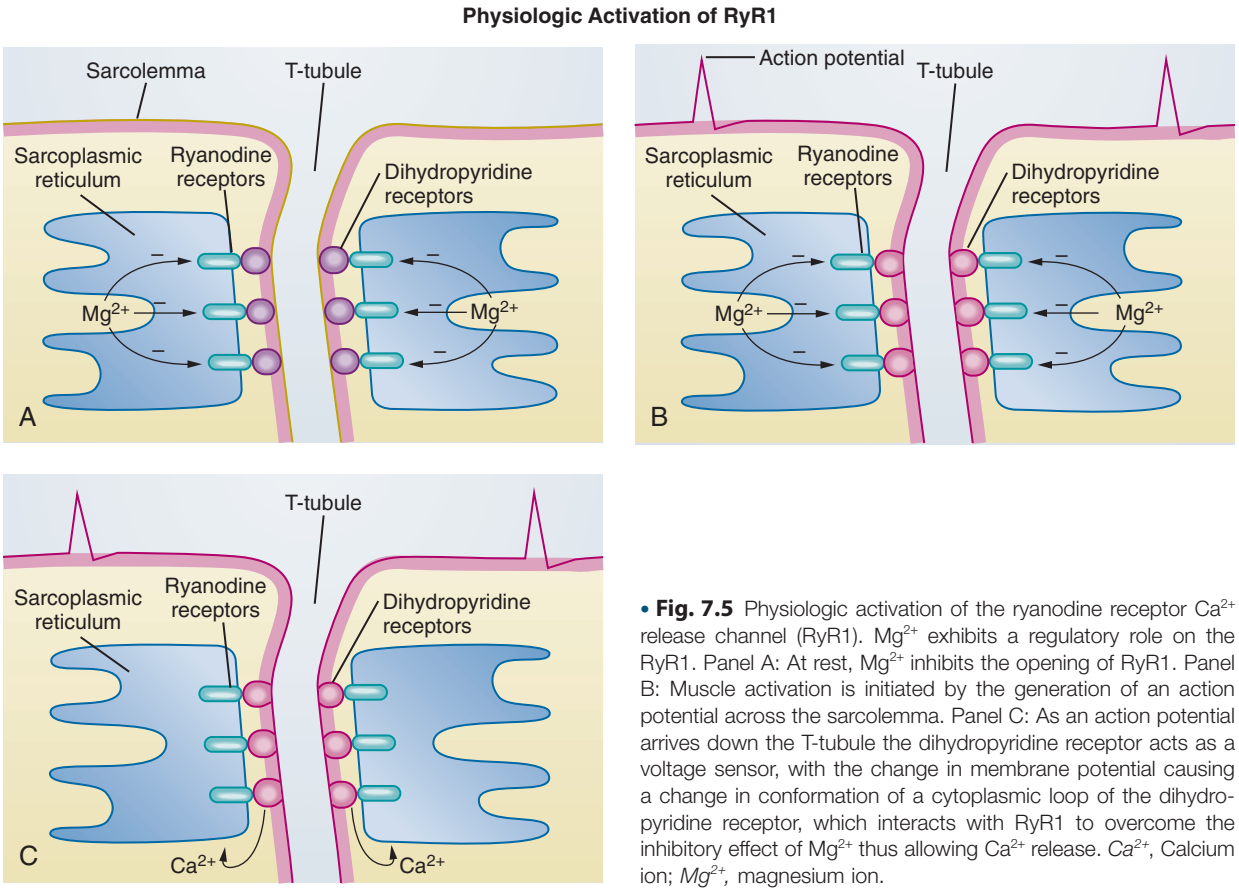
The cytochrome P450 family of enzymes is responsible for microsomal phase I oxidation reactions. They exist in four classes (CYP 1-4), each with several subgroups.[22] Most drugs can be metabolized by one or more of these subgroups. However, important polymorphisms have been found in four enzymes; therefore drugs metabolized predominantly by one of these enzymes could show a reduced clearance. Enzymes of particular interest to anesthesiologists include CYP 2D6, CYP 2C9, CYP 2C19, CYP 3A4-5, and CYP 2E1. The CYP 2D6 group is responsible for 25% of drug metabolism—most notably metoprolol, propranolol, amiodarone, flecainide, tricyclic and selective serotonin reuptake inhibitor antidepressants, phenothiazines, butyrophenones, and opioids. There is racial variation; 6% of Caucasians and 1% of Asians have reduced activity.[23] The CYP 2C9 enzyme group is important for warfarin metabolism and individuals with reduced activity of CYP 2C9 are prone to hemorrhagic complications.[24] CYP 2C19 is involved in the oxidation of diazepam and proton pump inhibitors with reduced activity more prevalent in Asians (20% vs. 3% in Caucasians).[25,26] Important for the metabolism of midazolam, lidocaine, fentanyl, and alfentanil is CYP 3A4-5, which is responsible for 50% of drug oxidation reactions and has reduced activity in 6% of Caucasians. The metabolism of acetaminophen and the fluorinated volatile anesthetics are predominantly by the CYP 2E1 enzyme.[27]

Plasma Cholinesterase Variants

Plasma cholinesterase (also known as pseudocholinesterase, serum cholinesterase, nonspecific cholinesterase, butyrylcholinesterase, S-type cholinesterase) is most notably responsible for the hydrolysis of the depolarizing muscle relaxant succinylcholine to succinyl monocholine and choline. It also accounts for the metabolism of the nondepolarizing muscle relaxant mivacurium and, to a lesser extent, ester local anesthetics, diamorphine, aspirin, and methylprednisolone. Genetic variation has accounted for reduced activity of this enzyme and is most clinically relevant to prolonged succinylcholine paralysis or *scoline apnea.* Investigating scoline apnea involves using inhibitors of plasma cholinesterase such as dibucaine (cinchocaine) and sodium fluoride and quantifying the reduction in activity that one should encounter in a normal enzyme. Four alleles—usual normal (Eu), atypical dibucaine-resistant (Ea), silent absent (Es), and fluoride-resistant (Ef)—have been identified on chromosome 3. Single–amino acid substitutions have resulted in each of these variants. Although most individuals are homozygous for Eu, up to 4% of the population have at least one deleterious allele, thus increasing the risk of a prolonged neuromuscular block, which can last between 10 minutes and several hours.

Glucose-6-Phosphate Dehydrogenase Deficiency

Erythrocytes are obligate glucose users and rely on the pentose phosphate pathway for its metabolism. Glucose-6-phosphate dehydrogenase (G6PD) is the rate-limiting enzyme in this pathway converting glucose-6-phosphate to 6-phosphoglucono-δ-lactone. The reaction usually provides energy for the cell in the form of reduced nicotinamide adenine dinucleotide phosphate, which is needed for the maintenance of reduced glutathione levels (Fig. 7.5). Reduced glutathione has an important role in combating hydrogen peroxide produced within the cell during periods of oxidative stress. Individuals with G6PD deficiency therefore can have dangerously high levels of hydrogen peroxide (resulting in protein damage and cell death) under periods of oxidative stress. This can occur when oxidizing drugs such as primaquine, chloroquine, chloramphenicol, some sulfonamides, and vitamin K analogs



• **Fig. 7.5** Physiologic activation of the ryanodine receptor Ca^{2+} release channel (RyR1). Mg^{2+} exhibits a regulatory role on the RyR1. Panel A: At rest, Mg^{2+} inhibits the opening of RyR1. Panel B: Muscle activation is initiated by the generation of an action potential across the sarcolemma. Panel C: As an action potential arrives down the T-tubule the dihydropyridine receptor acts as a voltage sensor, with the change in membrane potential causing a change in conformation of a cytoplasmic loop of the dihydropyridine receptor, which interacts with RyR1 to overcome the inhibitory effect of Mg^{2+} thus allowing Ca^{2+} release. *Ca^{2+}*, Calcium ion; *Mg^{2+}*, magnesium ion.

are administered in susceptible individuals with the ultimate consequence being hemolytic anemia. The highest prevalence of G6PD deficiency appears in falciparum malaria zonal populations as this deficiency appears to confer a survival advantage against the parasite.

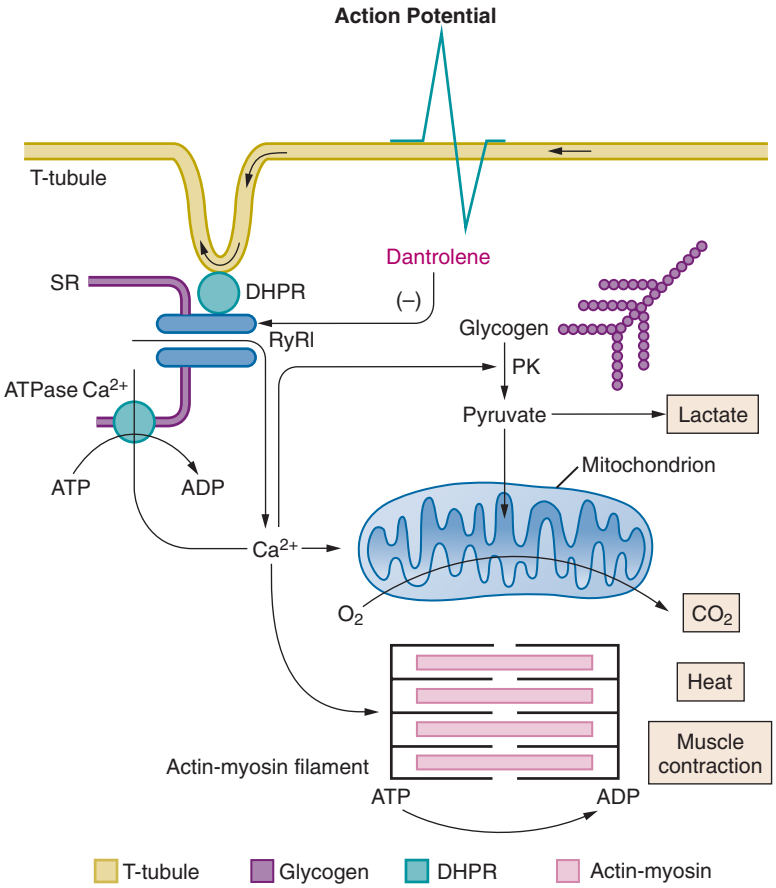
The Porphyrias

The porphyrias are a group of rare conditions caused by the excessive buildup of porphyrinogens, which are the precursors of heme. In affected individuals these porphyrinogens are excreted in urine and on exposure to light change color, resulting in the classic purple urine. The metabolic pathway for heme synthesis is shown in Fig. 7.6. Under normal circumstances heme tightly controls its own production by feedback inhibition of the first of the seven enzymes in the pathway, δ-aminolevulinic acid (ALA) synthetase. This feedback inhibition can be disrupted in periods of bleeding or metabolic stress (infection, dehydration, fasting) resulting in induced ALA synthetase activity. A block in any of the enzymes in the pathway will result in accumulation of porphyrin precursors. An acute attack can result in porphyrinogen disrupting the nervous system leading to motor, sensory and autonomic dysfunction. Of particular importance to anesthesia is the potential for many drugs to induce the activity of ALA synthetase. Drugs such as barbiturates, etomidate, halothane, clonidine, metoclopramide, lidocaine, prilocaine, diclofenac, and ranitidine have all been implicated in precipitating an acute attack in susceptible individuals.[28] There is some controversy surrounding the porphyrinogenicity of propofol. Animal experiments have shown it to induce ALA synthetase activity, and propofol infusions have resulted in raised porphyrin levels in humans with acute porphyria. Nevertheless, there are anecdotal reports of its safe use in patients with porphyria.[29,30]

Malignant Hyperthermia

Malignant hyperthermia (MH) is a potentially lethal pharmacogenetic disorder attributable to faulty skeletal muscle intracellular calcium homeostasis. The disorder is genetically heterogeneous, but the final common pathophysiologic path is a loss of regulation of the calcium-release units of the myocytes. Fundamental to normal functioning of the calcium-release units is a tightly regulated bidirectional interaction between the voltage sensor of the T-tubular sarcolemmal membrane (dihydropyridine receptor [DHPR]) and the calcium release channel of the sarcoplasmic reticulum (ryanodine receptor isoform 1 [RyR1]). A majority of families with MH subjected to genetic investigations have potentially causative variants in *RYR1*, the gene encoding RyR1. In other families, pathologic variants in *RYR1* have been excluded. A small minority of these have variants in *CACNA1S*, the gene encoding the α_1-subunit of DHPR. In the remaining 10% to 25% of families the gene or genes underlying MH remain to be identified. Potential candidate genes encoding proteins known to interact with RyR1 and DHPR number more than 30, but there is currently no evidence that any of these are implicated in MH. Further elucidation of the genetic etiology of MH will require genome-wide "next-generation" sequencing approaches.

Direct intracellular calcium measurements of muscle cells from humans and transgenic mouse models suggest, contrary to previous assumptions, that calcium cycling is abnormal even without exposure to triggering agents. Even though calcium sequestration



• **Fig. 7.6** Site of dantrolene action preventing a chain of intracellular mechanisms leading to muscle contraction, generation of heat, lactate, and CO_2. Release of Ca^{2+} is central to glycogen metabolism, mitochondrial respiratory function, and contraction of actin-myosin filaments. *ADP,* Adenosine diphosphate; *ATP,* adenosine triphosphate, *ATPase,* adenosine triphosphatase; *Ca^{2+},* calcium ion; *CO_2,* carbon dioxide; *DHPR,* dihydropyridine; *O_2,* oxygen; *PK,* pyruvate kinase; *SR,* sarcoplasmic reticulum; *RyR1,* ryanodine receptor isoform 1.

is upregulated, cytoplasmic resting calcium ion concentration is elevated and evidence is emerging that this may predispose to sarcopenia or even frank myopathy in the long term. The most obvious manifestation of MH susceptibility is, however, a pharmacologically triggered massive and persistent increase in cytoplasmic calcium ion concentration (see Fig. 7.6). This results in metabolic stimulation and sustained contractile activity with disruption of sarcolemmal integrity. The clinical consequences are increased oxygen consumption, carbon dioxide production and tachycardia, hyperthermia, acidosis, rhabdomyolysis, and muscle rigidity. A critical stage appears to be related to mitochondrial failure brought about by mitochondrial calcium accumulation secondary to the cytoplasmic calcium accumulation. Death results from any one, or a combination, of hyperkalemia, disseminated intravascular coagulopathy (secondary to hyperthermia), profound acidosis, or hyperthermia per se.

The pharmacology of MH triggering has been reviewed.[31] Essentially, the primary triggers of MH are the potent inhalation anesthetics, including all the currently available agents (isoflurane, sevoflurane, desflurane). They appear to act on RyR1 by overriding the physiologic magnesium inhibition of the channel. The clinical effect may be almost immediate and rapidly progressive or more insidious with signs in some reports delayed for more than 6 hours into anesthesia. Succinylcholine is likely to cause generalized or jaw muscle rigidity and also seems to enhance the onset and severity of a reaction triggered by subsequent exposure to a volatile anesthetic, but at worst is only a weak trigger of the hypermetabolic MH response when administered without a potent inhalation agent. There is no convincing evidence that any other drugs can trigger MH.

Successful treatment of MH depends on early recognition of the evolving reaction. A combination of unexplained tachycardia and an unexplained increase in carbon dioxide (CO_2) production makes the diagnosis likely. An increasing body temperature may be observed almost simultaneously or can be delayed for several minutes. Treatment involves discontinuation and enhancement of elimination of volatile anesthetics (including the use of adsorbents such as charcoal filters inserted in the anesthetic breathing circuit), hyperventilation with 100% oxygen (O_2), body cooling, and administration of dantrolene, a drug that reduces sarcoplasmic reticulum calcium release. General supportive measures are used to treat acidosis, hyperkalemia, myoglobinemia, arrhythmias, and disseminated intravascular coagulation.

Allergic Drug Reactions

Allergic reactions to drugs administered intravenously are acute type I hypersensitivity reactions. This requires an allergen to be exposed to an individual for a second or subsequent time. Epidemiologic data for anesthetic allergic reactions are divergent as some confusion remains as to the definitions of allergy and anaphylaxis. Indeed, some reactions that are accepted as side effects of certain drugs—for instance, histaminergic reactions owing to atracurium and mivacurium—may be underreported.[32] The European Academy of Allergy and Clinical Immunology defines allergy as follows:

> Allergy is a hypersensitivity reaction initiated by immunological mechanisms. Allergy can be antibody- or cell-mediated. In the majority of cases the antibody typically responsible for an allergic reaction belongs to the IgE isotype and these individuals may be

TABLE 7.2 Anaphylaxis Grades Defined for the NAP6 Project of the Royal College of Anaesthetists (2015)

Grade	Features
1 Not life-threatening	Rash, erythema, and/or swelling
2 Not life-threatening	Unexpected hypotension—not severe (e.g., not requiring treatment) And/or bronchospasm—not severe (e.g., not requiring treatment) ±Grade 1 features
3 Life-threatening	Unexpected severe hypotension And/or severe bronchospasm And/or swelling with actual or potential airway compromise ±Grade 1 features
4 Life-threatening	Fulfilling conditions for cardiopulmonary resuscitation
5 Life-threatening	Fatal

NAP6, Sixth National Audit Project.
(www.nationalauditprojects.org.uk/NAP6home#pt)

referred to as suffering from an IgE-mediated allergy. Not all IgE associated 'allergic' reactions occur in 'atopic' subjects. In non-IgE-mediated allergy the antibody can belong to the IgG isotype, e.g. anaphylaxis due to immune complexes containing dextran, and the classical, nowadays rare, serum sickness previously referred to as a Type III reaction. Both IgE and IgG antibodies are found in allergic bronchial pulmonary aspergillosis (ABPA). Allergic contact dermatitis is representative of allergic diseases mediated by lymphocytes.[33]

Anaphylaxis is essentially a severe, life-threatening, generalized or systemic hypersensitivity reaction.[34] It has recently been reclassified as a spectrum of disease, and for the purposes of recent national audits in the United Kingdom, was categorized into five grades based on severity of reaction and need of intervention (Table 7.2). The clinical features (hypotension, tachycardia or bradycardia; cutaneous flushing, rash or urticaria; bronchospasm; hypoxia; angioedema and cardiac arrest) usually occur within a few minutes but may be delayed for up to an hour. True allergic anaphylactic reactions involve mast cell degranulation resulting from production of allergen-specific immunoglobulin (Ig) E, IgG, or complement activation. Nonallergic anaphylactic reactions can occur through a direct drug action on the mast cell itself. True allergic anaphylaxis can occur after exposure to the smallest dose of antigen. Direct mast cell degranulation (non–IgE-mediated response) is probably dependent on the mass of drug and its rate of administration. However, in these circumstances there is unlikely to be any response to a test dose, but the full dose will cause the reaction. It is advisable, therefore, to administer intravenous drugs slowly.

The products of mast cell degranulation that are the mediators of the anaphylactic response include principally histamine and other vasoactive amines but also proteases (such as tryptase) and lipid-derived mediators (such as leukotrienes and prostaglandins). These mediators can affect the skin (flushing and urticaria), the vasculature (vasodilatation and increased capillary permeability), and the respiratory system (bronchoconstriction, inflammation, and increased bronchial secretions). Not all of these features occur in every anaphylactic reaction. Some reactions are characterized by the predominance of vasodilatation, whereas bronchoconstriction predominates in others. This probably reflects the presence of two main types of mast cells: mucosal mast cells that are located in the lungs and the gut and connective tissue mast cells that are ubiquitous.[35] The relationship between individual drugs and the spectrum of clinical features is not consistent between patients with reactions, although some drugs (e.g., atracurium, morphine) frequently produce cutaneous reactions without systemic vasodilatation or bronchoconstriction. This suggests that cutaneous connective tissue mast cells are particularly sensitive to these drugs.

Our ability to investigate suspected anaphylactic reactions is imprecise. Histamine release is difficult to measure because the half-life in the serum of the amine is so short. Its metabolite, methylhistamine, is more stable and can be detected in the urine. Alternatively, mast cell degranulation can be demonstrated by serum mast cell tryptase levels (taken as soon as practical after the reaction and compared with a baseline 24 hour later), whereas complement assays might point to a particular mechanism. The availability of allergen specific radioallergosorbent tests for drugs used during anesthesia is limited, although they are available for succinylcholine, penicillins, and chlorhexidine. Interestingly a radioallergosorbent test using morphine as the allergen has been shown to be a useful marker of sensitization to neuromuscular blocking drugs, where the quaternary ammonium group is the allergenic epitope. Cross-sensitization between IgE antibodies to pholcodine and neuromuscular blocking drugs has been proposed to explain the increased incidence of anaphylaxis to neuromuscular blocking drugs in countries where pholcodine-containing cough mixtures are used.[36]

The mainstay for diagnostic testing to identify the causative agent following perioperative anaphylaxis is skin testing in the form of skin-prick testing and/or intradermal tests. Skin-prick tests tend to be less sensitive but more specific than intradermal tests and guidelines generally recommend initial skin-prick testing, progressing to intradermal tests if skinprick test results are negative.[37]

There continues to be great controversy surrounding the anaphylactic potential of nondepolarizing neuromuscular drugs. A study in France demonstrated that muscle relaxants were implicated in 60% of anesthesia-associated type I hypersensitivity reactions; the largest proportion of these were caused by succinylcholine followed by rocuronium.[38] In North America and Australia the incidence of reactions to muscle relaxants other than succinylcholine is low. One explanation for this epidemiologic disparity is the conduct and interpretation of intradermal testing. A growing body of evidence suggests that using the correct dilutions for each drug may improve the specificity of this test.[39-41]

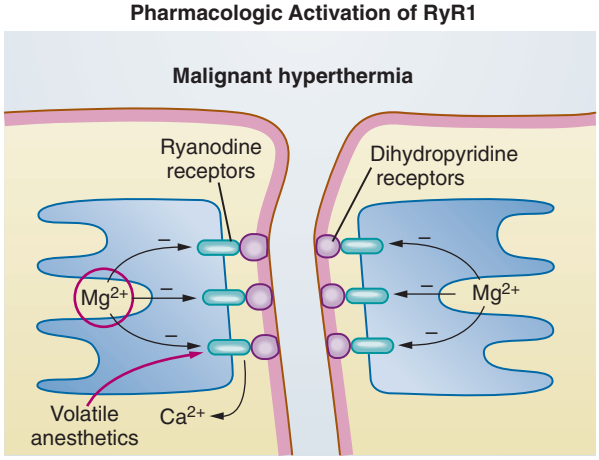
The difficulty in making an accurate diagnosis makes quantifying the incidence of anaphylaxis rather challenging, with estimates typically in the range of 1 : 4,000 to 1 : 13,000 anesthetics.[42,43] However, these estimates are based on reported cases and recent data suggest that 1 : 350 patients develop signs of anaphylaxis during anesthesia.[44] Other drug groups commonly implicated are intravenous anesthetic agents, plasma substitutes, and antibiotics. The emergence of teicoplanin as an alternative antibiotic for patients reporting a penicillin allergy has resulted in an increasing number of allergic reactions to teicoplanin.[45] With the decline in use of latex gloves, sensitivity to this allergen is becoming less of a problem. Reactions to latex are characterized by their development after 30

to 60 minutes of surgery, whereas drug reactions tend to occur within seconds or a few minutes of drug administration. The use of chlorhexidine as an antiseptic skin wash but also as an antibacterial coating to bladder and central venous catheters can be associated with severe systemic hypersensitivity reactions.[46] Anaphylactic reactions to local anesthetics are extremely uncommon; the esters more likely than amides to induce a reaction. Similarly, it is unlikely that a cutaneous histamine reaction to opioids (particularly morphine, meperidine, and codeine) is attributable to anaphylaxis. A careful history in this instance can prevent a patient from being labeled as allergic, thus limiting them from effective perioperative analgesia. It is well known that reactions to nonsteroidal antiinflammatory drugs can occur in susceptible individuals owing to the inhibition of the prostaglandin (PG) E_2 pathway, resulting in excessive leukotriene synthesis.[47] The subsequent mediator release is associated with bronchospasm and urticaria, yet an IgE-mediated reaction is reportedly rare. A U.K. guideline is a useful resource for managing allergy and anaphylaxis.[48]

Type C Reactions: Chronic (Direct Organ Damage, Dose-Related, and Time-Related)

Over time drugs can exert a cumulative unwanted effect. Examples in anesthesia include bleomycin resulting in oxygen-induced lung damage and volatile anesthetics causing hepatocellular (halothane) and renal (methoxyflurane) toxicity.

Bleomycin is a chemotherapeutic agent used to treat metastatic germ cell cancer and, in some regimens, non-Hodgkin lymphoma. The principal problem associated with the use of bleomycin is progressive pulmonary fibrosis in 10% of patients. This is dose related, occurring more commonly at cumulative doses greater than 400 units, creatinine clearance less than 35 mL/min, and in the elderly.[49] Both iron and oxygen are cofactors for DNA cleavage by bleomycin (Fig. 7.7). Basal lung crepitations or suspicious chest radiograph changes are an indication to stop therapy. Patients who have received extensive treatment with bleomycin are at risk of developing respiratory failure if subsequently exposed to a high inspired oxygen concentration. A case series of five patients by Goldiner and colleagues in 1978 highlighted that intraoperative inspired concentrations between 0.35 and 0.42 led to respiratory failure and subsequent death.[50] This resulted in a recommendation to use low concentrations of oxygen in such cases. In contrast, a 6-year audit of 13 patients similar to Goldiner's group showed no difference in lung complications between bleomycin-treated patients undergoing surgery with either 24% or 41% inspired oxygen.[51] One difference between these two studies was that Goldiner and colleagues had documented restricted lung disease and decreased CO_2 diffusion capacity secondary to bleomycin treatment. The other study did not perform pulmonary function tests on all their patients, and the majority of those who were tested had normal function. This would suggest that preexisting bleomycin lung damage as shown on lung function tests is a key factor in the risk of hyperoxic lung injury. Several case reports using differing fractions of inspired oxygen in patients with varied cumulative bleomycin exposure have shown mixed results, but it appears prudent to use the lowest concentration of oxygen possible for the shortest duration that the clinical condition can allow, a worthy practice in all patients.



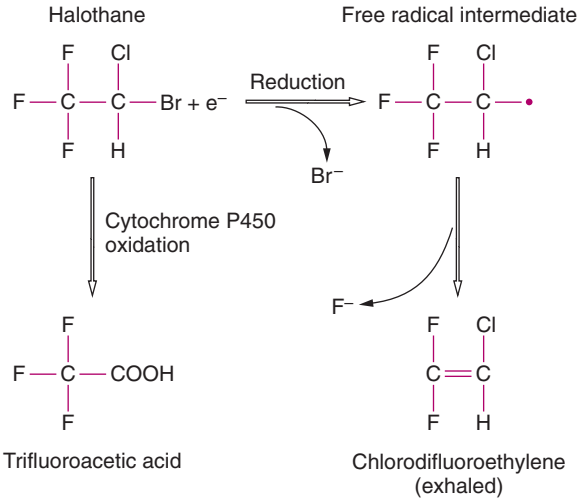
• **Fig. 7.7** Loss of inhibitory effect of Mg^{2+} on ryanodine receptor from inhalational anesthetics. The result is sustained Ca^{2+} release from the sarcoplasmic reticulum. Dantrolene acts by reducing pathologic release of Ca^{2+} from the sarcoplasmic reticulum that leads to muscle contraction, generation of heat, lactate, and CO_2. Release of Ca^{2+} is central to glycogen metabolism, mitochondrial respiratory function, and contraction of actin-myosin filaments. *Ca^{2+}*, Calcium ion; *CO_2*, carbon dioxide; *Mg^{2+}*, magnesium ion; *RyR1*, ryanodine receptor isoform 1.

The volatile anesthetics used in current practice can also lead to direct end-organ damage. All contain at least one fluorine atom, and following metabolism the fluorine ion (F^-) ion created can lead to nephropathy. Halothane undergoes the greatest amount of metabolism by hepatic cytochrome P450 (up to 25%) and desflurane the least (0.02%). Fluoride toxicity was first recognized in the 1960s with the introduction of methoxyflurane. A serum fluoride level greater than 50 µmol/L over a prolonged time was associated with polyuria, proteinuria, glycosuria, and impaired renal concentrating ability. However, about 5% of inhaled sevoflurane undergoes metabolic biotransformation (oxidative defluorination), readily releasing fluoride concentrations exceeding 50 µmol/L and yet studies have failed to demonstrate subsequent renal damage.[52]

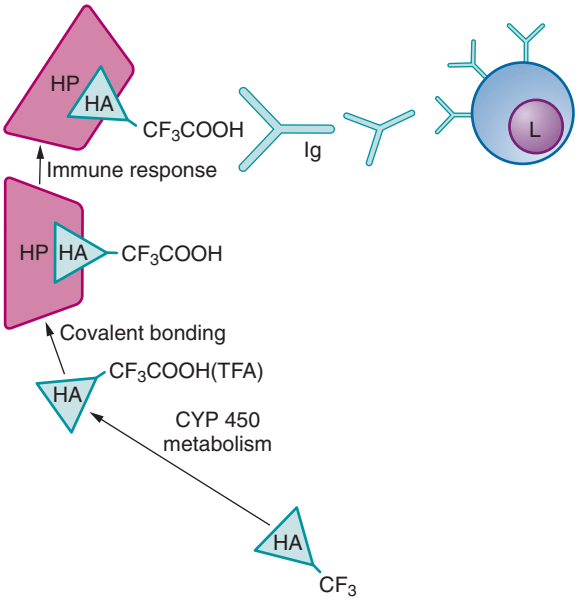
Another by-product of sevoflurane metabolism is compound A (fluoromethyl-2,2-difluoro-1-[trifluoromethyl] vinyl ether), which is produced by its interaction with CO_2 absorbents (see Chapter 3). There is debate surrounding the mechanism leading to renal toxicity with the renal cysteine conjugate β-lyase pathway (involved in the biotransformation of compound A) playing a significant role. The β-lyase pathway is up to 30-fold less active in humans than in rats. If this pathway is responsible, humans may be less susceptible to compound A renal toxicity than rats. Studies in humans have shown that long (8-hour) sevoflurane exposures and low fresh gas flow rates can result in significant production of compound A.[53] Urinalysis revealed transient changes in biochemical markers of renal injury; however, other studies using prolonged sevoflurane administration at low flow rates suggest no risk of this compound. A useful review of the association of sevoflurane and renal injury is available.[54]

Direct liver damage from halothane (halothane hepatitis) is becoming less of a problem in the developed world because of its decline in use. Its estimated incidence is 1:35,000 administrations, with risk factors including late middle age, female sex, and obesity. There are two reported types of halothane hepatitis. Type 1 is an asymptomatic, spontaneously resolving rise in serum transaminases within 2 weeks of exposure. It is most likely attributed to hepatic hypoxia secondary to hypoperfusion. A reductive pathway leading to an insertion of a single electron into the halothane molecule produces a highly reactive metabolite that undergoes debromination to another free radical intermediate (Fig. 7.8). These free radicals then lead to destruction of hepatocytes.

Type 2 hepatitis leads to fulminant hepatic necrosis with a mortality rate of 50% to 75%. There appears to be a correlation between the amount of halothane used and the severity of liver failure but not the likelihood of it occurring. An immune basis is responsible with the oxidative metabolite (trifluoroacetyl chloride) behaving as a hapten, covalently bonding to hepatic proteins and inducing antibody formation (Fig. 7.9). Onset can be by the seventh day after administration or relatively delayed compared with direct hepatotoxic drugs such as acetominophen for up to 28 days.



• **Fig. 7.8** Proposed metabolic pathway implicated in halothane hepatitis. A reductive pathway leading to addition of a single electron into the halothane molecule produces a highly reactive metabolite that then undergoes debromination to another free radical intermediate. These free radicals lead to destruction of hepatocytes and trifluoroacetic acid can react with proteins to form neoantigens. *Br^-*, Bromide ion; *e^-*, electron; *F^-*, fluoride ion.



• **Fig. 7.9** Neoantigen (hapten) formation. Halogenated anesthetics *(HA)* are metabolized by cytochrome P450 *(CYP 450)* enzymes into metabolites such as trifluoroacetic acid *(TFA)* that form covalent bonds with hepatic proteins *(HP)*. The modified proteins act as neoantigens that trigger an immune response, with immunoglobulin *(Ig)* production by lymphocytes *(L)* that then interact with the newly formed neoantigen.

Type D Reactions: Delayed (Time-Related)

Certain adverse drug reactions are not apparent until a significant amount of time has elapsed since the initial administration of the drug. Nitrous oxide (N_2O), one of the earliest inhalational anesthetic agents introduced, has been well reported to increase the risk of megaloblastic bone marrow changes and subsequent neurologic complications (subacute combined degeneration of the spinal cord) owing to vitamin B_{12} deficiency. Short exposure for a few hours can lead to bone marrow changes, and more prolonged exposure of several days can lead to agranulocytosis. The cobalt ion (Co^+) present in vitamin B_{12} is oxidized by N_2O (to Co^{2+}), thus preventing it from activating methionine synthase. This enzyme is responsible for the conversion of homocysteine into methionine, thymidine, tetrahydrofolate, which are essential steps in DNA synthesis (Fig. 7.10). The subsequent accumulation of plasma homocysteine could in theory increase the risk of perioperative myocardial events but no strong evidence appears to support this. An attempt to prevent this adverse effect with preoperative vitamin B infusions was not successful.[55]

The use of etomidate as an induction agent with sepsis continues to be a matter of debate. There is no doubt that a single dose of etomidate suppresses adrenocortical function by inhibiting enzymes (11β-hydroxylase and 17α-hydoxylase) essential for cortisol and aldosterone synthesis (Fig. 7.11). The effect can appear as early as 30 minutes after administration but may not occur until several hours later. These hormones play an important role in the stress response, and although there is evidence of increased mortality if etomidate is used in patients with sepsis, the studies are limited by their observational design.

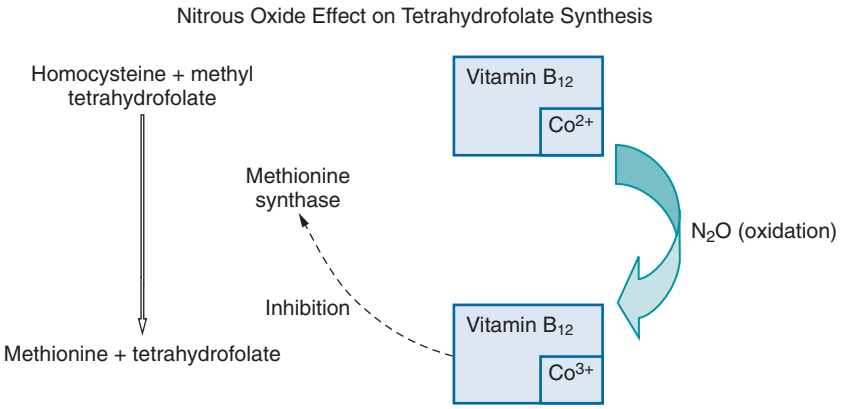
Type E Reaction: End of Use (Withdrawal)

Acute withdrawal of drugs is recognized to cause harmful effects. Of interest to anesthesiologists is the withdrawal of common drugs in the community such as alcohol, nicotine, and opioids to which patients become dependent. These effects usually result in detrimental psychiatric, neurologic, and cardiorespiratory consequences. Acute opioid withdrawal in patients on intensive care has also been shown to induce allodynia and hyperalgesic pain states. More recently the withdrawal of cardioprotective agents such as β-blockers and statins has been suggested to increase the risk of perioperative cardiac events, and certain centers advocate continuation of preoperative antihypertensive medication for the same reason.

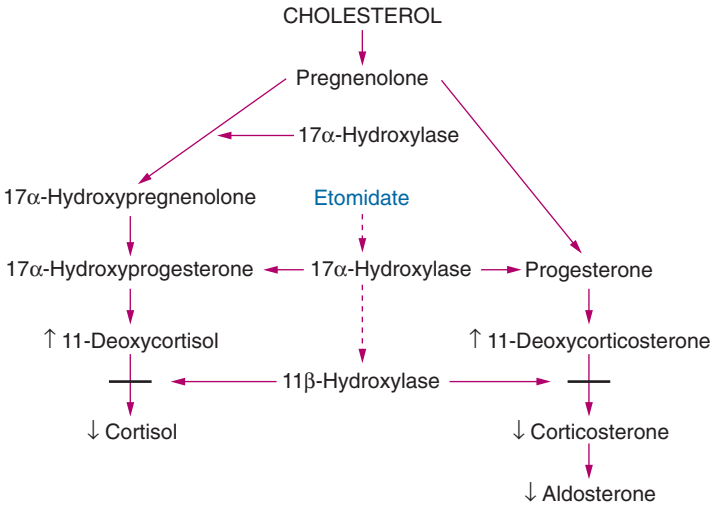
Owing to differences in blood-gas partition coefficients, acute withdrawal of inhaled N_2O can in theory lead to diffusion hypoxia. At the end of anesthesia, if an N_2O/O_2 mixture is replaced by air/O_2, the volume of N_2O that enters the alveolus from the blood will be greater than the volume of N_2 (from the air) entering the pulmonary capillaries. This can create an unwanted dilution of all the alveolar gases; thus supplemental oxygen is advised to prevent this (see Chapter 3).

Type F Reactions: Drug Failure

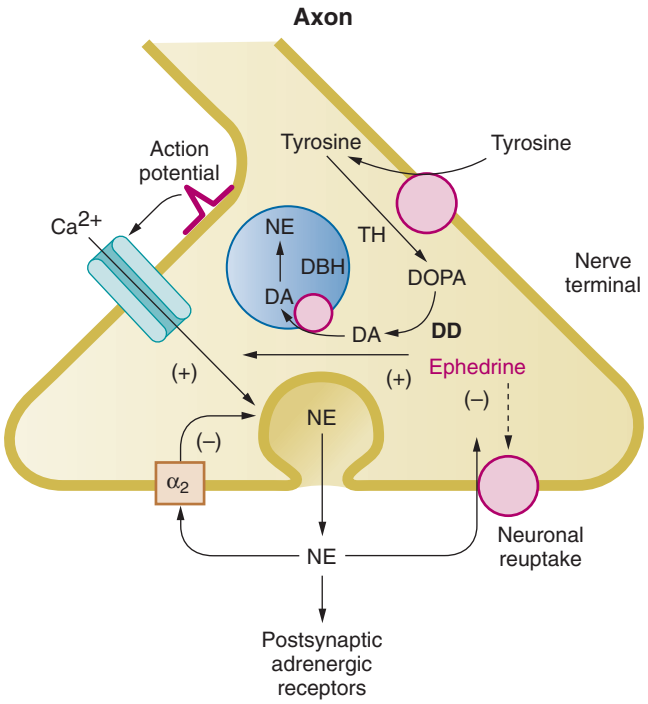
Any drug can fail. There can be a multitude of reasons why a drug fails to produce its desired effect, but by far the most common reason is inadequate dosing. As mentioned earlier, the response to a given dose range can vary within a population. Those at the lower end of the dose-response curve may not attain the desired effect of the drug. Another common reason for drug failure is



• **Fig. 7.10** Mechanism of nitrous oxide *(N_2O)* toxicity. The cobalt ion in vitamin B_{12} is oxidized by nitrous oxide, thus preventing it from activating methionine synthase. This enzyme is responsible for the conversion of homocysteine to methionine, and subsequently thymidine and tetrahydrofolate, which are essential for DNA synthesis. *Co^{2+}*, Cobalt (II) ion; *Co^{3+}*, cobalt (III) ion.



• **Fig. 7.11** Mechanism of immunosuppression by etomidate. The steroid synthetic pathway is shown highlighting enzymes (11β-hydroxylase and 17α-hydroxylase) essential for cortisol and aldosterone synthesis. 11β-Hydroxylase is inhibited by etomidate arrows leading to reduced adrenocortical steroid synthesis with possible adverse effects. (Dashed line = inhibitory.)



• **Fig. 7.12** Tachyphylaxis with ephedrine. Synthesis of norepinephrine *(NE)* depends on the hydroxylation of tyrosine by tyrosine hydroxylase *(TH)* to dihydroxyphenylalanine *(DOPA)*. DOPA is metabolized to dopamine *(DA)* by DOPA decarboxylase *(DD)*. DA enters vesicles where it is hydroxylated by dopamine β-hydroxylase *(DBH)* into NE. Release of NE is enhanced by ephedrine; if the rate of release exceeds norepinephrine synthesis, then ephedrine can fail to work. *Ca^{2+}*, Calcium ion.

interaction with other medications (e.g., antagonists as in the use of β-agonists in patients taking β-blockers; also see Chapter 6).

Despite the aforementioned reasons, there are other specific reasons a drug might fail in an individual depending on the pharmacogenomic profile of the patient. Many drugs rely on active enzyme systems for activation. As alluded to earlier, the cytochrome family of enzymes is responsible for metabolism of numerous drugs of relevance to anesthesiologists. An example is cytochrome CYP 2D6, which is responsible for metabolism of the weaker opioids codeine, dihydrocodeine, tramadol, oxycodone, and hydrocodone (see Chapter 4). The clinical effect of these drugs relies on the formation of more potent hydroxyl metabolites, such as morphine, dihydromorphine, and oxymorphone. The gene encoding CYP 2D6 exhibits significant polymorphism, with 100 variant alleles. This results in a number of clinical phenotypes: poor metabolizers, intermediate metabolizers, extensive metabolizers, and ultrarapid metabolizers. Approximate frequencies of these phenotypes for the Caucasian population are 5% to 10% for poor metabolizers, 10% to 15% for intermediate metabolizers, 65% to 80% for extensive metabolizers, and 5% to 10% for ultrarapid metabolizers.[56] Poor metabolizers are unlikely to attain beneficial effects of these drugs.

Another mechanism of drug failure includes depletion of critical substrates for drug action. *Tachyphylaxis*, the loss of effect with repeated or continuous use, describes this phenomenon with ephedrine (which depends on vesicular norepinephrine release, nitroglycerin, dobutamine, and hydralazine, for example). Tachyphylaxis with repeated ephedrine use is illustrated in Fig. 7.12. Similar loss in drug efficacy can occur with receptor *desensitization*, which results from post-translational modification or downregulation of receptors (Chapter 1). An example of this is densensitization to the effects of the β-agonist dobutamine with continuous infusion,

which results from downregulation of β_2-adrenoreceptor number. Drug-free intervals can replenish stores of necessary substrates or resensitization or transport of necessary receptors, allowing the drug to take effect once more.

Emerging Developments

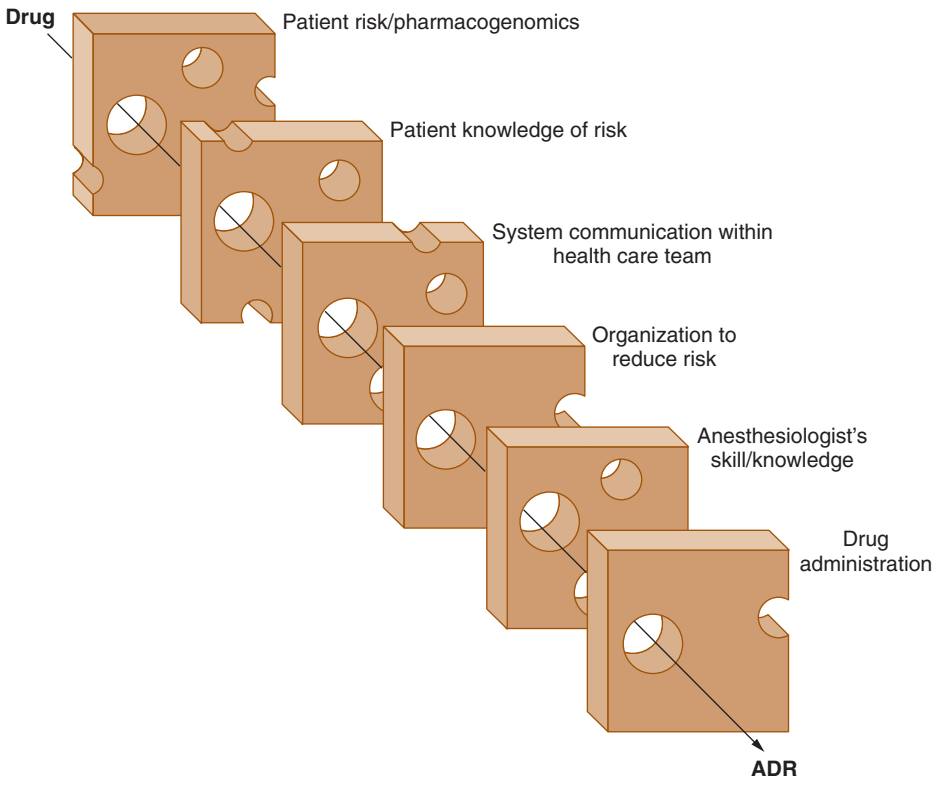
"Swiss Cheese" Model in Adverse Drug Reactions

Much current and future work surrounding adverse drug reactions focuses on prevention, in particular the prevention of drug errors. In practice there are many stages where error can occur, ultimately leading to an adverse drug reaction. A Swiss cheese model depicting human error has been described.[57] In the anesthetic context, patients can present for emergency surgery involving a multidisciplinary health care team whereby the anesthesiologist will ultimately administer a drug (Fig. 7.13). An adverse drug reaction can occur if all the deficiencies in the system (or holes in the cheese slices) align. The focus of modern medical practice is on the delivery of safe, effective care. Any adverse event or serious untoward incident is usually subject to an investigation or root cause analysis. The aim of these investigations is not to blame individuals but to understand deficiencies in a patient's care pathway that led to the unwanted incident. This is based on the logic that humans are prone to error and a system should be created to mitigate that error. The hope is that lessons learned from previous mistakes will guide alterations in future management, thus preventing further harm. A perfect flawless pathway is a goal that health care systems continue to strive for.

New developments that might prevent adverse drug reactions include toxicogenomics, which embraces the latest technology for compound classification, mechanistic studies, and detection of toxicity markers.[58] In addition, pharmacogenomics may help us understand more about genetic polymorphisms that underpin individual variance in drug response; however, this rapidly expanding field brings new ethical considerations regarding informed consent for clinical trials, pharmacogenomic profiling, and storage of genetic material.[59] Another developing area is metabonomics.[60] This is a powerful tool for translating disturbances in normal homeostasis of metabolic processes into drug-induced pathology. Using the latest advances in mass spectrometry and nuclear magnetic resonance spectroscopy, specific biomarkers can be detected, which is resulting in traditional chemical laboratories being replaced.

New Technology to Decrease Drug Errors in Anesthesia

Extensive work has been undertaken to research the causes and possible preventions of drug errors. Anesthesia is a unique specialty in which, for most cases, the same person prescribes, draws up, and administers medications to a patient without any secondary checks. Therefore such a process is more vulnerable to human error and any precautions that can be taken to prevent this should



• **Fig. 7.13** Swiss cheese model of anesthetic drug errors. Error can occur at any point in the medical care pathway, appearing as holes in cheese slices. If a patient has the genetic profile or an unknown risk factor for an adverse drug reaction *(ADR),* it is up to the health care team to elucidate this potential risk, communicate it to the team, and arrange appropriate measures to mitigate the risk of a hazardous drug being administered. If the anesthesiologist is unaware of which drugs are potentially hazardous or how to administer, then all the holes in the cheese slices align and an ADR occurs.

be considered. In a recent review, 138 recommendations from 74 articles were compiled and considered to help prevent drug errors.[61] Action has already been taken on some these in recent years; for example, efforts are being taken to remove the Luer-lock connectors on neuraxial injection devices to prevent accidental injection of the incorrect drug intrathecally/epidurally. Other suggestions (barcode labeling of drug syringes, for example), while using new technologies, have not been universally embraced.[61]

One area where technology has advanced in reducing medication errors is with infusion pumps. Although infusion pump technology has advanced, so has the potential for errors arising from more complex pump programming. Work undertaken by Syroid et al.[62] demonstrated that by simplifying programs using a graphic user interface, errors were reduced significantly, although this study was performed only in simulated scenarios.

Infusion pumps with built-in drug error–reducing software (DERS) have been available since 2004. This software is essential in helping to reduce the risk of overdosing/underdosing drug delivery to the patient based on a set of parameters entered into the program. Although efforts are continuing to promote the use of this type of pump, incorporating their use in the U.K. health care sector has been slow (39% in 2014).[63] Research into the effectiveness of this class of pumps is still ongoing, with some studies suggesting that, despite the presence of DERS, errors are still quite high, although better than when previously assessed.[64]

A trial involving the creation of an anesthetic medication template for anesthetists to place their drawn-up drugs and thereby standardize drug placement before administrations has recently been reported.[65] The results suggest that the system has the potential to reduce the rate of drug administration errors.

Key Points

- A large proportion of adverse drug reactions is due to preventable administration error. The latest trend is to ensure that drugs are double- or even triple-checked. This is of particular importance in pediatric anesthesia where the margins for error with some drugs are extremely small.
- Drugs can exhibit predictable dose-dependent adverse reactions, yet unpredictable idiosyncratic reactions are often the most life-threatening and most challenging to manage.
- Some drugs exhibit adverse effects over a period of time, occasionally a long time after initial administration. In the case of bleomycin, knowledge of prior use is important so administration of high concentrations of oxygen can be minimized.
- Anaphylaxis remains a relatively unpredictable and potentially fatal complication. The ability to investigate allergic and nonallergic anaphylaxis remains crude.
- Genetic variations within populations can have a major influence on the effect of the drug in an individual and can be a basis for an adverse drug reaction. Well-known genetic variations responsible for adverse drug reactions in anesthesia include pseudocholinesterase deficiency and malignant hyperthermia.
- The volatile anesthetics can lead to direct damage to the kidneys and liver; halothane hepatitis is the most severe complication.
- Withdrawal effect from a drug is a serious complication, which is of interest to anesthesiologists who usually have direct control over withholding a patient's medication.
- Genetic variations within populations can have a major influence on the effect of the drug in an individual. The genetic makeup that determines how individuals metabolize drugs can mean that some drugs have a greater effect or some will simply fail to act.
- The Swiss cheese model of adverse event evolution is applicable to understanding adverse drug reactions of some types. New technology and guidelines are emerging to mitigate and prevent adverse drug reactions in anesthesia that sometimes occur because of human error.

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8

Central Nervous System Physiology: Neurophysiology

AEYAL RAZ AND MISHA PEROUANSKY

CHAPTER OUTLINE

Historical Perspective

Glia
- CSF, Interstitial Fluid, and the Glymphatic System

The Neuron
- Basic Structure
- Excitability
- Communication
- Membrane Time Constant
- Neuronology

The Brain: Structure Determines Function
- Structure
  - *Spinal Cord*
- Function
  - *Default Mode Network*
  - *Brain Rhythms*

Emerging Developments
- Probing the Brain
  - *Optogenetics and Pharmacogenetics*

The neuron is the fundamental unit of information processing and transfer in the central nervous system (CNS). It is, however, the collective activity of hierarchically organized neuronal circuits and networks that underlies its behavioral and homeostatic functions. These functions are *emergent* properties of a complex system. Therefore the CNS has to be examined on different organizational levels: properties characteristic of a functional unit on one level of organization are absent from lower-level elements and cannot predict properties of a higher-level unit. How exactly behavior emerges from the activity of individual neurons, circuits, and networks is a question at the cutting edge of research.

Individual neurons and/or their organelles carry the primary molecular targets of anesthetic drugs. Current thinking attributes most of the desirable effects of general anesthetics to the modulation of membrane proteins. Drug-induced alterations in the function of many voltage-, transmitter-, and otherwise gated channels are relatively well characterized. By contrast, how these alterations propagate through increasing levels of complexity to finally result in sedation, amnesia, hypnosis, and immobility is less well understood. General anesthetics also affect second-messenger systems either directly or via effects on G-protein–coupled receptors and mitochondria. The significance of the latter effects for anesthesia is unclear.

Historical Perspective

The brain: ancient Egyptians tossed it when preparing the body for the journey into the afterworld. Aristotle thought it a radiator to cool the heart. But more than 2000 years and dozens of Nobel Prizes later, the American Society for Neuroscience alone counts more than 35,000 members, many of whom devote their lives to its study.

Except for the last decade of the 19th century, brain science in the 1800s was dominated by physicians such as Broca, Wernicke, Fritsch, and Brodmann. They and others started the process of a functional localization of the brain. Pavlov linked psyche to behavior and learning with the development of the concept of the conditioned reflex, which is still widely used in neuroscience today. His achievements were honored with the Nobel Prize in 1904. In 1906, Golgi shared the 1906 Nobel Prize with Ramón y Cajal, two central protagonists in the grand debate on the cellular versus reticular organization of the brain. The debate was settled in favor of Cajal's view that discrete cells as opposed to a reticulum formed the structure of the brain. However, as nature is not doctrinaire, some neurons (and parts of the glia) do act syncytially by maintaining specialized intercellular channels, common during embryogenesis, into adulthood. In 1897, Sherrington postulated communication via the synapse on theoretical grounds. This turned out to be a fundamental characteristic of the nervous system, which however, was incontrovertibly proven only decades later with the aid of electron microscopy.

The 20th century witnessed an exponential growth of science as a collaborative endeavor. Therefore individual names, no matter how outstanding, give progressively less and less justice to all those who contribute to important advances in science. Nevertheless, we use the names of Nobel Prize laureates to anchor a flash review of concepts particularly relevant to this chapter.[1] In 1915, while held in a Russian prisoner of war camp, Bárány received the Nobel Prize for his studies of the physiology and pathology of the vestibular system. In 1932, Adrian and Sherrington shared the Nobel Prize for their contributions to neuronal signal propagation. Dale and Loewi shared the Prize in 1936 for work on transmitter release,

Abstract

Novel tools in neuroscience (genetic, optical, pharmacological) are being used to advance our understanding of the complexity and functioning of the brain, the primary target of general anesthesia.

Anesthesiologists administer drugs to facilitate procedures that dramatically alter brain function on a daily basis to create loss of consciousness, amnesia, analgesia and immobility. Novel neuroscientific approaches are targeted towards decoding consciousness and memory, and are thereby contributing to our understanding of the mechanisms of anesthetic actions. This chapter reviews the neuroscientific understanding of the brain and the technical approaches leading to these discoveries. After a brief review of the major milestones in brain research, we describe the cellular mechanisms that govern neuronal activity as well as the neurophysiological basis of global network activity. The major structures of the brain and their neurophysiological roles as they pertain to anesthesia are then described.

Keywords

Neuron
Synapse
Action potential
Neural network
Brain structure

but Dale's principle (which states that each neuron releases only one type of neurotransmitter) was proven false by the end of the 20th century. Nevertheless, it underlies the familiar classification in widespread use today (e.g., adrenergic, gamma-aminobutyric acid [GABA]ergic). Hodgkin and Huxley shared the Nobel Prize with Eccles in 1963 for discovering the ionic mechanisms involved in excitation and inhibition of the nerve cell membrane. Their biologic model—the giant axon of the Atlantic squid—was so central to this quantum leap in understanding that a contemporary remarked that *Loligo pealei* should have been awarded the prize. Axelrod, von Euler, and Katz shared the prize in 1970 for work on neurotransmitter storage, release, and inactivation in the axon terminal. The Nobel Prize to Hubel, Wiesel, and Sperry in 1981 marked a shift in neuroscience toward a comprehensive, system-level understanding of the brain that remains the frontier of neuroscience today. Hubel and Wiesel suggested a hierarchical model for the identification of complex visual themes. Sperry was awarded the prize for his work on lateralized specialization of brain function. Advances in our understanding of the mammalian brain's navigation system were recognized by the 2014 Nobel Prize to O'Keefe and the Mosers underlining the increased attention of the neuroscience community to system- and network-level approaches.

Glia

Glial cells (or neuroglia: "nerve glue") are nonneuronal cells that outnumber neurons and are ubiquitous in the CNS. Glial cells take up, metabolize, respond to, and release neurotransmitters and modulators; control the microenvironment that surrounds neurons; and support communication. Glial cells also play a number of other roles in CNS homeostasis. However, glial cells are not known to actively transfer and process discrete information.

Two basic types of neuroglial cells can be distinguished: *macroglia* (oligodendrocytes, astrocytes) and *microglia*. Oligodendrocytes fulfill in the CNS the role that Schwann cells play in the peripheral nervous system with some adaptations. To conserve space, one oligodendrocyte cell body myelinates multiple axons and the myelin itself consists of a single sheet of oligodendrocyte plasma membrane without cytoplasm wrapped tightly around an axonal segment. Each myelinated segment is termed an internode because of the bare segments of axon present at each end of it—the node of Ranvier. The action potential can leap from node to node—a process known as saltatory conduction, allowing rapid conduction even along thin axons.[2]

Astrocytes constitute 20% to 50% of the volume in most brain regions. Two main forms predominate: protoplasmic in the gray and fibrous in the white matter. Astrocytes isolate the brain from the rest of the body by covering the surface of capillaries and ensheathing the nodes of Ranvier, synapses, and dendrites with extensions of their bodies, creating the blood-brain barrier. Astrocytes are connected to each other by gap junctions forming a syncytium that facilitates the diffusion of small molecules across the CNS. They also communicate with neurons via calcium ion (Ca^{2+})-induced transmitter release.[3] Astrocyte precursors (radial glia) guide neuronal migration in early development. Throughout life, astrocytes synthesize a plethora of growth factors and are the major source of extracellular matrix proteins and adhesion molecules.

Microglial cells are immune-competent cells, termed the *macrophages of the CNS*. They are the least understood cell type of the CNS even though they account for a substantial fraction of all cells (5%-20% in the mouse brain; human white matter has more microglia than its rodent counterpart).[4,5]

Glial cells are not known to be materially affected by anesthetics in a way that can be linked to acute behavioral changes.

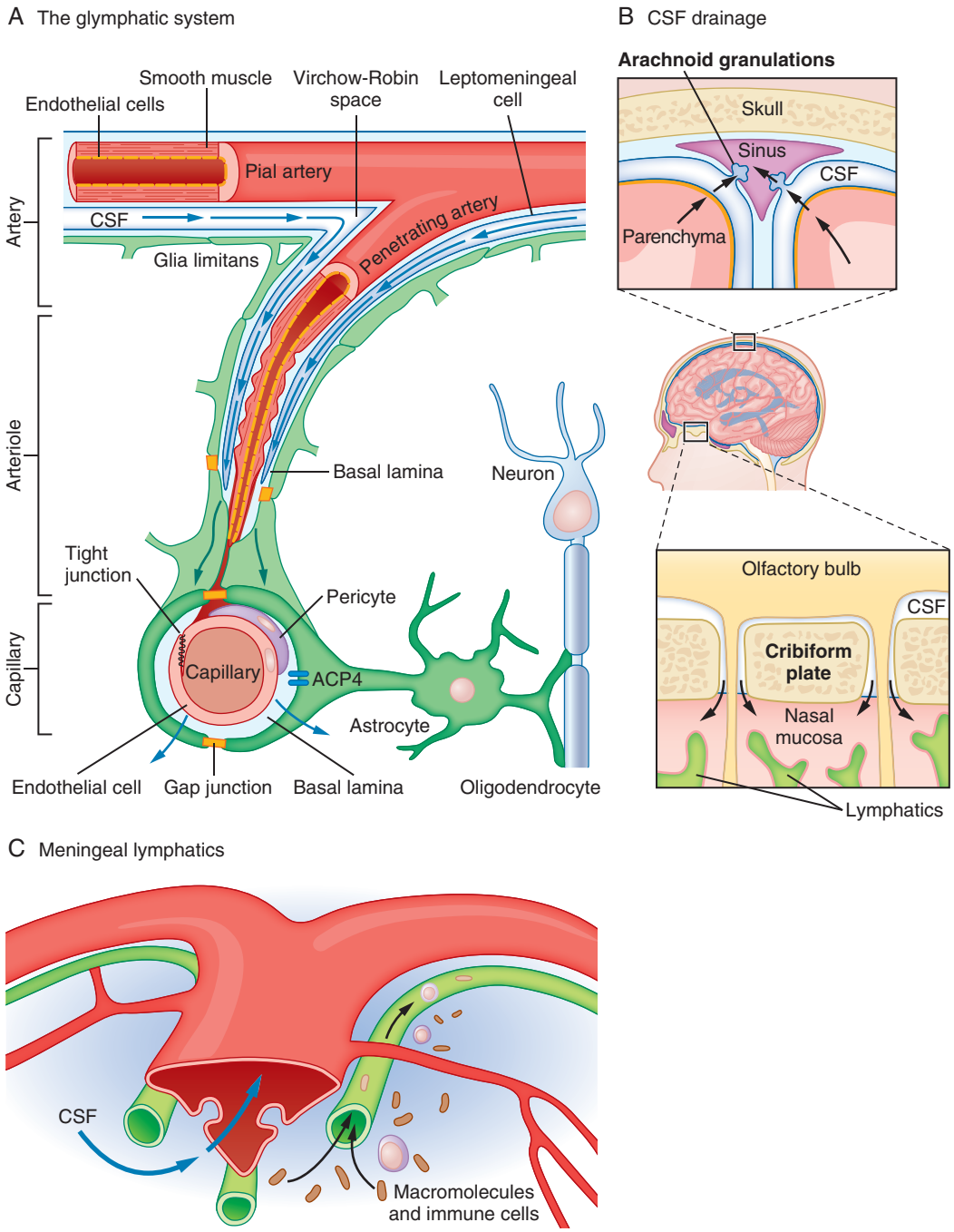
CSF, Interstitial Fluid, and the Glymphatic System

Over the past decades renewed interest in certain peculiarities of brain physiology, especially its immune-privileged status and the puzzling lack of a lymphatic system, has led to a series of elegant experiments that have added cutting-edge experimental techniques to older observations and are redefining important aspects of brain physiology with important implications for pathophysiology.

The brain's high metabolic rate (the average neuron is estimated to consume 4.7 billion adenosine triphosphate [ATP] molecules per second) results in proportional waste accumulation in the interstitial fluid. While the density of lymph vessels outside the brain correlates with the rate of tissue metabolism (lymph flow is essential for clearing waste from metabolically active tissues), the complete lack of conventional lymphatic vessels has been a conundrum of CNS physiology.[6] Related to the problem of waste disposal is the question of how the CNS fulfills the immunologic functions, which in the periphery, are carried by the flow of interstitial fluid and immune cells through the lymphatic vessels and lymph nodes.

The standard model postulates that small molecules and hydrophobic compounds move across the blood-brain barrier relatively unrestrictedly and specific blood-brain barrier transporters readily clear other molecules from the brain. For compounds not falling into these two categories, diffusion by way of the interstitial fluid to CSF-containing spaces (ventricles, subarachnoid space) was assumed to suffice. Clearance from the cranium was accomplished by CSF reabsorption into the dural sinuses via the arachnoid granulations and into peripheral lymphatic vessels of the nasal mucosa and neck along perineural spaces surrounding the cranial nerves. An important weakness of the model, however, is that the distances between much of the brain tissue and the CSF compartments are far too great for efficient clearance by simple diffusion, particularly for large molecules with low diffusion coefficients (such as peptides and proteins).

Recent research is providing a coherent, albeit not yet exhaustive, solution to these issues. Contrary to previously held views, the new model postulates that CSF is produced not only in the choroid plexus but also by filtration of water through capillary walls governed by hydrostatic and osmotic forces. CSF flows from the subarachnoid space along a system of perivascular tunnels known as the Virchow-Robin spaces (Fig. 8.1). These perivascular spaces act as low-resistance paths for CSF influx. Endfeet of astrocytes ensheathe the brain vasculature forming tunnels around the vessels. Fluid from these tunnels is taken up by aquaporin 4 water channels, which are expressed in a highly polarized manner in astrocytic endfeet and transferred into the interstitial fluid of the dense brain parenchyma. Influx of CSF on the arterial/capillary side of the circulation drives the flux of interstitial fluid toward the perivenous spaces surrounding the large veins. The interstitial fluid then drains out of the brain into peripheral lymphatic vessels into the deep cervical lymph nodes as described in the standard model. Acknowledging the central role of glia, the term "*glymphatic*" has been coined to describe this system. Moreover, while it remains accepted that no lymphatic vessels in the classic sense exist within the brain and spinal cord parenchyma, a network of lymphatic-like vessels has been identified in the dura mater of the mouse brain. Endothelial cells in these vessels share similarities with conventional



• **Fig. 8.1** The glymphatic system**.** A, The neurovascular unit allows bidirectional communication between the microvasculature and neurons, with astrocytes playing an intermediary role. Pial arteries in the subarachnoid space bathed in cerebrospinal fluid (CSF) become penetrating arteries upon diving into the brain parenchyma. The perivascular space around penetrating arteries is termed the Robin-Virchow space. As the penetrating arteries branch into arterioles and capillaries, the CSF-containing Virchow-Robin spaces narrow and finally disappear. CSF from the Robin-Virchow spaces continues its flow into the perivascular spaces around arterioles, capillaries, and venules, where the extracellular matrix of the basal lamina provides a continuity of the fluid space. Astrocytic vascular endfeet expressing aquaporin 4 *(AQP4)* surround the entire vasculature and form the boundary of the perivascular spaces. B, The CSF, flowing between the arachnoid and the pia mater of the meninges, can drain into the bloodstream through the arachnoid granulations located along the superior sagittal sinus and the transverse sinuses, or reach the lymphatic vasculature of the nasal mucosa by crossing the cribriform plate, localized under the olfactory bulbs, along the olfactory nerves. Not shown: CSF also drains through the perineural spaces of other cranial nerves. C, Macromolecules and immune cells localized within the CSF drain primarily through the recently rediscovered meningeal lymphatics to reach the deep cervical lymph nodes *(black arrows).* CSF drains back into the bloodstream *(blue arrow).* Note: the exact location of the lymphatics with respect to the meninges is still being clarified. (From Jessen NA, Munk AS, Lundgaard I, et al. The glymphatic system: a beginner's guide. *Neurochem Res.* 2015;12:2583–2599.)

lymphatics (e.g., expression of traditional markers of tissue lymphatic endothelial cells)[7] but with distinct adaptations to their function in the CNS. Meningeal lymphatics enable the drainage of the macromolecules and immune cells originating from the CNS to the deep cervical lymph nodes (see Fig. 8.1).[8,9] Remarkably, genetic ablation of this system did not lead to increased intracranial pressure, indicating the existence of separate specialized systems for CSF volume regulation (arachnoid villi, cribriform plate, perineural spaces) and immune surveillance (meningeal lymphatics).

Intriguingly, the glymphatic system functions mainly during sleep and appears to be largely quiescent during wakefulness. The biologic need for sleep across all species may therefore reflect the necessity to enter a state of activity that enables elimination of potentially neurotoxic waste products (including β-amyloid, a mediator of Alzheimer disease). Flux through the glymphatic system is energy-consuming and assisted by arterial pulsatility. It diminishes with age and undergoes changes associated with a number of conditions affecting the CNS (e.g., traumatic brain injury, neurodegenerative diseases, and diabetes mellitus).[10] The effect of anesthetics on flux through this system is unknown with the exception of ketamine-xylazine anesthesia, which increases flux similarly to sleep.[11]

In addition to waste elimination, the glymphatic system also facilitates the brainwide distribution of glucose, lipids (including cholesterol and its degradation products), amino acids, growth factors, neuromodulators, as well as β-amyloid.

The Neuron

The neuron is the fundamental building block of the nervous system. Neurons are diverse in nature, interconnected, adaptive, and therefore, as ensembles, give rise to the stunning complexity of the brain. A *complex* system is endowed with *emergent properties*—that is, properties that appear only in ensembles as opposed to being present fully in the individual element. The human brain contains more than 10^{11} neurons. Their cell bodies are located in gray matter areas of the CNS, whereas the white matter consists of fibers connecting neurons from different regions.

Neurons are excitable cells. This property is harnessed to receive, process, integrate, and transmit signals. Their structure is optimized to integrate multiple inputs and deliver what formerly was considered an all-or-none (binary), digital signal in the form of an action potential to other, potentially distant, elements. Action potentials, however, should not be interpreted as isolated events where information transfer is concerned. Both their rate modulation and their phase relationship with respect to ongoing oscillations encode information. Neurons in the CNS are connected by approximately 10^{14} synapses, which are specialized structures allowing information transfer and hence networking.

Basic Structure

The generic neuron contains three basic elements: dendrites (signal reception and processing), soma or cell bodies (signal integration and cellular housekeeping apparatus), and axons (information output). These three elements vary in complexity, shape, and length, giving rise to a dazzling variety of neuronal morphology (Fig. 8.2).

The *soma* is the part of a neuron that is most reminiscent of a conventional cell. It contains all the standard cellular components found in other cells, such as nucleus, protein production (ribosomes), and modification machineries and energy generators (mitochondria). The soma also undergoes neuron-specific long-term changes during development, plasticity, degeneration, and aging. In addition, the soma is the hub linking signal input to information output.

The *dendrites* are elongated cytoplasmic processes. Usually a neuron has more than one dendrite. Each dendrite bifurcates multiple times, creating a dendritic arbor in the vicinity of the soma; it can stretch to other cortical layers but does not spread to distant regions of the brain. The dendritic arbor creates a large, intricately organized membrane surface area to receive input from other neurons. The arbor hosts vast numbers of the postsynaptic component of chemical synapses—transmitter receptors—targeted by incoming axon terminals that form the presynaptic side. A typical pyramidal cell (e.g., in the hippocampus or in cortical layer V) receives many thousand synapses: excitatory inputs on dendrites, inhibitory on soma and dendrites. The structure of the dendritic tree and the location of each synapse on it determine the nature of input summation and local integration and hence their relative strength. Spines are small processes of varying shapes found on many dendrites. These processes are specialized sites of synaptic connections, increasing the dendritic membrane and subdividing the subsynaptic structures (Figs. 8.3 and 8.4). Spines are highly dynamic and can change their size and composition on a time scale of minutes in response to neuronal activity, thereby creating, changing, or eliminating synaptic points of contact.

The *axon* is a very thin cytoplasmic process that carries the output signal of the neuron (the action potential) to its targets. Typically, a single axon originates from and terminates in specialized structures termed *axon hillocks* at the soma and *presynaptic terminals* at its destination. Normally, it bifurcates multiple times on the way and creates an axonal arbor connecting with many other neurons. Axonal lengths range from less than a millimeter (local interneurons) to more than 1 m (spinal α-motoneurons).

Axons are usually much longer and thinner than dendrites; hence they require mechanisms that enable them to reliably and efficiently transfer information over long distances, supporting the presynaptic machinery in the terminal at the target while maintaining their own structural integrity. The myelin envelope and the axonal transport system are two mechanisms to this end.

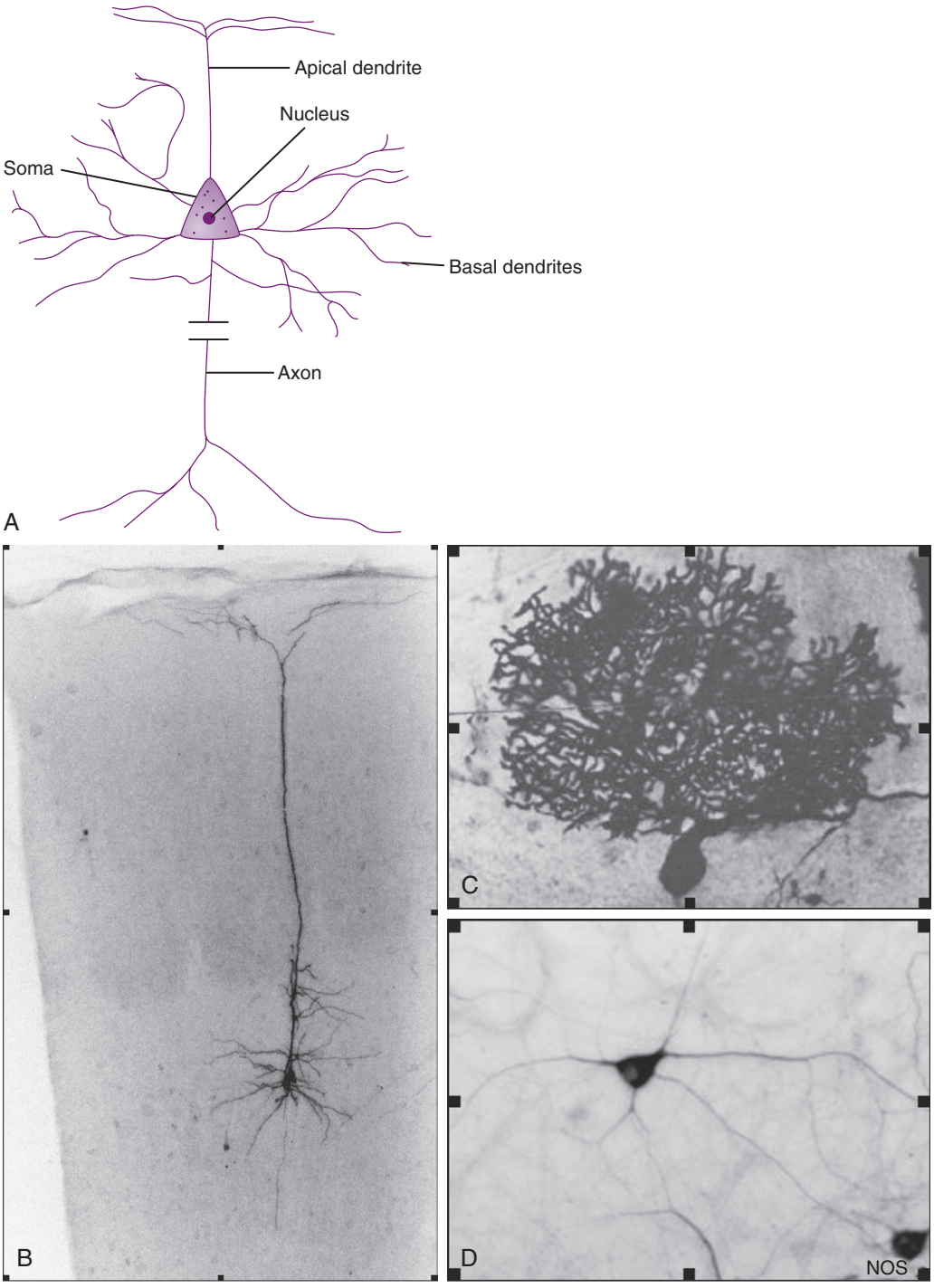
Myelin is a composite of multiple layers of lipid membranes formed by the oligodendroglia in the CNS (Schwann cells in the peripheral nervous system). Myelin electrically insulates the axon, enabling high-speed propagation of action potentials with minimal energy expenditure (varying with the degree of insulation).

Axonal transport is a "housekeeping" mechanism that moves vesicles and proteins from their site of synthesis in the soma along the whole length of the axon, and reverse transport relays signals back to the soma. It is an active, energy-consuming process using the cytoskeleton (e.g., microtubules) to meet the metabolic needs of the axon, its collaterals, and the presynaptic terminals because diffusion alone would not suffice.[12]

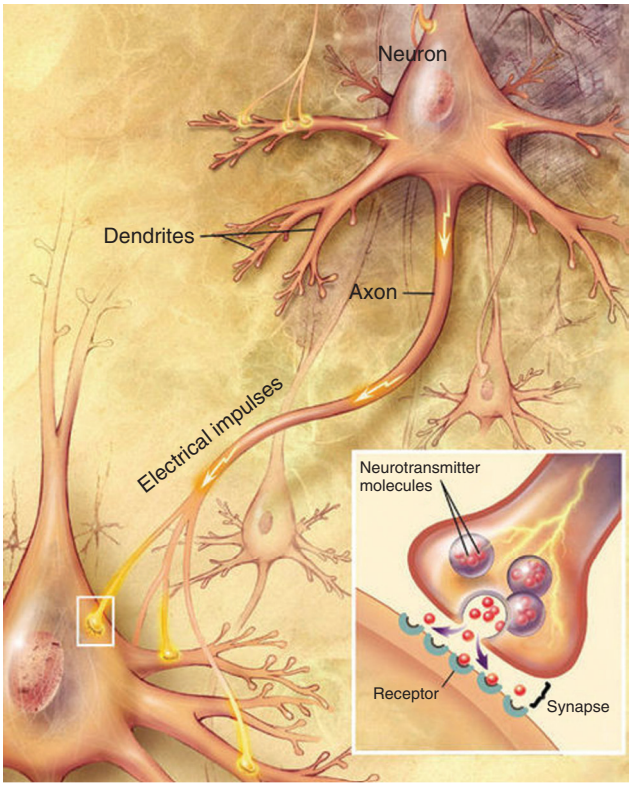
Excitability

Excitable cells are characterized by the ability to dynamically change the electrical potential across their cell membrane. Typical examples are muscle cells and neurons. Neurons use this property to integrate and disseminate information with precise and independent control of excitability in different functional compartments. Alterations in excitability are an important aspect of anesthetic drug action.

A living cell is defined by its ability to remain segregated from its environment. This fundamental property is made possible by the selective permeability of *the cell membrane* (the lipid bilayer and the proteins embedded into it). The intracellular ions are



• **Fig. 8.2** The neuron. A basic plan (A) underlies the stunning variety of neuronal shapes found in the mammalian brain. The morphology reflects individual computational needs and architectural constraints. Three examples are shown to illustrate this diversity. A, Schematic plan of a pyramidal neuron; notice the apical and basal dendritic arbors providing ample space for synaptic inputs and the long axon projecting to a distant location (symbolized by the interruption). B, Photomicrograph of a biocytin-filled cortical pyramidal neuron. Notice the dendritic arbor stretching toward the superficial layers. C, Golgi-impregnated Purkinje cell in the cerebellum. D, Photomicrograph of striatal interneuron immunostained by anti-nitric oxide synthase (NOS) antibodies. (B, Adapted from Cauller LJ, Connors BW. Synaptic physiology of horizontal afferents to layer I in slices of rat SI neocortex. *J Neurosci*. 1994;14:751–762; C, adapted from Calvet MC, Calvet J, Camacho-Garcia R. The Purkinje cell dendritic tree: a computer-aided study of its development in the cat and in culture. *Brain Res*. 1985;331:235–250; D, adapted from Schock SC, Jolin-Dahel KS, Schock PC, et al. Striatal interneurons in dissociated cell culture. *Histochem Cell Biol*. 2010;134:1–12.)



• **Fig. 8.3** Schematic representation of synaptic connections between two neurons. The action potential travels along the axon of neuron A (upper right side) and leads to the release of neurotransmitter containing synaptic vesicles from the presynaptic terminal of A. Neurotransmitter molecules diffuse across the synaptic cleft to activate receptors on the postsynaptic membrane of neuron B (lower left side) . The axon of A contributes to multiple synapses on B and also innervates many other neurons. The axons of interneurons in particular target specific areas of the postsynaptic neuron (e.g., distal apical dendrites, proximal basal dendrites, or soma). This target specificity has been well characterized in hippocampal interneurons (not shown). The content of one vesicle is thought to lead to a miniature postsynaptic potential that can be either inhibitory or excitatory. (Adapted from drawing illustrating the process of synaptic transmission in neurons, cropped from original in a National Institute on Aging brochure. http://en.wikipedia.org/wiki/File:Chemical_synapse_schema_cropped.jpg#file.)

dominated by potassium ions (K^+), while extracellularly high sodium ions (Na^+) and chloride ions (Cl^-) hark back to the ionic composition of sea water (Table 8.1). Because of its hydrophobic interior, the lipid bilayer prevents charged molecules and most ions from crossing the membrane. By contrast, water and other small uncharged molecules (e.g., urea) diffuse freely. Membrane-spanning proteins selectively control the movement of ions and other small molecules across the membrane, rendering this lipid envelope semipermeable. Membrane transport systems can be divided into two principal categories: catalytic and stoichiometric.[13] The proteins responsible for this property are traditionally grouped into pores and channels (catalytic) on one hand and pumps and transporters (stoichiometric) on the other. Catalytic systems carry out movement only "downhill"—that is, toward the electrochemical equilibrium—while stoichiometric systems can carry out transport "uphill" —away from the equilibrium with energy expenditure. Cells also have special mechanisms to transport large molecules across the cytoplasmic membrane. Excitable cells in particular are endowed with a rich assortment of ion channels.

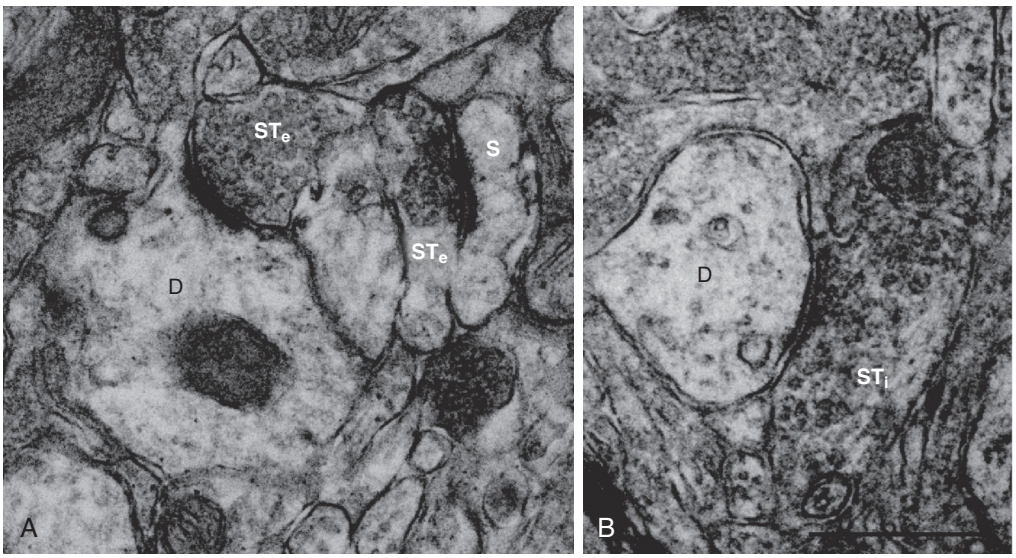
The differential distribution of ions inside and outside the cell creates chemical concentration gradients. For example, the concentration of K^+ is high inside and low outside the neuron. This creates a tendency for K^+ ions to diffuse out of the cell through K^+ channels that are typically open at *the resting membrane potential (RMP)*. Because K^+ is positively charged, this creates a redistribution of electrical charge, with the inside of the cell becoming more negative because the membrane is impermeable to large molecules like negatively charged proteins. The excess negative charge inside the cell attracts K^+ ions and, at some point, the tendency to diffuse out of the cell along the chemical concentration gradient will be offset by the electrical attraction from inside the cell, reaching electrochemical equilibrium. This equilibrium is dynamic as ions continuously cross the membrane while the net flow of charge is zero. The relation between an ion's concentration gradient and the electrical gradient it creates was described in the 19th century by Nernst in his classic equation:

$$E = \frac{RT}{zF} \ln\left(\frac{[Ion]_{out}}{[Ion]_{in}}\right), \quad [1]$$

TABLE 8.1 Cytoplasmic and Extracellular Ion Concentrations

Ion	Intracellular Concentration (mm)	Extracellular Concentration (mm)	Steady-State Potential at 37°C (mV)
Na^+	10	145	+70
K^+	140	5	–87
Ca^{2+}	10^{-4}	1.5	+125
Mg^{2+}	6.5	2	–15
Cl^-	4	110	–86
HCO_3^-	12	25	–19

Na, Sodium, *K,* Potassium; *Ca,* Calcium; *Mg,* magnesium, *Cl,* chloride; HCO_3^-, bicarbonate.



• **Fig. 8.4** Chemical synapses are the mainstay of interneuronal communication. Morphology of excitatory (A) and inhibitory (B) synapses as seen with the electron microscope. Note that in A one excitatory terminal *(ST$_e$)* forms an asymmetric synapse with a dendrite *(D)* and a dendritic spine *(S)*. Note the cloudlike electron-dense material known as the postsynaptic density, which is characteristic of excitatory synapses. The inhibitory terminal *(ST$_I$)* forms a symmetric synapse with a dendrite *(D)*. Scale bar = 500 nm. (Courtesy S.L. Feig, PhD, University of Wisconsin, Madison, Wisconsin.)

where E is the electric potential across the membrane (in millivolts) at equilibrium, R is the ideal gas constant, T is the temperature in degrees Kelvin, z is the ion's charge, F is Faraday's constant, and $[\text{ion}]_{out}$ and $[\text{ion}]_{in}$ are the concentration of the ion on the two sides of the membrane. All the ions that are differentially distributed between the inside and the outside of a neuron create electrical gradients/potentials across the cell membrane.[14]

Because most of the values in the Nernst equation are constant under biologic conditions, the equation can be simplified assuming intracellular and extracellular K^+ concentrations of 140 and 5 mmol/L at 37°C as:

[2]

$$E = 60\log\left(\frac{[K^+_{out}]}{[K^+_{in}]}\right) = 60\log\left(\frac{5}{140}\right) = -86.8\,mV$$

This means that, at −86.8 mV and the K^+ concentrations given above, no net flow of K^+ occurs even if the membrane is freely permeable to K^+. Similarly, for each ion there is a membrane potential at which its concentration gradient will be balanced by its electrical gradient. These equilibrium potentials become significant determinants of the membrane potential when opening of appropriate channels renders the membrane permeable to a specific ion (e.g., Na^+). Table 8.1 lists the Nernst potential of some common ions that influence the neuronal membrane potential.

The membrane potential of a cell is determined by the gradients of all the intracellular and extracellular ions, scaled in proportion to their permeability through the membrane: the greater the permeability of the cell membrane to a specific ion, the stronger its effect on the membrane voltage. This is described by the Goldman-Hodgkin-Katz equation[15]:

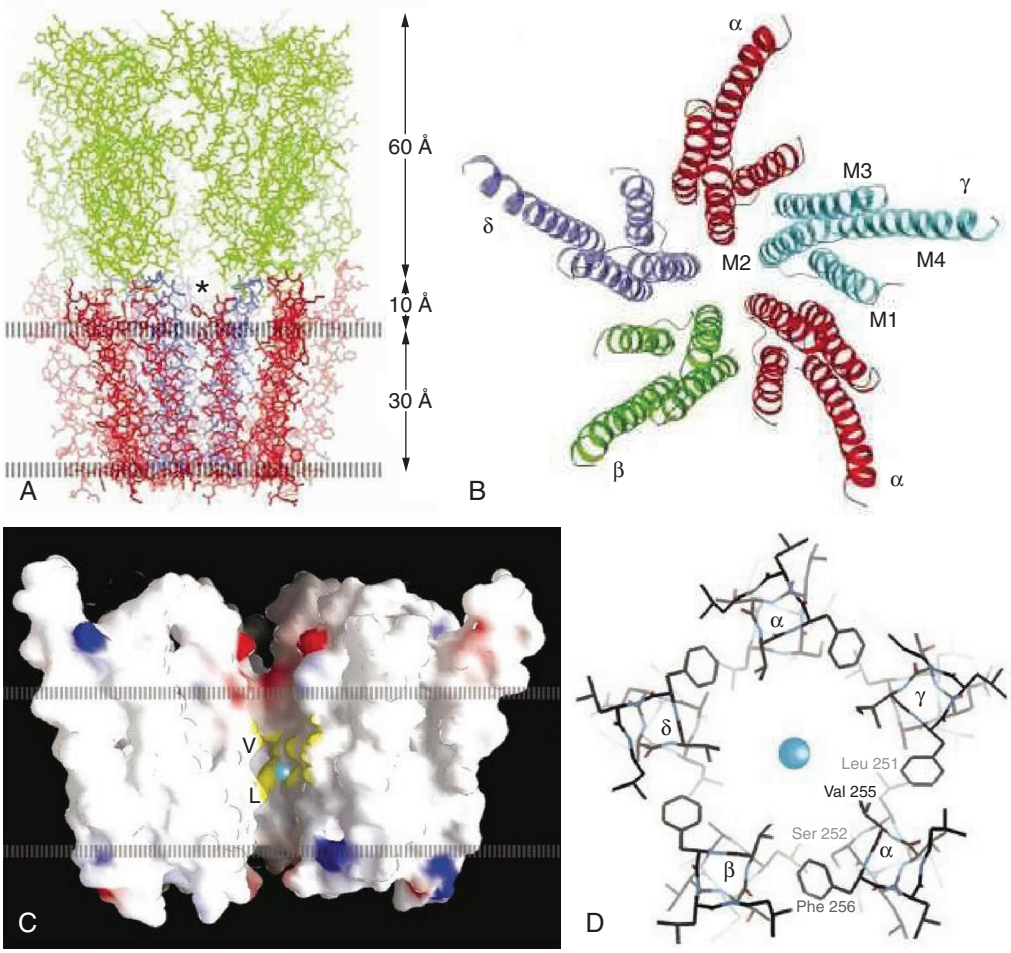
[3]

$$E = \frac{RT}{F}\ln\left(\frac{\sum_i^N P_{Ci}[Ci]_{out} + \sum_j^M P_{Aj}[Aj]_{in}}{\sum_i^N P_{Ci}[Ci]_{in} + \sum_j^M P_{Aj}[Aj]_{out}}\right),$$

where P is the permeability, Ci the cations, and Aj the anions; the rest of the variables are the same as in the Nernst equation. In a "resting" neuron, the membrane potential typically is −60 to −70 mV. An increase in membrane permeability to K^+ (equilibrium potential of −90 mV) will "pull" the membrane potential toward −90 mV, hyperpolarizing the cell. An increase in permeability to Na^+ (equilibrium potential of +70 mV) will depolarize it. Under resting conditions, the permeability of the cell membrane for K^+ dominates and therefore the RMP is largely determined by the equilibrium potential for K^+.[14]

Ion channels are pores allowing diffusion of ions across the cell membrane along their electrochemical gradient. Typically, these proteins are composed of a number of subunits, each containing multiple transmembrane domains (Fig. 8.5). The three-dimensional folding of the subunits and their arrangement with respect to each other create a hydrophilic pore across the membrane lined by specialized sections of the transmembrane domains, which determine the ion selectivity of the channel. When open, channels are typically permeable to either cations or anions, but within each group the degree of permeability can vary widely depending on the selectivity of the specific channel.

Changes in the structural conformation of the subunits lead to opening and closing of the channel pore. The state of a channel is controlled by the electrical potential gradient across the membrane (voltage-gated channels), by the action of a chemical substance on receptors linked to the channel (ligand-gated receptor-channel



• **Fig. 8.5** The structure of a ligand-gated ion channel. Like other members of the cys-loop ligand-gated ion channel superfamily that also includes the gamma-aminobutyric acid $(GABA)_A$, $5\text{-}HT_3$, and glycine receptors, the nicotinic acetylcholine receptor-channel complex consists of five subunits (i.e., it is a pentamer), with each subunit containing multiple transmembrane domains and their intracellular and extracellular connecting loops. A, View along the receptor axis showing the pore structure (*blue,* pore-facing; *red,* lipid-facing helices) in relation to the membrane surfaces *(broken lines)* and the β-sheet structure *(green)* comprising the ligand-binding domain; the *asterisk* denotes open space at a subunit interface. B, View of the pore from the synaptic cleft, with the five subunits shown in different colors (note two α-subunits in *red*). C, Molecular surface of the pore domain with front subunit removed. *Red* and *blue* indicate areas of high negative and high positive charge, respectively; the hydrophobic gate-containing area is highlighted in *yellow;* the letters *V* and *L* identify individual amino acids (α-Val 255 and α-Leu 251). D, Symmetric arrangement of side chains forming the gate. The blue spheres in C and D indicate the size of a sodium ion. (Adapted from Miyazawa A, Fujiyoshi Y, Unwin N, et al. Structure and gating mechanism of the acetylcholine receptor pore. *Nature.* 2003;423:949–955.)

complexes) (see Fig. 8.5), by the intrinsic gating properties of the channel itself (e.g., many voltage-gated Ca^{2+} ions exist within the presynaptic terminal sharing voltage sensitivity and ion selectivity but nevertheless having different functional properties), and by its sensitivity to modulation. Channel modulators include intracellular and extracellular factors, such as neuromodulators, phosphorylation state, pH, temperature, membrane tension, metabolic products, and the preceding activity of the neuron. Table 8.2 shows a partial list of ion channels that are abundant in the CNS and are implicated in anesthetic action.

Ion pumps are proteins that deliver ions across the cell membrane against their electrochemical gradient. The coupling of transport to an external energy source in an energy-consuming process distinguishes transporters. Maintenance of gradients across the cell membrane may account for more than 50% of the total energy expenditure in a spiking neuron. The most common ion pump—the sodium-potassium adenosine triphosphatase (Na,K-ATPase) pump—uses energy released by hydrolysis of one ATP molecule to pump three Na^+ ions out in exchange for admitting two K^+ ions into the cell. This process, resulting in the net transfer of one positive charge out of the cell for each ATP molecule, generates a hyperpolarizing current.

Transporters carry molecules across the membrane along or against their electrochemical gradient following enzyme kinetics.

TABLE 8.2 Common Ion Channels of the Brain

Receptor (R)/Channel	Ion Permeability and Normal Flow Direction	Transmitter/Gating Mechanism	Principal Roles
$GABA_AR$	Cl^- ↓ HCO_3^- ↑	GABA	Major inhibitory transmitter
Nicotinic Acetylcholine R	Na^+, K^+ ↓	Acetylcholine	Synaptic transmission in the brain and at the neuromuscular junction
Glutamate R			Major excitatory transmitter
AMPA-type GluR	Na^+, K^+ ↓	Glutamate, provides depolarization for NMDAR	Depolarization
NMDA-type GluR	Na^+,Ca^{2+} ↓	Glutamate/glycine is coagonist depolarization (to release the Mg^{2+} block) required	Depolarization, synaptic plasticity, excitotoxicity if excessive
Voltage-gated Na	Na^+ ↓	Membrane depolarization	Action potential initiation/propagation
Voltage-gated K^+	K^+ ↑	Membrane depolarization	Action potential termination and repolarization of the membrane
Voltage-gated Ca^{2+}, many subtypes	Ca^{2+} ↓	Membrane depolarization	Burst firing (T-type); dendritic depolarization (H-type) neurotransmitter release (P, N, R types)
Ca^{2+}-activated K^+ channels	K^+ ↑	Intracellular Ca^{2+} concentration increase	Synaptic plasticity, after hyperpolarization and smooth muscle tone
Hyperpolarization-activated cyclic nucleotide-gated channels (HCN)	K^+ ↑ (I_{funny})	Membrane hyperpolarization Intracellular cAMP	Pacemaker/rhythmic oscillation activity Synaptic plasticity
Cyclic nucleotide gated ion channels	Na^+, K^+, Ca^{2+}, Mg^{2+}	Intracellular cGMP and cAMP	Light detection in photoreceptors
Two-pore domain K^+ channel	K^+ ↑	Oxygen tension, pH, mechanical stretch, etc.	Resting membrane potential, "leak channels"

The table shows common ion channels of neuronal cell membranes. Transmitter-activated receptor channel complexes are organized by the principal transmitter, voltage-activated channels by principal ion. Down/up pointing arrows indicate the inward/outward flow of ions.
AMPA, 2-Amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid; *Ca,* calcium; *cAMP,* cyclic adenosine monophosphate; *cGMP,* cyclic guanosine monophosphate; *Cl,* chloride; *GABA,* gamma-aminobutyric acid; *HCO_3^-,* bicarbonate; *K,* potassium; *Mg,* magnesium, *Na,* sodium, *NMDA,* N-methyl-D-aspartate; *NMDAR,* NMDA receptor.

Transportation against the gradient is achieved by transporting two substrates simultaneously, using the energy from the downhill transport of one substrate to drive the uphill transport of another substrate. This type of transporter is termed *cotransporter* or *symporter*—for example, the potassium-chloride cotransporter (KCC2). KCC2 delivers one K^+ together with one Cl^- across the membrane along their combined electrochemical gradient. Because the internal K^+ concentration is kept high by the activity of the Na,K-ATPase, the transporter carries K^+ and Cl^- out of the cell. In this example, the transporter allows the cell to use energy stored in the K^+ gradient to create a Cl^- gradient across the membrane.

Communication

The nervous system is a network of units communicating on each organizational level, from the individual neuron to the whole brain. An important part of integration and communication is carried by changes in electrical potentials that can be either depolarizing or hyperpolarizing and shunting carried out by increasing the membrane permeability for ions with a Nernst potential more positive and more negative than the RMP, respectively.

Membrane Time Constant

The cell membrane of the neuron can be modeled as an electrical circuit composed of a resistor and a capacitor (RC circuit). The lipid bilayer functions as a capacitor. Ion channels and transporters that allow ion flow across it function as resistors. When ions pass through a channel, the potential across the membrane does not change instantly. Rather, as in the RC circuit, the current needs time to charge the capacitance of the membrane. The inverse process occurs after a channel closes. The rise and fall of the membrane potential follow exponential patterns and lag behind the current. The time course of voltage change is described in the following equation:

[4]

$$\Delta V = IR_m\left(1 - e^{\frac{-t}{R_m C_m}}\right),$$

where V is the potential, I is the current, R_m is the resistance, and C_m is the capacitance of a membrane segment. The term R_mC_m is the time constant of the membrane, the dimensionless τ. The larger the value of τ, the faster the change in voltage. τ is an important factor in the ability of a cell to perform temporal summation of different inputs.[16]

Current spreads spatially as charged molecules diffuse along the membrane. This spread allows neurons to perform summation of inputs from neighboring synapses—one type of intraneuronal integration. The electrical potential caused by the current decays along a segment of membrane with a first-order exponential (determined by the length constant λ). λ depends on the membrane properties (e.g., its conductance or permeability) and determines the spread of the potential change.[17]

Action Potential

Frequently referred to as a "spike," describing its rapid time course, the action potential (AP) is driven by the sudden opening of fast voltage-gated Na^+ channels, activated by a local depolarization of the cell membrane beyond the activation "threshold" (typically around −50 mV) when a positive feedback loop results in an extremely fast regenerative process. Within 1 ms, the cell membrane potential is driven beyond 0 mV and toward the Nernst equilibrium for Na^+. The AP is rapidly terminated by inactivation of Na^+ channels and opening of slower K^+ channels limiting the duration of an AP to a few milliseconds (Fig. 8.6).[18]

The threshold of AP generation is the basis of "neuronal calculation." A neuron integrates the barrage of many inputs it constantly receives: positive (depolarizing) and negative (hyperpolarizing) and shunting (increase in conductance without voltage change). Whenever the sum of these signals pushes the membrane potential beyond the threshold, the neuron "fires" an AP. After an AP, Na^+ channels are inactivated for a few milliseconds. During this refractory period the cell cannot fire again. The firing threshold is dynamic: the amount of available voltage-gated Na^+ channels and the threshold for AP generation change depending on the activity of the cell. For example, hyperpolarization increases the number of available Na^+ channels, thereby facilitating AP generation once hyperpolarization terminates. Subthreshold depolarization, by contrast, inactivates Na^+ channels and a stronger depolarizing current is necessary to force the cell to fire.

An AP is initiated in a specialized membrane area extending from the axon hillock to the end of the unmyelinated axon initial segment (Fig. 8.7). Synaptic inputs impinge on the distal end of the axon initial segment and, in conjunction with a diverse set of ion channels, suggest that the axon initial segment is capable of signal integration in addition to being a low-threshold area for AP triggering.[19] From the axon initial segment, the AP invades and rapidly travels along the axon either by a rolling depolarization or by saltatory conduction. In principle, any segment of axon can conduct APs in either direction. The directionality of spread is given by the gating state of Na^+ channels on both sides of the depolarized segment. The AP will spread in the direction of nonrefractory channels (exogenous stimulation can initiate "retrograde" spread of APs, see Chapter 17).

Synapses

The synapse is an information relay between two neurons. It usually connects the axon terminal of the presynaptic cell with the dendrite of the postsynaptic cell. Signal transmission can be either electrical or chemical and synapses are also found between axon and soma, two axons, and two dendrites.

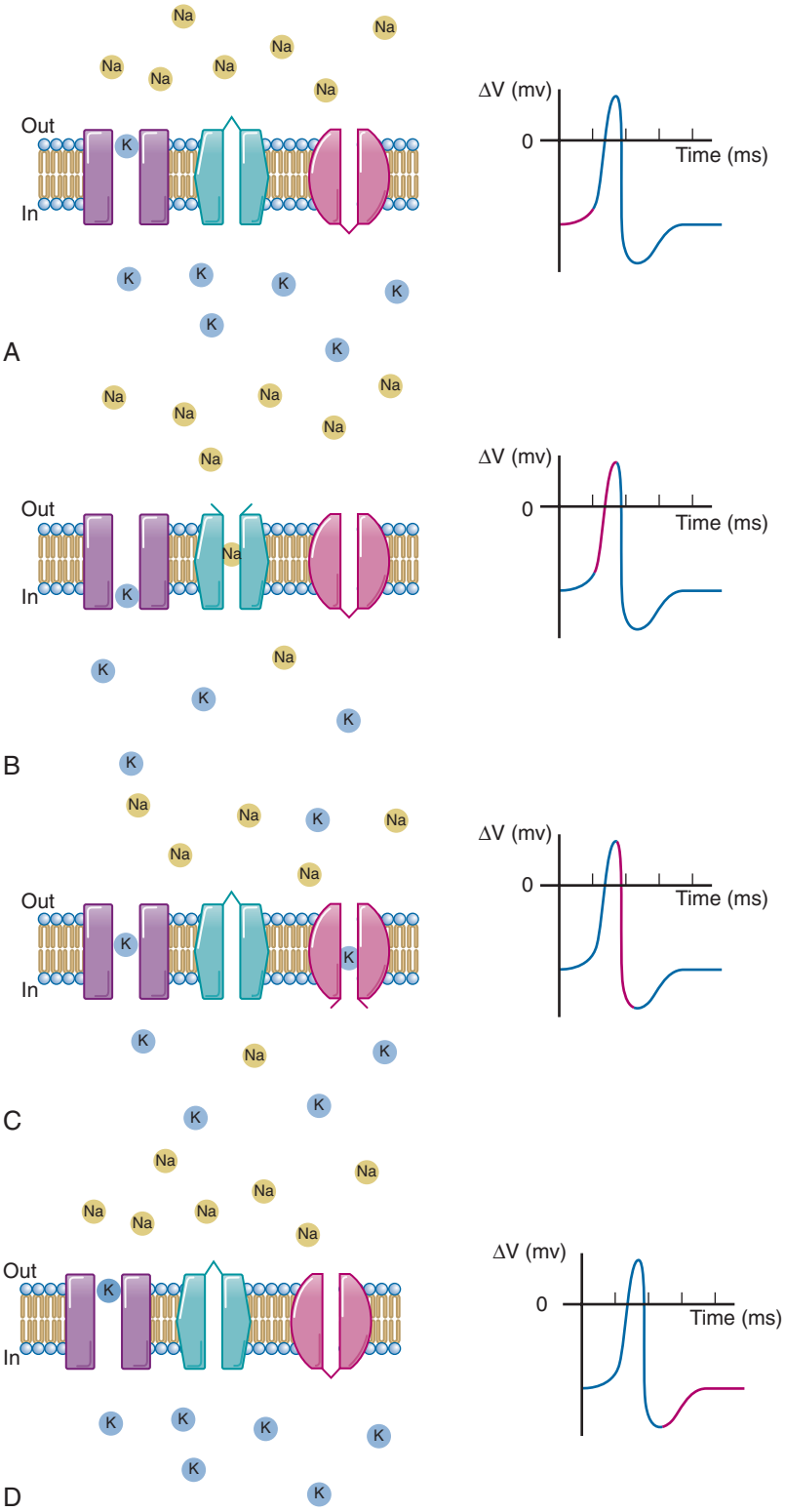
The *electrical synapse* (also called the *gap junction*) is a channel formed of proteins. Electrical synapses form a minority of all synapses and are enriched in specific brain areas—for example, the thalamus where they create a syncytium-like continuity of cytoplasm and membrane directly passing electrical current between neurons. They can transmit action potentials, as well as subthreshold membrane potential fluctuations practically without any delay. Gap junctions also undergo plasticity.[20]

The chemical synapse consists of specialized presynaptic and postsynaptic elements separated by the synaptic cleft. Communication across the cleft is via a neurotransmitter stored in presynaptic vesicles. An AP initiates a cascade of events that leads to the release of a neurotransmitter. The neurotransmitter then diffuses through the synaptic cleft, binds to transmitter-specific receptors on the postsynaptic membrane, and sets off a signaling cascade. Release, diffusion, and activation of receptors impose a delay of approximately 1 ms on signal transfer. The transmitter may bind to an ionotropic receptor, which is a receptor-ion channel complex. Binding to this receptor type leads to the opening of the ion channel (fast synaptic transmission), which will hyperpolarize or depolarize the cell depending on the ions conducted by the receptor channel. A different type of receptor is the metabotropic receptor, which does not directly open an ion channel but rather exerts its effect via a second-messenger cascade (slow synaptic transmission). These receptors are often G-protein–coupled but may be coupled to other enzymes (e.g., tyrosine kinase). Transmitter-specific mechanisms ensure that the chemical signal is limited to a brief pulse that barely outlasts the incoming electric signal but exceptions are well known (see later text).

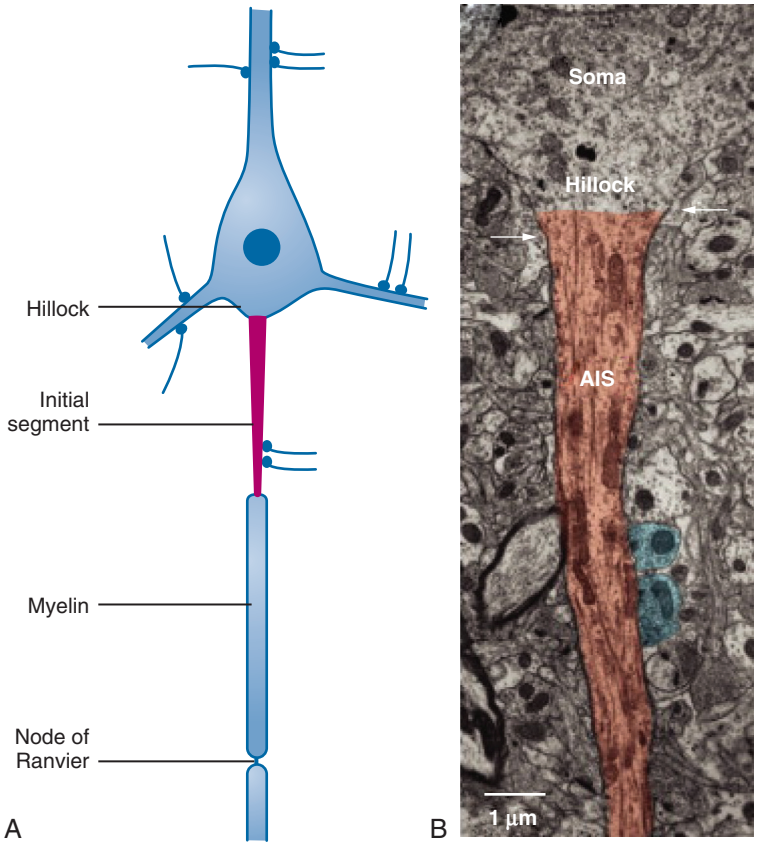
Neurotransmitters are typically small organic molecules, some derived from amino acids (GABA, L-glutamate, dopamine). Each transmitter can activate multiple receptor subtypes, providing a tremendous flexibility of signal transmission. For example, GABA, glutamate, and acetylcholine all activate different subtypes of both ionotropic and metabotropic receptor classes. Anatomically defined synapses are typically excitatory or inhibitory in nature, but neurotransmitters act also on receptors outside classic synapses where their action is more modulatory in nature. Some synapses simultaneously release more than one transmitter (e.g., the release of GABA and substance P from the same striatal spiny projection neurons). In addition to falsifying Dale's rule with respect to transmitter exclusivity, recent research has also shattered the long-held belief that the identity of the transmitters expressed by neurons is unchanging. Electrical activity can respecify the neurotransmitter phenotype of an individual neuron both during development and in the mature nervous system.[21]

Transmitter Release and Action

Release of neurotransmitter can be either conventional (quantal) or unconventional. *Conventional (quantal) release* indicates that transmitter release occurs in discrete quantities or quanta (singular: quantum) dictated by the storage of transmitter in synaptic vesicles, discrete membrane vesicles of defined capacity within the terminal. An AP depolarizes the terminal opening voltage-gated Ca^{2+} channels. The subsequent Ca^{2+} increase in the terminal leads, via a complex cascade, to fusion of transmitter-loaded vesicles with the presynaptic membrane and release of neurotransmitter into the synaptic cleft. The amount of neurotransmitter released is determined by the number of vesicles that fuse with the membrane. Spontaneous fusions of individual vesicles with the membrane are observable as "quantal" postsynaptic events when APs are blocked.[22] Some ionotropic channels (e.g., the



• **Fig. 8.6** The action potential (AP, schematic A-D) originates in the axon initial segment (AIS, E). A, Membrane at rest; voltage-activated sodium ion (Na^+) *(triangular)* and potassium ion (K^+) *(circular)* channels are closed. K^+ leak current *(square)* dominates the membrane potential. B, When the membrane potential crosses the threshold for activation, Na^+ channels open. Because during this phase Na^+ permeability dominates, the membrane rapidly depolarizes. C, Na^+ channels slowly become inactivated and voltage-activated K^+ channels open. The membrane potential rapidly hyperpolarizes to below baseline. D, Na^+ and K^+ channels are inactivated. The cell is refractory and an AP cannot be initiated.



• **Fig. 8.7** A, Schematic of a pyramidal neuron axon showing the location of the axon hillock, the axon initial segment (AIS; *red*), and the axon proper. Synaptic input onto the AIS is shown in *blue.* B, Electron micrograph of the AIS (in *red*) of a cortical pyramidal neuron, including the soma and the axon hillock. *Blue* areas indicate presynaptic terminals onto the AIS. *Arrows* (white) point to the beginning of the AIS. (Adapted from Peters A, Proskauer CC, Kaiserman-Abramof IR. The small pyramidal neuron of the rat cerebral cortex. The axon hillock and initial segment. *J Cell Biol*. 1968;39:604–619; Kole MH, Stuart GJ. Signal processing in the axon initial segment. *Neuron*. 2012;73:235–247.)

N-methyl-D-aspartate [NMDA] type of glutamate receptor) can pass Ca^{2+} in addition to Na^{+}. Ca^{2+} is a universal second messenger triggering complex physiologic or pathologic cascades ranging, in the case of NMDA receptors, from synaptic plasticity to necrosis (Table 8.3).

Unconventional release and action is frequently associated with slower and longer-lasting but spatially localized modulatory effects: a slow background "offset" signal as opposed to the brief quantal information packet. The terms *paracrine* and *neurocrine* are used to describe this mode of release. Typically still AP-dependent, this mode allows rapid communication with larger population of cells over long distances while remaining more selective than neuroendocrine communication via the bloodstream. Small, gaseous molecules, including carbon monoxide, hydrogen sulfide, and nitric oxide as well as others, that are difficult to store such as cannabinoids (and probably other, yet undiscovered, substances) are released in a nonquantal fashion.[23] Some of these mediators make feedback communication from the postsynaptic to the presynaptic side of a chemical synapse possible (e.g., endocannabinoids modulate transmitter release from hippocampal GABAergic synapses).[24] Nonquantal release of conventional neurotransmitter such as acetylcholine also occurs under certain circumstances (e.g., during embryonic development.)[25]

Transmitter diffusing out of the synaptic cleft can activate receptor populations located extrasynaptically, as best described for GABA. Extrasynaptic $GABA_A$ receptors have distinct gating properties: they are activated by low concentrations of ambient GABA and they inactivate very slowly.[26] This mode of transmitter action is called *tonic* as opposed to the classic phasic action outlined earlier. Intermediate forms of transmitter action, such as on receptors located perisynaptically, also exist and give rise to slow phasic synaptic potentials.[27] Extrasynaptic NMDA receptors have also been described.

Termination of transmitter action can be effected either by diffusion away from the synapse, by active enzymatic degradation, and/or reuptake either into the terminal or into glial cells. The latter processes allow local recycling.

Plasticity

Structural and functional refinements of neural circuits, including those underlying learning and memory, are essential processes throughout the entire life of an organism. With few known exceptions, no new neurons are generated after the neonatal period. Therefore modifications of connections between existing neurons underlie all forms of behavioral modification based on experience. Information is stored by modifying the synaptic strength of

TABLE 8.3 Common Neurotransmitter Receptors

Neurotransmitter	Receptor	Type	Effect	Structure
Glutamate	NMDA	Ionotropic	Na^+, K^+, Ca^{2+} permeability	4 subunits: 2 GluN1, 2 GluN2
	AMPA	Ionotropic	Na^+, K^+ permeability	4 subunits:
	KA	Ionotropic/metabotropic	Na^+, K^+, Ca^{2+} permeability	out of GluA1-4, usually
	$mGluR_{1-8}$	Metabotropic	Different types exert different second-messenger effects	2 GluA2 and 2 of either GluA1, 3, or 4
Acetylcholine	Nicotinic	Ionotropic	Na^+, K^+, Ca^{2+} permeability	5 subunits: 3α, 2β (neuron) 2α, β, ε, δ (NMJ)
	Muscarinic	Metabotropic	↑ IP_3/DAG	
GABA	$GABA_A$	Ionotropic	Cl^- permeability	5 subunits: 3α:2β:γ
	$GABA_B$	Metabotropic	↓ cAMP	
Glycine	Glycine	Ionotropic	Cl^- permeability	5 subunits: 3α,2β or 4α,1β
Serotonin (5-hydroxytryptamine)	$5\text{-}HT_1$	Metabotropic	↓ cAMP	
	$5\text{-}HT_2$	Metabotropic	↑ IP_3/DAG	
	$5\text{-}HT_3$	Ionotropic	Na^+, K^+, Ca^{2+} permeability	5 subunits
Norepinephrine	$\alpha_{1,2}$	Metabotropic	↑ IP_3/DAG	
	$\beta_{1,2}$	Metabotropic	↑ cAMP	
Dopamine	$D_{1,5}$	Metabotropic	↑ cAMP	
	$D_{2,3,4}$	Metabotropic	↓ cAMP	
Substance P	NK_1	Metabotropic	↑ IP_3/DAG	
Opioids	μ, δ, κ	Metabotropic	↓ cAMP	

AMPA, 2-Amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid; *Ca,* calcium; *cAMP,* cyclic adenosine monophosphate; *cGMP,* cyclic guanosine monophosphate; *Cl,* chloride; *DAG,* diacylglycerol; *GABA,* gamma-aminobutyric acid; *IP_3,* inositol triphosphate; *K,* potassium; *Na,* sodium; *NK_1,* neurokinin 1; *NMDA,* N-methyl-D-aspartate; *NMDAR,* NMDA receptor; NMJ, neuromuscular junction.

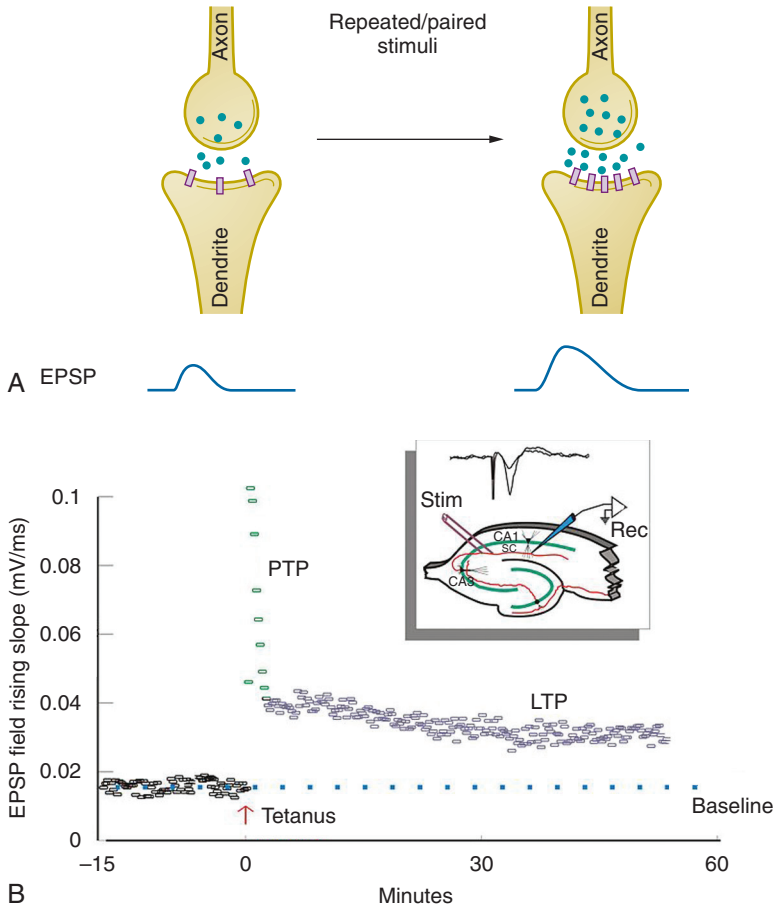
connections in a process called *synaptic plasticity*. Synaptic plasticity occurs on a number of time scales and is present from the ganglion of an invertebrate to the neocortex of a mammal. The forms of plasticity usually associated with long-term storage in the mammalian brain are termed long-term potentiation (LTP) (Fig. 8.8) and long-term depression (LTD). LTP and LTD have been best described at glutamatergic synapses but occur also at GABAergic synapses. The fundamental principle of synaptic plasticity was postulated by Hebb in 1949.[28] In the most generic terms, rapid repeated depolarization of a glutamatergic presynaptic terminal will depolarize the postsynaptic neuron (with or without actual spiking) and cause Ca^{2+} entry.[29] Depending on the circumstances the synaptic strength between these neurons will be either upregulated or downregulated, resulting in LTP and LTD, respectively.

The temporal requirements of plasticity are captured in the concept of spike-timing–dependent plasticity (STDP): LTP results when a synaptic input is followed within a narrow temporal window by spiking of the postsynaptic cell. The length of this window varies depending on the nature of the connection and the cell types involved.[30,31] Spiking outside this window has either no effect or results in LTD. Obviously, synchronization between cell populations is necessary for appropriate timing of synaptic inputs and spikes for STDP to occur and might be one of the functions of high-frequency brain oscillations.[32] Depotentiation/LTD-like processes are thought to occur during slow-wave sleep to "reset" the brain for a new day of learning.[33]

Transmitters and Receptors

Release of the major excitatory transmitter L-glutamate activates both ionotropic and metabotropic receptors. The three major types of ionotropic glutamate receptors (KA, AMPA, and NMDA) are named after their selective agonists (kainic acid, α-amino acid-3-hydroxy-5-methyl-4-isoxazole, and N-methyl-D-aspartate). The non-NMDA group (KA and AMPA) is permeable to monovalent cations and underlies fast excitatory postsynaptic potentials (EPSPs).[34]

NMDA receptors are blocked by extracellular Mg^{2+} at the concentration present in the extracellular fluid (see Table 8.1). Therefore the NMDA channel does not contribute substantially to a regular EPSP. However, as the Mg^{2+} block is relieved by depolarization, repetitive or particularly strong stimuli can depolarize the postsynaptic membrane sufficiently to open NMDA receptor-associated channels, such as when the postsynaptic cell fires an AP. Open NMDA channels allow Ca^{2+} into the cell. NMDA receptors act therefore as "voltage sensors" and allow a "conditional" Ca^{2+} signal to occur. For this reason, NMDA receptors play a pivotal role in processes that lead to synaptic plasticity. The Ca^{2+} influx via NMDA receptors is also responsible for glutamate toxicity (excitotoxicity) that occurs when high levels of glutamate are sustained for a long time, such as during status epilepticus. NMDA receptors have slower kinetics than their non-NMDA counterparts and, under appropriate conditions such as when the cell is depolarized or when Mg^{2+} is omitted from the extracellular fluid, slow



• **Fig. 8.8** Synaptic plasticity illustrated by long-term potentiation *(LTP)*. A, LTP can be caused by a variety of mechanisms that can be primarily presynaptic or postsynaptic. The preponderance of mechanisms varies between circuits and the exact mechanisms are still debated. The end result is a use-dependent increase in the postsynaptic response illustrated here as occurring via an increase in both the number of postsynaptic receptors and the amount of transmitter release. Typically, an individual synapse shows only one of these changes. B, Time course of experimental LTP induction in the CA1 area of the hippocampus where plasticity has been studied since the 1970s. The inset shows the iconic cross section of the hippocampus as seen in a transverse slice. Areas of projection neurons are shown in *green* and the principal excitatory pathways in red. Tetanic stimulation of the Schaffer collaterals (excitatory axon collaterals connecting the hippocampal areas CA3 and CA1) with one electrode (Stim) leads to an increase in field excitatory postsynaptic potentials *(EPSPs)* recorded by a second electrode (Rec) placed in the termination zone of the Schaffer collaterals in the dendritic arbor of CA1. Stimulation using a different pattern results in long-term depression *(LTD)* of the same pathway. *Rec,* recording electrode; *Stim,* stimulating electrode. (From An example of long-term potentiation recorded at Schaffer collateral/CA1 synapses in the hippocampus of rat brain. http://en.wikipedia.org/wiki/File:LTP_exemplar.jpg.)

NMDA EPSPs can be observed. The NMDA receptor is a target of the hallucinogen phencyclidine (PCP) and of the anesthetic drug ketamine.[35]

Metabotropic G-protein–coupled glutamate receptors can be excitatory or inhibitory. Glutamate binding to the receptor stimulates the activity of phospholipase C, leading to the formation of inositol 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG), which function as intracellular second messengers. Similar to NMDA receptors, this pathway leads to increase in intracellular Ca^{2+}, but in this case by release of Ca^{2+} from intracellular stores. This release causes a slow depolarization by reducing membrane permeability to K^+. On the other hand, glutamate binding to these receptors on the presynaptic terminal (autoactivation) causes presynaptic inhibition.[35]

GABA is the major inhibitory neurotransmitter in the brain and follows the ionotropic and metabotropic pattern with $GABA_A$ and $GABA_B$ receptor types, respectively. $GABA_A$ receptors are receptor/channel complexes passing anions: mostly Cl^-, but also HCO_3^-. The receptor has two binding sites for GABA, and the channel opens when both sites are occupied. This channel is the major target for a variety of drugs, including many anesthetics.[36] Interneurons are the main source of GABAergic synaptic transmission. They display a remarkable morphologic and neurochemical diversity that reflects a "computational" role of GABAergic transmission.[37,38] $GABA_B$ receptors are G-protein–coupled receptors, the activation of which leads to opening of K^+ channels via a second-messenger cascade.[39]

Glycine is also a major inhibitory neurotransmitter, primarily in the spinal cord. It is released by local inhibitory interneurons and activates ligand-gated Cl^- channels. Metabotropic glycine receptors have not been described. The structure of the glycine

receptor is very similar to that of $GABA_A$ and nicotinic acetylcholine receptors (they are all members of the cys-loop family of pentameric ligand-gated ion channels). However, it requires three glycine molecules to open the channel.[40] Glycine also acts as coagonist of glutamate at NMDA receptors.

Acetylcholine also follows the ionotropic-metabotropic scheme with nicotinic and muscarinic receptors, respectively. Nicotinic receptors are ionotropic and are present at the CNS in addition to their well-known role at the neuromuscular junction and in the autonomic nervous system. Structurally, they are related to $GABA_A$ and glycine receptors.[40] There are several types of muscarinic G-protein–coupled receptors. Acetylcholine is released by neurons of brainstem nuclei that send projections to wide areas of the cortex and striatum. It is involved in regulation of wakefulness, attention, learning, and motivation.[41,42]

Neuronology

The brain displays a large variety of neurons of many different shapes and functions. Principal neurons, also referred to as projection neurons, send their projections to distant locations, either at a different brain structure or, for some cortical neurons, to a different area of cortex. The white matter is composed of their axons crossing from their origin to their targets. Projection neurons can be glutamatergic (e.g., layer V pyramidal neurons, hippocampal pyramidal cells) or GABAergic (e.g., cerebellar Purkinje cells, striatal medium spiny neurons). Pyramidal neurons are the major excitatory neurons in the cortex and hippocampus. They are named so due to the triangular shape of their soma. They have an axon leaving the base of the pyramid, a long dendrite arising from the apex to higher layers of the cortex, and a number of basal dendrites arising from the base and branching in the same layer. The populations of pyramidal and principal neurons overlap to a large degree. Interneurons typically synapse within local circuits. Their axons do not cross via the white matter. Interneurons in the cortex are mostly inhibitory. However, excitatory and modulatory interneurons exist in other brain areas. In some areas of the brain such as the hippocampus, interneurons display a dazzling variety that is reflected in the picturesque nomenclature (e.g., chandelier cells, ivy cells, neurogliaform cells). Recent work has begun to unravel the functional implications of their highly diverse anatomy (especially the highly selective projections of their axons).

The Brain: Structure Determines Function

For obvious reasons, the brain is frequently compared to a computer.[43] While the similarities are obvious on a superficial level, the fundamental differences illuminate why brains, unlike computers, are complex (in addition to being complicated) systems.

- Diversity: individual transistors are homogenous while neurons are diverse.
- Adaptation: transistors lack adaptability while neurons and their connections adapt constantly and on different time scales.
- Connectivity: the interconnectivity of transistors is very low, typically in the single digits per gate, while interneuronal convergence and divergence rates range in the (tens of) thousands.
- Integration: strict separations between memory and computation as well as hardware and software are standard features of computer architecture but are interwoven on multiple levels in the brain.
- Last but not least, in contrast to computers, brains wire themselves up during development and continue to "rewire" during their functional life.

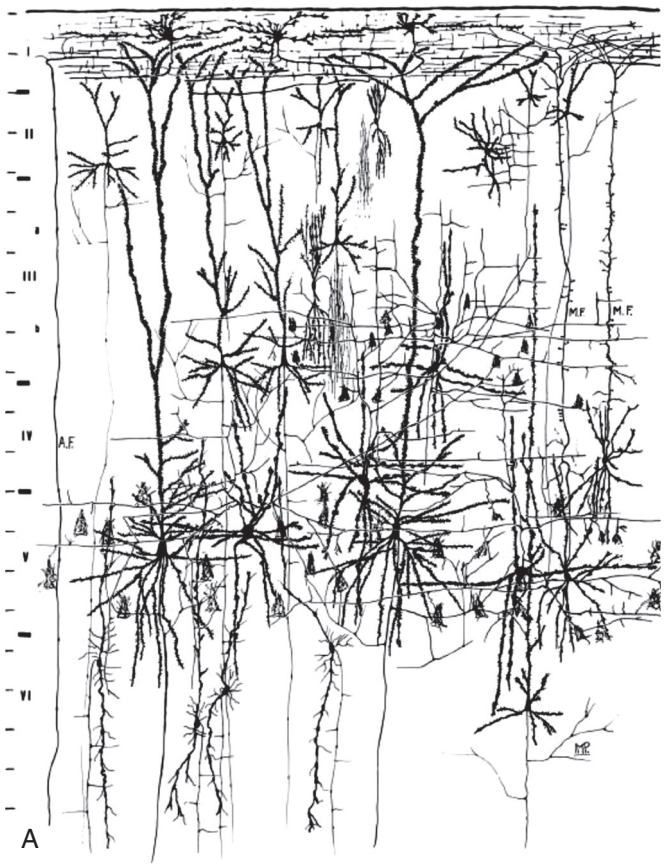
Structure

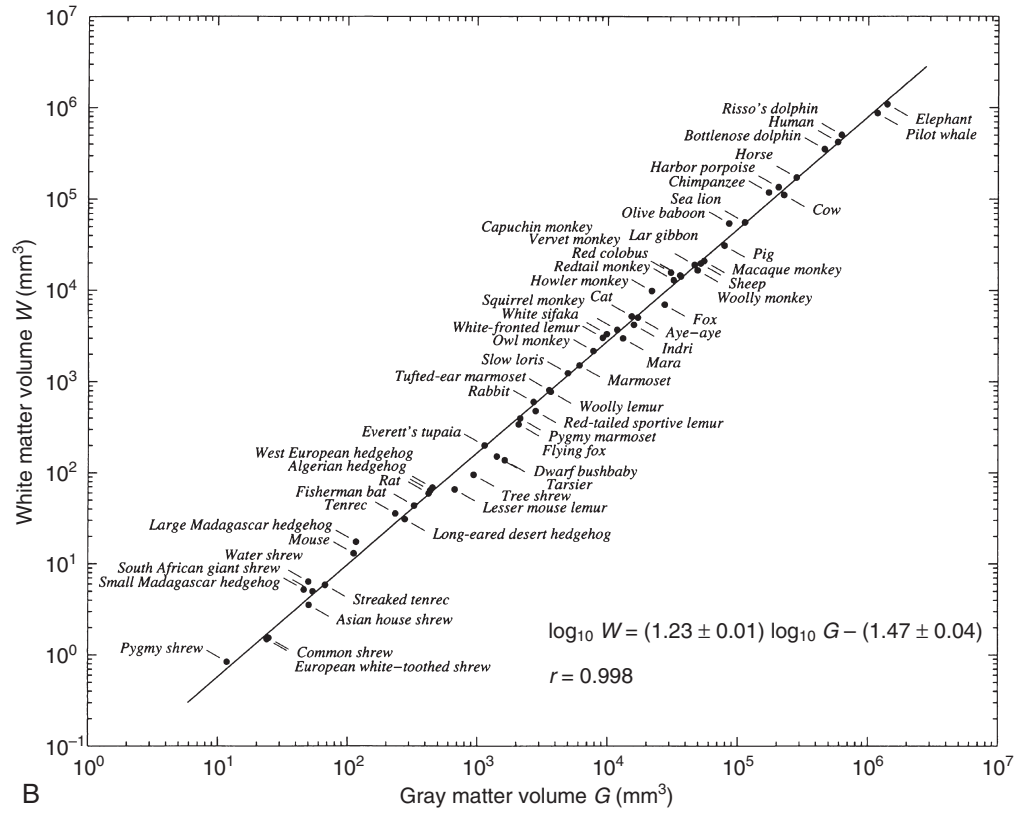
Brains evolved to allow movement. Once in place, sensors to find food and avoid harm as well as adjusting activity to the dark/light cycle became indispensable for evolutionary success. On top of the basic circuitry necessary to allow the aforementioned functions, additional parallel circuits (neuronal loops) were superimposed during evolution and linked "vertically," generating a hierarchical organization among parallel loops. Older loops are located at the bottom while the more recently added rest on top. The more layers (i.e., the more complex the animal), the more complex and controlled the response to an identical stimulus becomes.

Connectivity is the essential challenge as the number of potential connections between the 10^{11} neurons of the human brain is both unimaginable and inefficient. The solution has to accommodate two competing principles: the degree of local clustering (the density of connections) and the degree of separation (synaptic path length) between distant parts of the brain. High clustering is desirable for coordinated computation—as between neurons in a single visual column. Low synaptic path length is also essential for fast integration of information between physically remote areas, a particular feature of the cortex. Both are expensive with respect to axonal length. The proposed solution is known as "small world networks" (originally proposed outside the field of neuroscience) in which, by replacing a small fraction of local connections with random long-distance connections, the average path length can be dramatically shortened with minimal reduction of clustering.[44] Furthermore, the larger the network, the greater the impact of each random link: a smaller fraction of random connections is required in the human brain than in the mouse brain to achieve the same short synaptic path length despite the difference in size. Nevertheless, cortical white matter volume expands more than gray matter volume with increasing brain size (Fig. 8.9).[45]

The *cortex* is a scalable structure that has expanded greatly during mammalian evolution: the neocortical gray matter and the adjacent white matter occupy 10% to 20% of total brain volume in insectivores but 80% in humans. It has been suggested that the smallest functional division of the monkey cerebral cortex (analogous to a single nephron) that can perform the typical "cortical" computational tasks (e.g., a single location in visual space) is about 1 mm^2.[46] Even though the boundaries of a module are difficult to determine, it can be estimated that the total number of cortical modules increases about 10,000-fold from the smallest mammal to the human brain. The human brain, however, is of course not like thousands of mouse brains lumped together.

The cortex can be subdivided into the isocortex, which has a six-layer structure, and the allocortex (heterotypical cortex), which has a variable number of layers. The modular plan of the cortex is identical in all mammals: the isocortex consists of five layers of neurons and a superficial layer of mostly dendrites and axons. Its thickness is only about 1 to 3 mm. The cortex is built up by multiplication of fundamentally identical "modules" that are variably referred to as *columns, barrels,* or *stripes,* and each contains roughly 50,000 to 100,000 neurons. The allocation of space to different functions is a compromise of evolutionary needs, metabolic and wiring costs, and spatial constraints. This is optimized for making predictions and inferences most valuable in the physical niche inhabited by the owner of the brain: echolocation for bats, accurate topography using snout whiskers for many rodents, or pictorial representation of the environment in the primarily visual primates.[38] In the most complex brains, a large proportion of the cortical mantle specializes in processing and generating activity



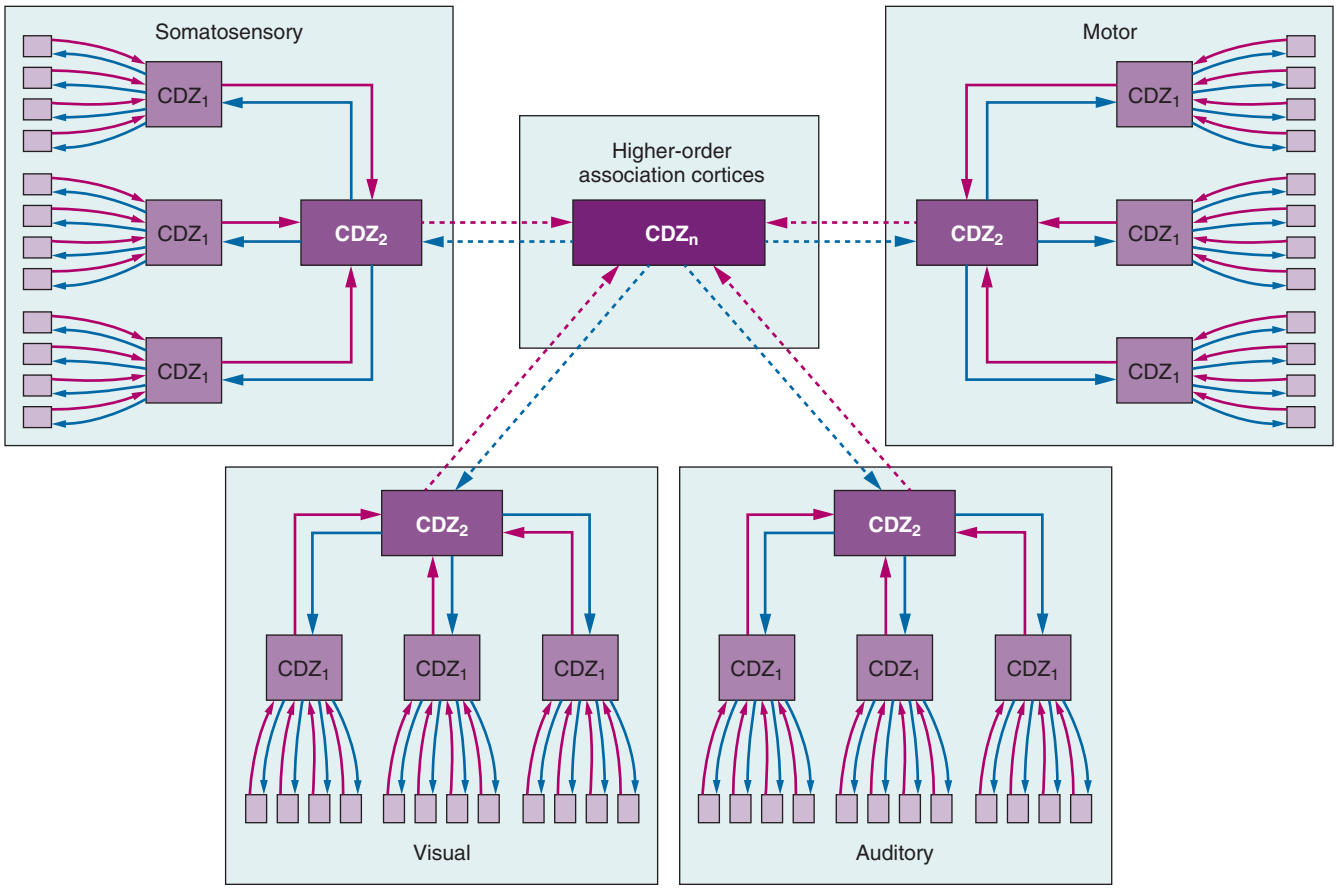


• **Fig. 8.9** The neocortex: layers and the demands of connectivity. A, Camera lucida drawing based on a Golgi preparation of the motor cortex. Note the layered organization with diverse types of neurons dominating in the different horizontal layers. This basic structure is typical for the neocortex. Neurons are tightly packed: a column with a cortical surface area of 1 mm^2 is populated by thousands of neurons. To function, cortical modules must be well connected to their neighbors and to more distal areas. B, With increasing cortical size, more space is required for efficient communication pathways. The cortical white and gray matter volumes are related by a power law that spans five to six orders of magnitude in extant mammals demonstrating the "real estate" cost of maintaining high interconnectivity characteristic of advanced brains. (A, Adapted from Marin-Padilla M. Prenatal and early postnatal ontogenesis of the human motor cortex: a Golgi study. I. The sequential development of the cortical layers. *Brain Res*. 1970;23:167–183; B, Adapted from Zhang K, Sejnowski TJ. A universal scaling law between gray matter and white matter of cerebral cortex. *Proc Natl Acad Sci U S A*. 2000;97:5621–5626.)

only indirectly related to immediate sensory input or direct motor output; these areas are referred to as *associational areas* and are also hierarchically organized. Importantly, connections between functional brain areas are always bidirectional. With ascending hierarchy, an area becomes ever less directly linked to it sensory modality and ever more interconnected with associational areas of other modalities, as proposed in the convergence-divergence-zone framework (Fig. 8.10).[47]

The hippocampal formation includes the hippocampus proper, dentate gyrus, subiculum, and entorhinal cortex and is the main constituent of the allocortex. In addition to being part of the limbic circuit, it is the brain's ultimate memory machine specialized for, on the one hand, forming quickly updatable cognitive maps of the environment and, on the other hand, forming the flexible expression of declarative, episodic memories.[48] As a corollary, it is also essential for projecting one's experience forward in time and space, thereby "predicting the future." While it is not the long-term storage site for memories, the hippocampal formation remains the "librarian of the brain," facilitating the retrieval of stored memory traces.

The need to organize individual experiences within temporal space is shared by both spatial and episodic memories. Coincidentally, the hippocampal formation expresses one of the most prominent synchronized rhythmic oscillations of the mammalian CNS—the theta (θ) rhythm that serves as a timing mechanism (see later text). The distinct anatomy of the allocortex reflects these specialized computational needs. Contrary to the small-world organization of the neocortex, the whole hippocampus forms a single huge neuronal space, analogous to one oversized cortical module creating a giant random connection space that is necessary for combining arbitrary information (analogous to RAM in computers). The circuitry is dominated by the famous trisynaptic excitatory loop from the entorhinal cortex to dentate gyrus granule cells to pyramidal cells of the hippocampal CA3 and on to CA1 pyramidal cells, which then project back to the entorhinal cortex. The distribution of contacts in the dentate gyrus/CA3/CA1 network is reminiscent of a random graph with very low clustering—only about 2% to 5% connection probability—but with equal likelihood of contacting near and remote neurons (unlike the small-world arrangement of the neocortex). The axon of a CA3 neuron in the



• **Fig. 8.10** Hierarchical organization of the brain. Contrary to the Jamesian view, the model proposed by Damasio's laboratory in the "convergence-divergence zone" *(CDZ)* framework accentuates the bidirectionality and cross-modality of intracortical communication on each level of information processing. Neuronal ensembles in early sensorimotor cortices of different modalities (represented by the smallest *rectangles*) send converging forward projections *(red arrows)* to first-order CDZs (CDZ_1s), which, in turn, project back divergently *(blue arrows)* to the early cortical sites. Similar convergent-divergent connectivity patterns interlink CDZ_1s with CDZ_2s and CDZ_2s with CDZ_ns in higher-order association cortices (via several steps not represented here; *dashed arrows*). (Reprinted with permission from Meyer K, Damasio A. Convergence and divergence in a neural architecture for recognition and memory. *Trends Neurosci*. 2009;32:376–382.)

rat is between 150 and 400 mm long establishing 25,000 to 50,000 synapses within the ipsilateral and about half as many within the contralateral hippocampus. This amounts to a total of 40,000 meters of axon collaterals and 5 to 10 billion synaptic contacts in each hemisphere of the walnut-sized rat brain.[49] The mnemonic functions of the hippocampal formation can be conceptualized and allocated to the components of the trisynaptic circuit as follows: dentate gyrus—pattern separation or disambiguation, that is, differentiation between similar-appearing contexts; CA3—pattern completion, that is, reconstruction of a whole representation based on fragmentary information; CA1—mismatch detection, that is, detection of unpredicted novelty in the environment, a task essential for survival.

Sequential, recurrent, and reentrant excitatory connections have the propensity to create runaway excitation. However, through tight control by intricate multifaceted inhibitory networks, excitation can be harnessed into useful computation.[50,51] Because these powerful excitatory loops are notorious for becoming unbalanced, the medial temporal lobe has become the preferred substrate for in vitro studies of epilepsy, and the target of surgical attempts to cure this disease. In the healthy brain, a complex array of inhibitory loops consisting of diverse, specialized interneurons precisely controls the balance and timing of excitation and inhibition.

The *thalamus* is located in the very center between the two hemispheres, minimizing the length of reciprocal wiring and maximizing communication speed, which is optimal to function as a relay of information transmission to the cortex. It is a collection of nuclei that receives and processes all primary sensory input to the neocortex with the exception of olfaction; however, there are many more nuclei than sensory modalities and a large part of the thalamic circuitry is unrelated to early processing of sensory information. Thalamocortical neurons send their axons predominantly to layer 4 of the neocortex but also to layers 5 and 6. In return, thalamic nuclei are the only target outside the cortex of cortical layer 6 pyramidal cells. Thalamocortical neurons support a complement of membrane channels that can convert them into oscillators—nature's delta-frequency clocks. Unlike the cortex, most GABAergic inhibitory cells are localized in the reticular nucleus, forming a shell surrounding the thalamic space. Reticular thalamic neurons are connected not only by classic chemical synapses but also by dendrodendritic synapses and gap junctions.[52,53] The dense reciprocal connectivity with the cortex paired with the special oscillatory propensity of thalamocortical neurons generates the diverse array of thalamocortical oscillations in different frequency bands. These oscillations show dramatic transitions between waking and sleep states and, in fact, might be the driving force behind them. A pivotal role of these thalamocortical oscillations in the mechanisms underlying consciousness and anesthetic action has been suggested.[54]

The *cerebellum* is, from the point of view of circuitry, the antipode of the neocortex in that its distinctive computational arrangement is in parallel loops favoring autonomic (as opposed to interactive) activity. The cerebellum contains as many cells as the rest of the human brain combined—the granule cells alone are more numerous ($\sim 10^{11}$) than all neurons of the neocortex. The cerebellum continuously monitors the activity of skeletal muscles and communicates with brain areas controlling these muscles. These computations, carried out in the anterior and posterior lobes, are largely subconscious and can therefore take place at speeds unattainable via conscious sensory systems. The phylogenetically older flocculonodular lobe attends to posture and eye movement. The cerebellum exists in all vertebrates. Deep cerebellar nuclei (interposed, fastigial, and dentate) act as relays for incoming and outgoing information, controlling ipsilateral limb movements, trunk movements, and motor planning, respectively. There is no equivalent to the corpus callosum and no intermediate or long-range associational paths within the cerebellum.

The granule cells are the only intrinsic excitatory neurons; the other four neuron types (Purkinje, basket, stellate, and Golgi) involved in computation are all inhibitory and target deep cerebellar nuclei, soma of Purkinje cells, and dendrites of Purkinje and granule cells, respectively. The elaborate dendritic arbor of the Purkinje cell is one of the most recognizable features of CNS histology. In diametric difference to the three-dimensional expansion and rich lateral connectivity of cortical pyramidal cell dendrites, Purkinje cells appear two-dimensional with minimal contacts to their neighbors providing for maximal computational autonomy. Purkinje cells receive a direct excitatory input by way of the climbing fibers that originate in the inferior olivary nucleus of the brainstem. This pathway can be seen as a shortcut. The overall organization of the cerebellum results in two parallel feed-forward inhibitory loops that control the output of deep cerebellar nuclei.[55]

The *basal ganglia* are a group of nuclei located below the cerebral cortex. They includes the striatum (caudate and putamen), globus pallidus (external and internal segments), subthalamic nucleus, and substantia nigra (pars compacta and pars reticulata). These nuclei create a feed-forward loop that receives information from most of the cerebral cortex, and after processing returns its output to the frontal and motor cortex via the thalamus. These nuclei are unique in that the major neurotransmitter they use is GABA, which is used in this system not only locally by interneurons but by the projection neurons as well, creating a variety of inhibitory and disinhibitory responses (inhibition of inhibition that leads to excitation). Other important neurotransmitters in this system are the neuromodulator dopamine that is released in the striatum by substantia nigra neurons and acetylcholine released from local interneurons.[56]

The basal ganglia play a major role in the motor system. This was deduced from the clinical manifestations of basal ganglia disorders: loss of dopaminergic cells in the substantia nigra leads to Parkinson disease, a disease manifested by difficulty initiating movement, slowness of movement, and tremor during rest. Loss of striatal neurons in Huntington disease, on the other hand, leads to uncontrollable jerking movements. Basal ganglia also play a role in other tasks such as procedural learning, motivation, and response to reward and addiction.[56]

Spinal Cord

Despite the anatomic separation, the spinal cord and the brain share most of the molecular targets of anesthetic drugs. The spinal cord does, however, have distinct arrangements on the circuit and network levels that can influence its responsiveness to anesthetic drugs. The spinal cord is organized segmentally (31 segments in the human); pairs of spinal nerves exit the cord at each segment. The nerve rootlets forming the sensory (dorsal) and motor (ventral) component combine into a mixed nerve. Each segment of the spinal cord is associated with a pair of dorsal root ganglia located just outside the cord and harboring the cell bodies of sensory neurons.[55]

Behavior is determined by the motor output of the CNS, and the absence of movement is an important component of anesthesia. Motor output, in turn, is the function of three inputs: sensory (reflexive), cognitive (voluntary), and intrinsic (behavioral) state. The relative importance of these inputs varies from species to species and between individuals. All three are affected by anesthesia.

The main determinant of movement in the context of anesthesia is the skeletal muscle system. It is organized hierarchically with the α-motoneurons (their cholinergic axons synapse directly on muscles) on the bottom. The next higher level consists of motor pattern generators (MPGs)—circuits of interneurons that innervate unique sets of motoneuron pools. MPGs are also organized hierarchically. For locomotion, simple MPGs coordinate antagonistic muscle movement across one joint, more complex MPGs coordinate activity of simpler MPGs for all joints of an extremity, and higher-order MPGs coordinate activity between limbs. A still higher level consists of motor pattern initiators that "plan" movements. Each of the three types of inputs (sensory, voluntary, intrinsic) can go directly to each hierarchical level.[57]

Interneurons are the critical components of MPGs; in the spinal cord, interneurons have many convergent and divergent connections allowing them to integrate signals from different sources, including both supraspinal and primary sensory. The most common fast inhibitory transmitters in the spinal cord are glycine and GABA, whereas glutamate dominates excitation (with one notable exception being the cholinergic α-motoneuron to Renshaw-cell synapse). Interneurons are also organized in pools that can be partially activated by an input. The activation by two inputs can produce a greater output than the sum of the individual inputs. This can lead to spatial and/or temporal facilitation depending on timing and origin of the stimuli. However, once the whole pool is activated, further increases in stimulation intensity have no effect. On the output side, interneurons connect to several different targets, including other interneurons and motoneurons. Those interneurons synapsing on motoneurons are called *last-order interneurons*.[57]

For a movement to be considered valid for the purpose of minimum alveolar concentration (MAC) determination of anesthetic potency (see Chapter 3), it has to be "gross and purposeful."[58] This definition, while practical, disregards the "neural content" of a movement. Considering the complexity of circuitry underlying any but the most basic reflexes (which are excluded by the definition of MAC), it is almost surprising that systematically reproducible results are obtained at all. Nevertheless, more in-depth analysis reveals that accurate interpretation of the movement response under anesthesia is more complicated than the deceptively simple all-or-none definition suggests.[59] Moreover, whether explicitly stated or not, an assumption implicit in the definition is that anesthetic suppression of movement involves a "higher agency" and hence that the state of the brain should be predictive of the occurrence of movement in response to noxious stimulation under general anesthesia. However, in the decades since the introduction of the MAC concept into research and clinical practice, it became obvious that, regardless of which analytical techniques were applied to extract information from the electroencephalogram (EEG), attempts to predict movement under anesthesia remained unsuccessful.[60] The reason for this conundrum was discovered in the 1990s—anesthetic-induced immobility (with the exception of some injectable agents) is mediated by action in the spinal cord.[61,62] It is noteworthy that experiments early in the 20th century had already indicated that the spinal cord contains circuits, now collectively referred to as *central pattern generators*, capable of generating coordinated patterns of muscle activity including actual locomotion. Therefore the spinal cord even on the segmental level provides a rich substrate for anesthetic action.

Interestingly, the brain, far from mediating anesthetic-induced immobility, appears to counteract it. After the description of this finding in goats, the site mediating this antagonism has been identified (at least in the rat): the mesencephalic locomotor region facilitates ventral spinal locomotor centers—a potential mediator of the "anti-immobilizing" effect of the brain on anesthetic action in the spinal cord.[63]

Function

The traditional Jamesian view of the brain as an organ whose function is primarily determined by responses to sensory input is undergoing a thorough revision. The brain is a foretelling, not a reflecting, device whose power to predict relies on a variety of synchronous rhythmic activities it constantly generates internally. Simultaneously, the brain is also a highly adapted observational device of the environment, with an ability rooted in flexible neuronal firing patterns within rhythmic oscillatory activity of networks organized in hierarchical structures. Central pattern generators of varying complexity have long been recognized as underlying rhythmic activities from peristalsis of the gut, writhing of lampreys to locomotion—from bipedal to centipede walking, respiration, and so on. An exciting breakthrough in the neurosciences of the past 20 years was the recognition that (complex) rhythmic activity patterns (but without an easily definable generator) also underlie higher cognitive functions. A corollary of this view is that, far from being primarily driven by external inputs, the brain constantly generates a dynamic internal state that is only gradually perturbed by exogenous input. However, these external perturbations are necessary to generate behaviorally useful computations that sculpt the familiar "real-world" experience.

Default Mode Network

The advent of magnetic resonance imaging (MRI) in its manifold permutations, and especially functional MRI (fMRI, see later text), has opened a new dimension of in vivo human brain structure and activity investigation. fMRI has revealed a task-independent constellation of brain areas that are functionally linked in a distributed network during "intrinsic" brain activity—that is, in the absence of goal-directed behavior. This network is reproducible both within and across subjects and has come to be called the default mode network.[64] The default mode network includes discrete brain regions whose metabolic activity (which is indirectly measured by fMRI) predictably covaries during seemingly "idle" (not directed at specific activity) states of the brain. The exact nature of the processes underlying this signal and their quantitative contribution to it have not been fully clarified because the fMRI signal is a composite measure of changes in cerebral oxygenation, blood volume, and blood flow. Recent research indicates that fMRI signal changes in the cerebral cortex are linked closer to synaptic than to spiking activity.[65] Whatever its underlying content, the existence of the default mode network supports the notion of a dynamic intrinsically generated state of the brain.

Brain Rhythms

The brain constantly generates macroscopic electrical signals that vary with physiologic activities and pathologic states. With the exception of high-resolution implantable electrodes, all electrical brain signals reflect the sum of the activity of large neuronal pools. The surface EEG, in particular, is driven by the activity of layer V cortical pyramidal cells. The dendritic trees of these neurons extend toward and then parallel to the surface of the cortex. The synaptic inputs to these dendrites cause alternating potential differences that are the predominant basis of the EEG signal rather than action potentials (somewhat similar to the fMRI blood oxygenation level–dependent [BOLD] signal). The activity in the dendritic trees of approximately 50 to 500,000 pyramidal neurons is reflected in each surface EEG electrode.

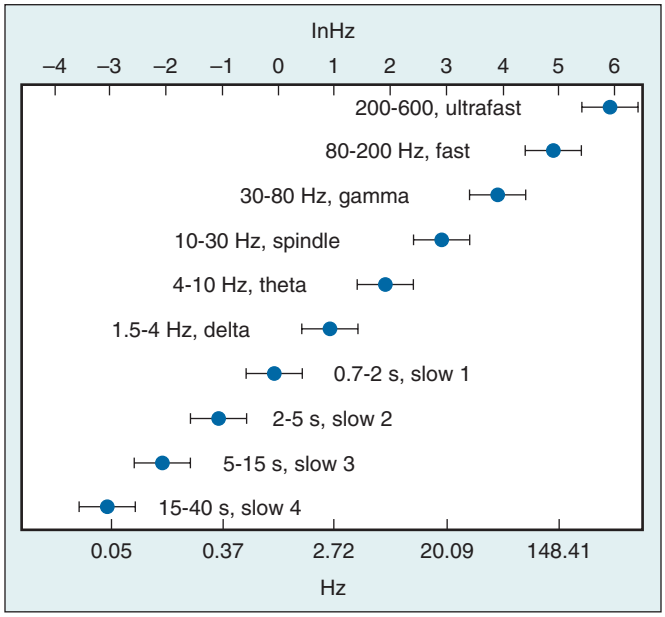
TABLE 8.4 Electroencephalogram Wave Categorization by Frequency

Rhythm	Frequency (Hz)	Typical Occurrence	Comments
Slow	<1	SWS	Cortical up/down states, generated by corticothalamocortical loops
δ	0.5-4	Frontal, SWS, deep sedation	
θ-	4-8	Frontal and midline Hippocampal θ difficult to record in humans unless implanted electrodes used	Hippocampal θ linked to mnemonic function; Surface θ appears with altered states of vigilance, also meditation
α-	8-13	Occipital with eyes closed and mental relaxation	Intermittent, waxing-waning pattern during SWS stage II as sleep spindles
β	13-30	Frontal, sensorimotor systems	Preparation and inhibitory control
γ	30-90	Diffuse, generated by local circuitry	Awake, hypervigilant desynchronized EEG; REM sleep; nested into hippocampal θ
γ	>100		Hippocampal ripples during non-θ states

EEG, Electroencephalography; *REM,* rapid eye movement; *SWS,* slow-wave sleep.
The table shows commonly described rhythms observable in mammals. The frequency range varies somewhat between species. The δ-range has been recently further subdivided into various slow rhythms, particularly during sleep. Slower rhythms have higher power density than faster ones. Rhythms faster than slow γ-spectrum cannot be resolved with surface electrodes. Rhythms of different frequencies occur concurrently: θ-γ nesting, sleep spindles during δ. The same frequency does not indicate the same mechanism and physiology: continuous α and intermittent sleep spindles share frequency but nothing else.

A summary of commonly observed EEG rhythms is presented in Table 8.4. Oscillations in a mammalian brain do not present a continuum even though their period ranges from seconds to milliseconds. As illustrated in Fig. 8.11, discrete oscillation bands form a linear progression on a natural logarithmic scale (a geometric progression on a linear scale), thereby avoiding unwanted harmonic interference that would be a hazard with integer steps between peak frequencies. As a general rule, higher frequency patterns emerge locally, whereas slower frequencies involve larger brain areas.[66]

While the functional significance of these rhythms has long been questioned—they were seen as mere epiphenomena with respect to higher cognitive functions—research in the past 20 years has changed this interpretation dramatically. Synchronized activity in different frequency bands is now thought to allow communication and integration of information between physically separate brain areas, an indispensable functionality for all manifestations of the mind, even though it remains elusive to conclusively demonstrate a causal relationship between specific brain processes and synchronous oscillations.



• **Fig. 8.11** Brain electrical oscillations. The mammalian brain generates oscillations in electroencephalographic recordings ranging from ultraslow to ultrafast without major gaps to allow neuronal networks of different sizes to cooperate in a coordinated manner. Slower frequencies are thought to allow more complex integrations. Higher frequencies enable more precise and spatially limited representations. The analysis of Pentonen and Buzsáki demonstrates the peak frequencies of discrete oscillation bands forming a geometric progression on a linear scale or a linear progression on a natural logarithmic scale. (From Penttonen M, Buzsáki G. Natural logarithmic relationship between brain oscillators. *Thalamus Relat Syst*. 2003;2:145–152.)

Emerging Developments

Probing the Brain

Recently developed methodologies applied to the study of anesthetic effect on the brain on a wide range of scales: from point mutations that enable the study of a single locus in a specific gene to measuring the activity of thousands of neurons using the fMRI BOLD signal.

Gene knock-ins, knockouts, and point mutations refer to genetic engineering techniques. In knock-in animals novel externally supplied genes are expressed, whereas in knockouts native genes are deleted or suppressed. Point mutations involve the expression of genes with targeted modifications in the nucleotide sequence of the DNA leading to changes in the amino acid sequence of the protein product. These models are useful in understanding the effects of specific genes: a loss of behavior following a gene knockout suggests that the gene is involved in that specific behavior. For example: TREK-1 knockout mice display a reduced sensitivity to volatile anesthetics but not to barbiturates, suggesting that TREK channels are a target of volatile anesthetic action.[67]

Nonsynonymous point mutations provide molecular-level resolution of drug-receptor interaction. Replacing the asparagine residue at position 265 in the β3 subunit of the $GABA_A$ receptor to

methionine renders the mutated mice insensitive to etomidate and propofol, strongly suggesting a critical role of β3 subunit–containing $GABA_A$ receptors in the mechanism of action of two important anesthetics.[68,69]

A variety of electrophysiologic tools are available with a resolution ranging from individual neuron activity to averaging of hundreds of neurons and performing simultaneous recording from multiple locations possible,[70] providing high temporal and spatial resolution at the price of being resource-intensive and analytically complex. Intracellular recordings allow unparalleled access to and control of an individual neuron's activity,[71] and cutting-edge advances of this technology make it feasible to record simultaneously from multiple neurons, from dendrites, from certain presynaptic terminals, and also in vivo.[72]

Optogenetics and Pharmacogenetics

Genetic engineering in vivo opened the door to a new generation of experimental interventions. Initially genes encoding fluorescent proteins were used as reporters to verify the expression of knock-in genes.[73] The subsequent insertion of functional genes encoding light-activated channels represented a major advance in our ability to exogenously control neuronal function. Channelrhodopsin,[74,75] a light-activated cation channel originating from algae, followed by halorhodopsin and archaerhodopsin, made it possible to activate and silence neurons using light sources of different wavelengths. Combining these techniques with genetic engineering methods (such as Cre-Lox recombination technology) allows the expression of these genes in specific neurons and hence targeted exogenous control of entire cell populations[76] (Fig. 8.12). Combining these genetically introduced activators/inhibitors of neuronal activity with sensitive fluorescent biosensors for neuronal activity, such as intracellular Ca^{2+} or membrane potential, heralds an era of optophysiology.

Designer receptors exclusively activated by designer drugs (DREADDs) technology uses G-protein-coupled receptors originally mutated from muscarinic receptors. These receptors are insensitive to naturally occurring neurotransmitters, but are activated by the synthetic drug clozapine N-oxide (CNO). When transgenically expressed, administration of CNO to an animal expressing DREADDs will specifically activate only subsets of cells that express. These receptors[77] allowing noninvasive, external control of neurons by administration of CNO. Using receptors that activate different G proteins allows flexibility in the effects that CNO administration will cause.[78]

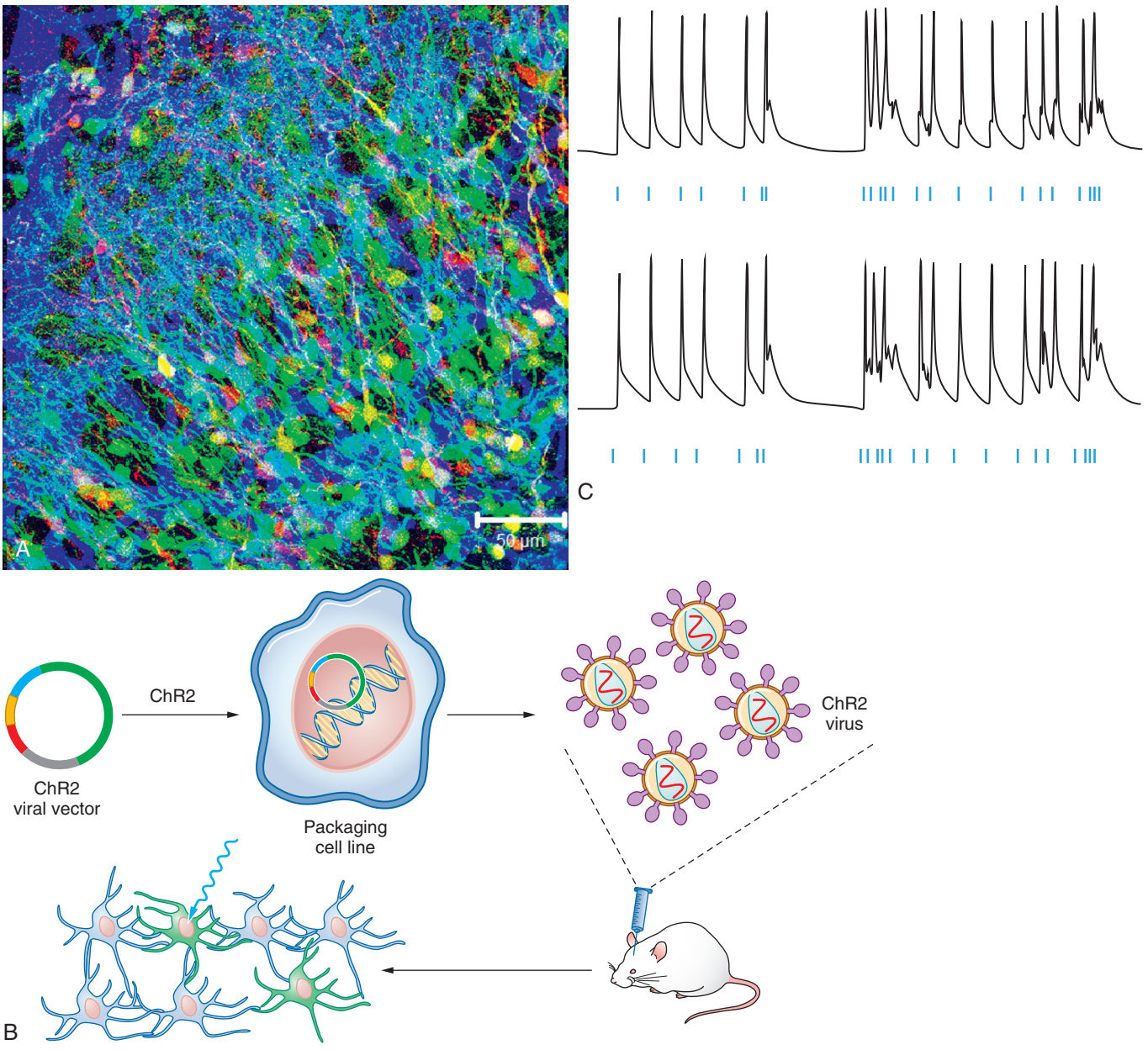
Electroencephalography is a noninvasive technique in which the electrical activity of the brain is measured using scalp electrodes. The measured signal reflects synchronized activity of thousands of neurons over a large area. High-density EEG, with up to 256 contacts, is often used to improve the spatial resolution and source localization. Frequency content analyses and new advanced analysis such as transfer entropy and complexity measures are often used to investigate the signal.[79,80] Electrocorticography and depth electrodes use electrodes implanted directly on the surface of the brain (electrocorticography) and deep inside the brain (depth electrodes), respectively. The result is a signal with no interference from skull and scalp, which allows precise localization of the signal source. At the extreme, depth electrodes can record the activity of a single neuron in an identified brain region. The location of the electrodes is governed by the clinical setting that led to the procedure, limiting wider utilization of these tools.

fMRI creates a BOLD image,[81] reflecting the increased blood flow that follows neuronal activation. As multiple areas are imaged simultaneously, maps of coherent changes in activity are sometimes used to evaluate the "functional connectivity." Conditions that change vascular responsiveness and blood flow (including anesthesia[82]) affect the image obtained. Table 8.5 provides an overview of clinically used techniques.

TABLE 8.5 Clinically Used Techniques to Study the Effects of Anesthetics on the Brain

Technique	EEG	ECoG	Depth Electrodes	fMRI
Signal	Electric potential	Electric potential	Electric potential	Change in magnetic field
Brain activity underlying the signal	Neuronal activity —synaptic potentials	Neuronal activity —synaptic potentials	Neuronal activity— either spikes or synaptic potentials	Blood oxygen level– dependent (BOLD), reflecting the change in metabolic requirements following neuronal activity
Signal generated by	Thousands to millions of neurons	Thousands of neurons	From single neuron up to thousands of neurons	Thousands to millions of neurons
Temporal resolution	Milliseconds	Milliseconds	Submillisecond	Seconds
Spatial resolution	Centimeter range, improved with high density EEG	Better than EEG (few mm)	Very good—specific location or sometimes single neuron	Limited—mm up to a centimeter (depending on the strength of the magnet), higher spatial resolution decreases the temporal resolution
Invasiveness/cost	Noninvasive, cheap	Very invasive and expensive (requires neurosurgery)	Very invasive and expensive (requires neurosurgery)	Noninvasive, expensive
Studied brain regions	Superficial, cortex	Cortex—usually in areas with underlying pathology (epileptic foci)	Depending on the site of implantation cortex and deep nuclei	Whole brain

EEG, Electroencephalography; *ECoG*, electrocorticography; *fMRI*, functional magnetic resonance imaging.



• **Fig. 8.12** New genetic and optic methods. A, An example of green fluorescent protein (GFP) labeling. A confocal image of neural progenitors *(red)* and GFP-positive control neural progenitor cells *(green)* in the rat olfactory bulb. B, In vivo optogenetics: channelrhodopsin (ChR2)-expressing virus vectors are prepared using a packaging cell line. Viruses are injected into the mouse brain to create overexpression in neurons. C, Electrophysiologic readout shows spikes from two cultured neurons receiving the same light pattern (light in *blue*). (A from Tsupykov O. Neural progenitors in the olfactory bulb. https://commons.wikimedia.org/w/index.php?curid=44043828. B and C from Deisseroth K. Optogenetics: 10 years of microbial opsins in neuroscience. *Nature Neurosci.* 2015;18:1213–1225).

Key Points

- Neuroglial cells are nonneuronal support cells that outnumber neurons in the central nervous system. Oligodendrocytes, astrocytes, and microglia form myelin sheaths, create the blood-brain barrier, and attend to immune functions, respectively.
- The recently (re)discovered glymphatic system plays an important but not yet fully characterized role in brain homeostasis.
- The generic neuron receives and integrates information in the dendrites and soma and sends out information via its axon.
- The synapse is the physical contact point between neurons that mediates intercellular communication.
- A generic cortical neuron receives thousands of synaptic inputs on its dendrites that form dendritic arbors to provide the

necessary surface area. The axon is typically ensheathed in myelin, making rapid communication with hundreds to thousands of other, sometimes remote, neurons.

- The typical neuron has a resting membrane potential of −60 to −70 mV (inside relative to outside). The underlying electrochemistry is described in the Nernst and Goldman-Hodgkin-Katz equations. The resting cell membrane is permeable mostly to K^+; hence the resting membrane potential is close to the K^+ equilibrium potential.
- Focal changes in membrane potential, such as depolarization and hyperpolarization from excitatory and inhibitory synaptic inputs, respectively, spread along the membrane, decaying exponentially over time and space.
- Chemical synapses are the mainstay of communication between neurons. Physiologic transmitter release occurs in response to an action potential that depolarizes the presynaptic terminal and allows Ca^{2+} entry through voltage-gated channels to trigger synaptic vesicle fusion and transmitter release.
- Transmitter release occurs in discrete increments (quanta) that reflect the fusion of prepackaged transmitter-containing synaptic vesicles with the membrane of the terminal. Electrical synapses are common in certain brain areas.
- The strength of synaptic connections between neurons undergoes constant, use-dependent modification—both increase and decrease—termed synaptic plasticity.
- L-glutamate and gamma-aminobutyric acid are the major excitatory and inhibitory neurotransmitters, respectively, in the brain.
- The architecture of neuronal circuits and the mode of long-range connectivity differ strikingly between brain areas. The modular "small-world" organization of the neocortex, the random synaptic space of the hippocampus, and the strictly parallel organization of the cerebellum are examples.

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Deisseroth K. Optogenetics: 10 years of microbial opsins in neuroscience. *Nat Neurosci*. 2015;18:1213–1225. Karl Deisseroth—one of the pioneers of optogenetics—reviews the development of this technology and the scientific achievements obtained in the first decade of its use. (Ref. 76)

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Physics: Basic Electronics and Electrical Hazards

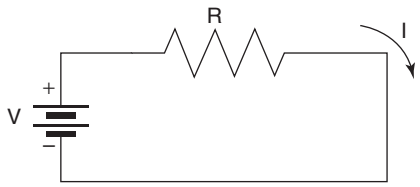
Kai Kuck

OUTLINE

Background

Basic Electrical Concepts
- Simple Circuits
- Electrical Circuit Elements

Electrical Hazards



• **Fig. P3.1** A simple electrical circuit. The voltage V supplied by the battery drives the current I through the resistance R. Ohm's Law stipulates that $V = I \times R$. Even though the electrons making up the current flow from the negative terminal toward the positive one, by convention, the current is drawn in the opposite direction (the flow of positive charges).

Background

Electrical and electronic equipment play an important role in anesthesia and are abundant in the operating room (OR). It is important that the anesthetist understands basic electrical concepts and electrical hazards for patients and OR personnel.

Basic Electrical Concepts

Electrical current, often denoted by the letter I and measured in **amperes** (abbreviated "A"), is the flow of electrical charges between points of different potential electrical energy. **Voltage** is the difference in potential electrical energy, or electromotive force, measured in **volts** (abbreviated "V"). Electrical current flows in a closed circuit, driven by a voltage source, and through a resistance. A **resistance** opposes the flow of electrical current; the unit of resistance is Ohm (Ω). **Ohm's Law** states that in a simple electrical circuit, the voltage V required to drive a current I flowing through a resistance R is proportional to the current and the resistance (Fig. P3.1):

$$V = I \times R.$$

Power is needed for a current to pass through a resistance. Power is dissipated, often as heat or light, and is expressed as **electrical power**, measured in watts (abbreviated "W") and often symbolized by the letter P. It is determined as the product of voltage and current:

$$P = V \times I.$$

Substituting relationships from Ohm's Law and relating them to P,

$$P = V \times I = I \times R \times I = I^2 \times R$$

$$P = V \times I = V \times V/R = V^2/R.$$

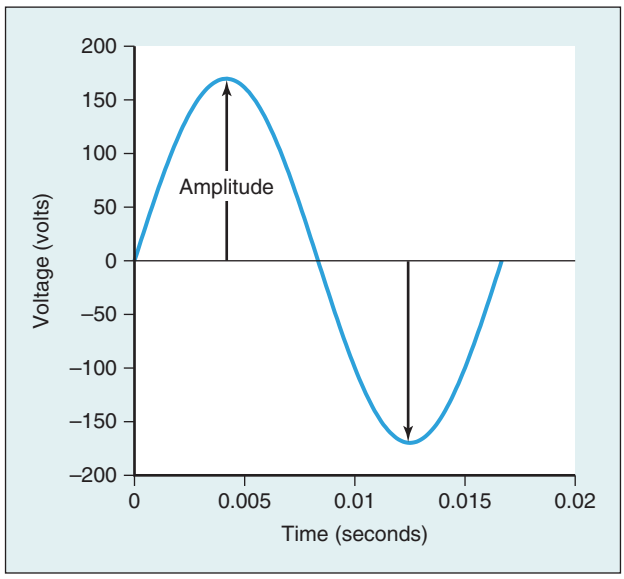
This rearrangement confirms that electrical power (and heat) varies with voltage squared and is inversely proportional to resistance. These relationships govern the possible flow of hazardous electrical current or the generation of dangerous levels of heat from electrical devices in the OR.

Thermodynamically, power is work done per unit time. **Electrical work** is measured in watt-seconds as, for example, the energy discharged by a defibrillator. On a larger scale (e.g., when measuring the energy used in an OR) watt-seconds are scaled to kilowatt-hours, kWh. **Electrical energy** is measured in the same terms but describes a potential to do work.

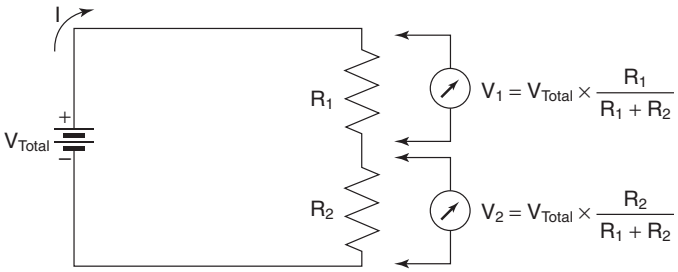
If electrical current flows in only one direction, as depicted in Fig. P3.1, it is referred to as **direct current (DC)**. Current that frequently changes its direction is called **alternating current (AC)**. The line electricity supplied by power companies, for example, changes sinusoidally, and its voltage and current are described by their amplitude and root mean square (RMS) value, which is the average of the squared values of the waveform value (Fig. P3.2). In addition to the current and voltage, AC is also described in terms of its frequency (f), measured in Hertz (Hz), where 1 Hz indicates that the current is changing its direction once per second. These concepts are important because AC and DC forms of electrical current have substantially different characteristics in terms of the propensity for device interference and injury to humans.

Simple Circuits

For two or more resistances placed in series (Fig. P3.3), the voltage that can be measured across each resistor is proportional to its respective resistance. The sum of these voltage drops is the total



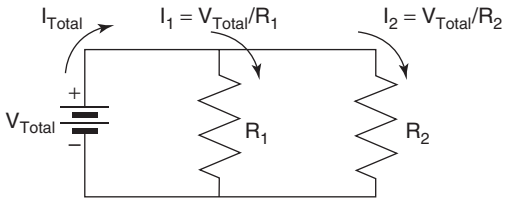
• **Fig. P3.2** One cycle of alternating current (AC) electricity. The electricity supplied by power companies to hospitals is an example of AC electricity. It is sinusoidal in shape. In the United States, it changes direction 60 times per second (60 Hz) and has an amplitude of 169.7 V. The voltage of AC electricity is often described as its RMS value, the average of the squared value of the waveform (e.g., 110 V for electrical power supplied in the United States).



• **Fig. P3.3** A basic circuit with two resistors (R_1 and R_2) in a series with a battery that supplies a voltage V_{Total}. The voltage that can be measured across each resistor R_1 and R_2 is proportional to its respective resistance if the resistors are placed in a series. V_{Total} equals the sum of V_1 and V_2. The same amount of current (I) flows through both resistors.

voltage across the resistors. If a patient completes a circuit and represents the largest resistance in that circuit (e.g., because the other circuit elements are wires that have low resistance), the voltage experienced by the patient will be a large portion of the total supply voltage. The current is the same for both resistances. According to the **Kirchhoff voltage law**, the directional sum of all voltages in the circuit is zero (e.g., in Fig. P3.3: $V_1 + V_2 - V_{Total} = 0$).

For 2 or more resistances placed in parallel (Fig. P3.4), both experience the same voltage, but the current through them is reciprocal to their resistance. This is illustrated by the colloquial, if not completely accurate, expression "the current seeks the path of least resistance." For example, in case of an electrical fault, a high-voltage wire contacting the metal outer case of a device presents a danger to a person touching the case, because the high voltage would drive a current through the body toward ground. Such devices are required to be grounded (i.e., the metal case must have a connection through a ground wire in the device power cable to



• **Fig. P3.4** A basic circuit with two resistors (R_1 and R_2) in parallel to a battery supplying a voltage V_{Total}. When resistors are placed in parallel, the current (I_1 and I_2, respectively) through them is reciprocal to their respective resistance. The smaller the resistance, the more current will flow through it. The total resistance is calculated as the reciprocal of $1/R_1 + 1/R_2$.

the ground). The ground wire provides a very low resistance path to the ground that is in parallel to the person so that the majority of the current will flow through the ground wire instead of the person. The **Kirchhoff current law** states that at any node in a circuit, the sum of the currents flowing into that node equals the sum of the currents flowing out of the node (e.g., in Fig. P3.4, $I_1 + I_2 = I_{Total}$).

Electrical Circuit Elements

In addition to resistances, important basic concepts in electrical circuits are conductance, capacitance, inductance, and impedance. Electrical current requires movement of charged particles. Substances that allow such movement are **conductors**. Metals are typically excellent conductors, as are ions in water. Conductivity is measured in **Siemens** (S) and is the reciprocal of resistance (Ω).

In its simplest form, a **capacitance** consists of 2 parallel metal plates that are a short distance from each other with a nonconducting substance between (e.g., a capacitor). A capacitance can store an electrical charge. The larger the metal plate's surface area and the shorter the distance between the plates, the greater is the electrical charge that can be stored in a capacitance. Capacitances are denoted "C" in electrical circuits and measured in **Farad** (abbreviated as "F").

Direct current (DC) cannot flow through capacitances, with the exception of a brief current while the capacitance changes its charge. Since alternating current (AC) constantly reverses direction, it charges and then discharges the capacitance, resulting in movement of electrons (i.e., current). As a consequence, capacitances appear to AC as complex resistances, called **impedance**. A capacitance's impedance is lower for higher frequencies of AC current.

Capacitances can be used to store electrical energy, which can then be quickly discharged, for example, in defibrillators. Unintentional **capacitive coupling** of AC signals (e.g., from building power lines or from electrocautery) can add noise to sensitive physiologic signals (e.g., electrocardiogram, processed electroencephalogram) and can also lead to hazards from small leakage currents.

Inductance describes the effect exerted by a magnetic field that builds up around an electrical wire with electrical current flowing through it. To the current, this is effectively a resistance. This effect is particularly strong if the electrical current changes rapidly, as with AC, or if the wire is coiled and made of ferromagnetic material, such as iron. Electrical extension cords used for high-wattage appliances should not be coiled up to avoid the cord from heating up and melting its insulation (and perhaps presenting a fire risk).

The term **impedance** is a more general term for resistance and is used to describe the resistive effects to AC current of not only linear resistors but also capacitances and inductances. Impedance

changes with the frequency of AC, but its effect on the amplitude of AC current and voltage follow Ohm's Law. For example, small changes in electrical impedance across the thorax resulting from the changes in lung volume during breathing or in heart volume during the cardiac cycles are exploited for measuring respiratory rate and cardiac output, respectively.

Electrical Hazards

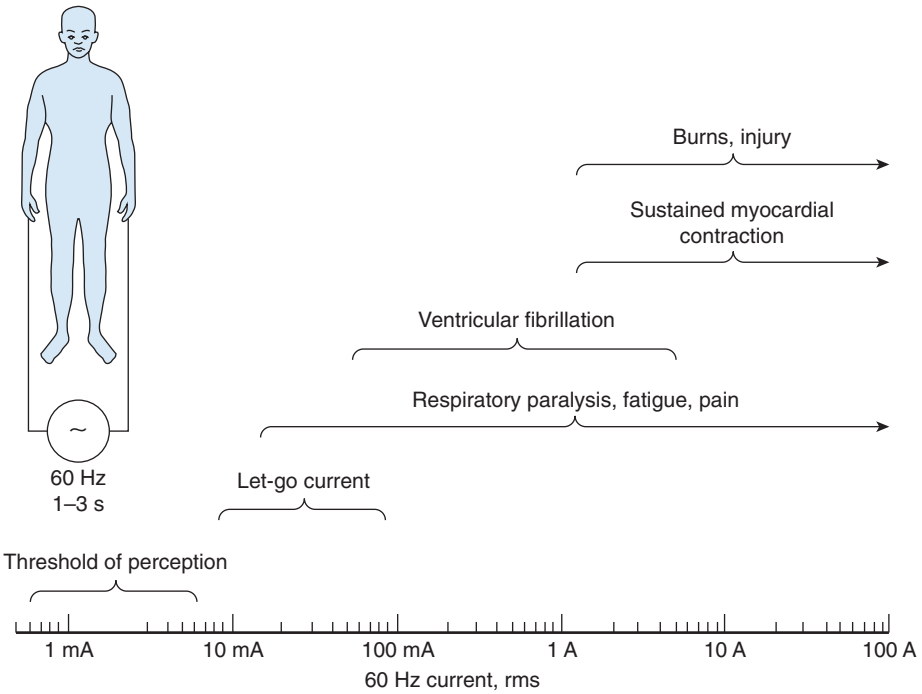
Anesthetized patients in the OR are particularly vulnerable to electrical hazards. They are unclothed, wet, surrounded by and connected to electrical devices, and unable to withdraw from electrical contacts or let it be known that they are experiencing an electrical shock.

If a part of the human body closes (i.e., completes) an electrical circuit, damaging effects of electricity can occur as a result of energy delivered by electricity (e.g., causing burns) or through effects on the electrophysiologic properties of tissue, especially nervous and muscular tissue (including the myocardium, central nervous system, and skeletal muscles). The degree of damage, if any, depends on the duration of the exposure, the voltage, the current, the frequency, and the **current density** (amount of current per area). Neuromuscular tissue is particularly sensitive to stimulation by electricity from standard electrical outlets (e.g., in the United States, from AC current flowing at 60 Hz). Electricity of very high frequencies does not cause stimulation of neuromuscular tissue. Electrocautery units apply ultra-high frequencies to avoid dangerous stimulation of electrically sensitive tissues.

Macroshock occurs when electrical currents flow through the body, usually from a skin entry site to a skin exit site. Damage can occur when current flows through the heart, electrically stimulating the heart. Because the current is distributed over a larger cross-sectional area, substantial current is required for inflicting significant injuries. Fig. P3.5 shows the damaging effects of different currents at 60 Hz AC. Dry skin has a typical resistance of about 50,000 Ω, which would result in a current of 2.4 mA if the macroshock is caused by electricity from an electrical outlet of 120 V, 60 Hz.[1] This is above the perception threshold but would not cause damage in most instances. Wet skin and electrodes reduce skin resistance to about 1000 Ω, resulting in a current of 120 mA under the same conditions, which is well within the range known to cause ventricular fibrillation.

Typically, electricity supplied through standard electrical outlets is grounded (i.e., there is a voltage of 120V between the "hot" wire and ground or earth). If a high-resistance circuit is unintentionally completed between a person and the electrical outlet, current can flow through the lower-resistance ground wire (and also trip the circuit breaker, arresting current flow). For similar reasons, most metal cases of electrical devices are also grounded. In the case of faulty wiring, the majority of the electrical current will flow through the ground wire instead of through an individual touching the metal case. In many macroshock situations, an individual is connected to the hot wire and touches the ground at the same time. This is why it is important to avoid grounding the patient (e.g., by preventing the patient from touching any metal equipment that is grounded).

In isolated electrical systems, the hot wire has no relationship to the ground (i.e., even if a person were to touch the hot wire and the ground at the same time, no current would flow). In some ORs, where it is very difficult to completely avoid having the patient "touch" the ground, using an isolated electrical system provides additional safety. In these systems, electrical power is supplied through an "isolation



• **Fig. P3.5** Effects of electrical macroshock by electrical 60 Hertz (Hz) AC of different current levels (measured in milli-Ampere, mA). Let-go current refers to the current level above which sustained muscle contractions occur, which do not allow the victim to let go of the wire that delivers the electricity. (From Webster JG, ed. *Medical Instrumentation: Application and Design*. 4th ed. Hoboken, NJ: Wiley; 2009.)

transformer" that isolates ("ungrounds") the electrical power from the ground. A line isolation monitor continuously monitors the integrity of this isolation and reports the amount of leakage current that would occur in the case of faults in devices or wiring.

Microshock damage is due to electrical current delivered directly to myocardial tissue (e.g., through a pulmonary artery catheter filled with an electrolyte solution). Due to the larger current density in close proximity to susceptible tissue, much smaller currents are sufficient to cause adverse effects. Ventricular fibrillation can be caused by microshock currents as small as 100 μA. The minimum acceptable microshock current is less than 10 μA. Current flow sufficient for injury can occur in part because the circuits involved in microshock are typically low resistance.

Electrical hazards from electrocautery are often due to the return plate inadequately contacting the patient or being disconnected. During proper operation, the current flows from the tip of the electrocautery instrument through the body to leave the body through the return pad. The return pad is large by design so that the current density (the amount of electrical current per square centimeter) at the exit site is decreased, reducing the heat generated from current flow. If part of the return pad is disconnected from the patient, all the current flows through the smaller area that is touching the patient. The current density in that area is much higher than normal and can result in burns. If the connection to the return pad is disrupted, the current from the electrocautery will flow through alternate routes to leave the body (e.g., through ECG electrodes, through parts of the patient touching metal parts of the OR table, or through catheters that are connected to an electrical device). The high frequencies used in electrocautery (500 kHz to > 1 MHz) increase the chance of alternate current pathways through unintentional capacitive coupling even if the electrosurgery device is electrically isolated from the ground. Electrocautery devices include resistance-sensing mechanisms to detect return plate failures (alternative circuits for current flow are virtually always higher resistance than the resistance in the return pad). Because current flow from electrocautery units can disturb the function of implanted electronic equipment, such as pacemakers, the return pad should be placed to prevent current flow from the operative site through the implanted device to the return pad.

Reference

1. Webster JG, ed. *Medical Instrumentation: Application and Design*. 4th ed. Hoboken, NJ: Wiley; 2009.

9

Central Nervous System Physiology: Cerebrovascular

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CHAPTER OUTLINE

Cerebrovascular Anatomy
- Vascular Architecture
  - *Arteries and Arterioles*
  - *Venous Circulation*
  - *Anterior Circulation*
  - *Posterior Circulation*

Regulation of Cerebral Blood Flow
- Chemical Regulation of Cerebral Blood Flow
  - *Cerebral Metabolic Rate*
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  - *Pao_2*
- Myogenic Regulation (Autoregulation) of Cerebral Blood Flow
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- Vasoactive Agents
  - *Systemic Vasodilators*
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  - *Intravenous Anesthetics*
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  - *Age*

Cerebral Spinal Fluid Dynamics
- Production
- Circulation
- Function
- Blood-Brain Barrier

Pathophysiology of Cerebral Ischemia
- Critical CBF Thresholds
- Energy Failure and Excitotoxicity
- The Nature of Neuronal Death
- Timing of Neuronal Death

This chapter focuses on central nervous system (CNS) physiology and pharmacology relevant to anesthesiology. The molecular and cellular substrates of specific drugs affecting the nervous system are covered in Chapter 8 and in the appropriate chapters in this section.

Cerebrovascular Anatomy

The cerebral arterial vasculature is divided into anterior and posterior circulations that are interconnected through a vascular loop referred to as the *circle of Willis*. This anastomotic loop provides potential for collateral blood flow between the anterior and posterior circulations, as well as between cerebral hemispheres in case of impaired flow in one of the proximal feeding vessels. As one of the most highly perfused organs in the body, the brain is supplied by two paired arteries: the right and left vertebral and the right and left internal carotid arteries. Flow is then distributed throughout the cranium primarily by three paired cerebral arteries arising from the *circle of Willis:* the anterior cerebral, middle cerebral, and posterior cerebral arteries (Figs. 9.1 and 9.2). However, a complete circle of Willis may be present in only about 40% to 50% of the population.[1] A variety of incomplete (containing a noncontinuous, hypoplastic, or absent segment) variants that can compromise collateral flow have been identified. In such cases, secondary sources of collateral flow can occur through distal leptomeningeal connections, or by way of retrograde flow though the ophthalmic artery from the external carotid circulation to the internal carotid artery.

Vascular Architecture

Arteries and Arterioles

The cerebral arteries distributing flow from the circle of Willis continuously branch into smaller arteries and arterioles that course along the surface of the brain. At their distal end, before entering the brain parenchyma, they are known as leptomeningeal vessels. The leptomeningeal vessels are found within the pia-arachnoid membrane and are surrounded by cerebral spinal fluid (CSF). The highly branched pial arterioles form an extensive collateral network on the surface of the brain before giving rise to a relatively unbranched system of penetrating intraparenchymal arterioles.

Venous Circulation

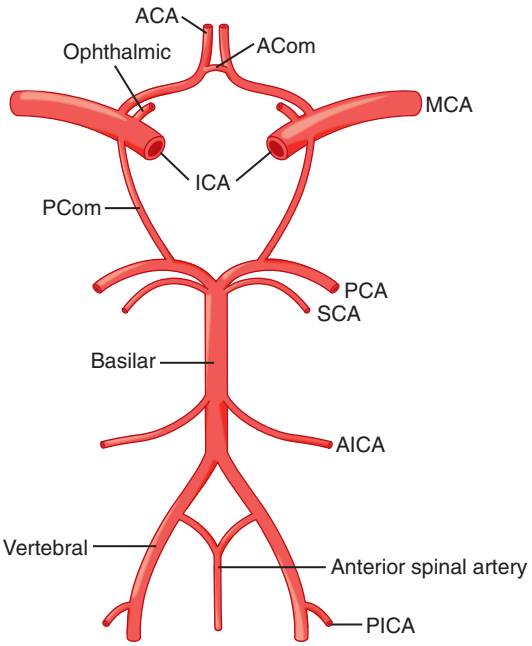
The venous circulation consists of an interconnected system of veins and sinuses. Venous outflow from the cerebral hemispheres

Abstract

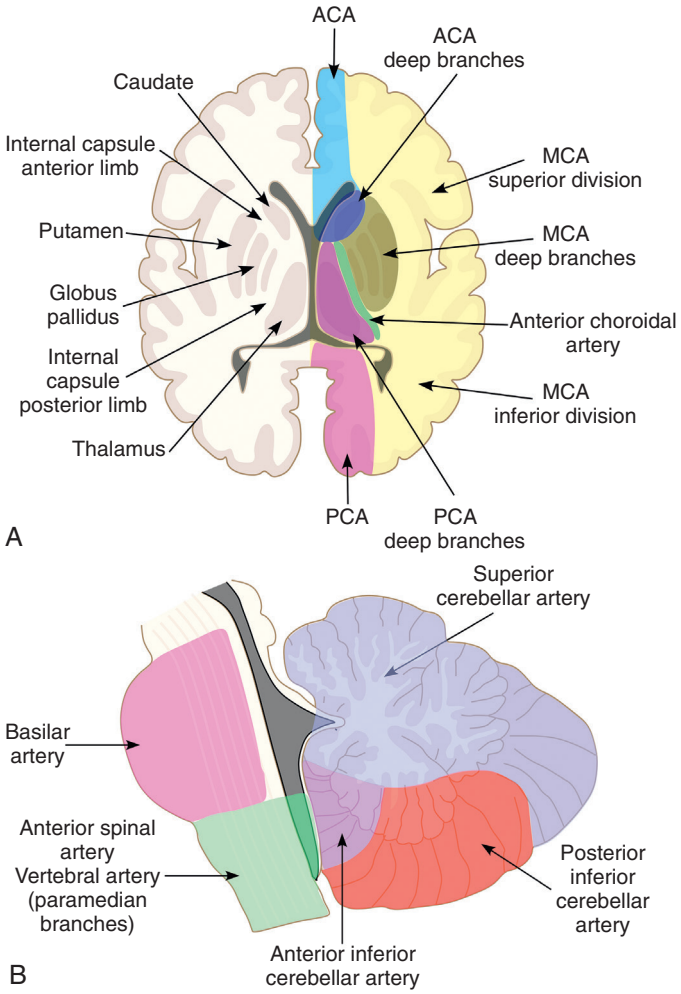
The metabolic demands of the brain are substantial and must be met with a continuous supply of glucose and oxygen. The cerebrovascular anatomy and physiology is designed to distribute and regulate the flow of blood throughout the cranium to continuously meet these demands. Distribution occurs through a well-developed system of conducting vessels that form a proximal anastomotic loop referred to as the circle of Willis. Adjacent vascular territories also communicate via small leptomeningeal collaterals on the surface of the brain. Cerebral blood flow is regulated and influenced by chemical mediators, myogenic regulation, neurogenic input, blood viscosity, patient age, vasoactive agents, anesthetics, and various CNS injury states. Neuronal dysfunction occurs when CBF is reduced below 20 mL/100 g/min. Further reductions below 15 mL/100 g/min result in a progressive decrease in energy supply that will lead to membrane failure and death over the time course of hours to minutes depending of the level of CBF. Energy failure is characterized by cell membrane depolarization, influx of Na^+, and Ca^{2+}, and downstream cell signaling pathways that result in cell damage and death. Ischemia induced cell death may be apoptotic or necrotic depending on various factors involved. More recent understanding of ischemic injury suggests that it is a dynamic process that continues well beyond the initial ischemic event. While anesthetic agents can reduce the vulnerability of the brain to ischemic injury, maintenance of physiologic homeostasis is of greater importance in the prevention or exacerbation of ischemic injury.

Keywords

cerebral blood flow
chemical regulation
flow metabolism coupling
myogenic regulation
neurogenic regulation
volatile anesthetics
intravenous anesthetics



• **Fig. 9.1** *Circle of Willis,* major cranial supply and distributing vessels. Supply vessels include the left and right internal carotid arteries *(ICA)* and the left and right vertebral arteries. The major distributing vessels include the anterior cerebral arteries *(ACA),* middle cerebral arteries *(MCA)*, and posterior cerebral arteries *(PCA).* The anterior and posterior communicating arteries *(ACom, PCom)* complete this vascular loop and allow for collateral blood flow between vascular territories. The major branches of the vertebrobasilar system are also labeled. *AICA,* Anterior inferior cerebellar artery; *PICA,* posterior inferior cerebellar artery; *SCA,* superior cerebellar artery.



• **Fig. 9.2** Anatomic distribution of blood flow from major intracranial vessels in the cerebral hemispheres (A) and infratentorial structures (B). *ACA,* Anterior cerebral artery; *MCA,* middle cerebral artery; *PCA,* posterior cerebral artery; *AICA,* anterior inferior cerebellar artery; *PICA,* posterior inferior cerebellar artery; *SCA,* superior cerebellar artery.

occurs via cortical veins within the pia mater on the surface of the brain as well as deep central veins. Cortical and deep veins may empty into the superior sagittal sinus. Deep veins may also empty into either the inferior sagittal sinus or great vein of Galen. Venous flow is directed toward a confluence of sinuses (torcular herophili) then on toward the central circulation via the transverse sinus, sigmoid sinus, and jugular vein (Fig. 9.3). Cerebellar drainage occurs primarily via the inferior cerebellar veins and occipital sinuses. Extensive collateralization between cortical veins as well as the deep veins and sinuses can augment venous drainage when primary routes are compromised.

Anterior Circulation

The anterior circulation arises from the intracranial extension of the internal carotid arteries. The most prominent branches of the anterior circulation are the anterior cerebral, middle cerebral, and posterior communicating (PCom) arteries. The PCom provides communication with the posterior circulation through direct connection with the posterior cerebral artery (PCA). An absent or hypoplastic PCom potentially compromises collateral flow between the anterior and posterior circulations. Likewise, collateral flow between the left and right anterior circulation can be compromised by a hypoplastic or aplastic anterior communicating (ACom) artery.

Posterior Circulation

The posterior circulation arises from paired vertebral arteries. At their rostral end, the vertebral arteries typically join together on the anterior surface of the brainstem to form the basilar artery. The vertebral and basilar arteries have multiple branches that supply the thalami, brainstem, cerebellum, and spinal cord. The basilar artery branches distally into the left and right PCAs. The branches of the PCA provide blood flow to the thalami, brainstem, choroid plexus, and cerebrum (occipital and portions of parietal and temporal lobes see Fig. 9.2A, B) and provide a point of connection with the anterior circulation. Like the anterior circulation, there are many anatomic variants that may compromise collateral blood flow and predispose to ischemia in various clinical scenarios.

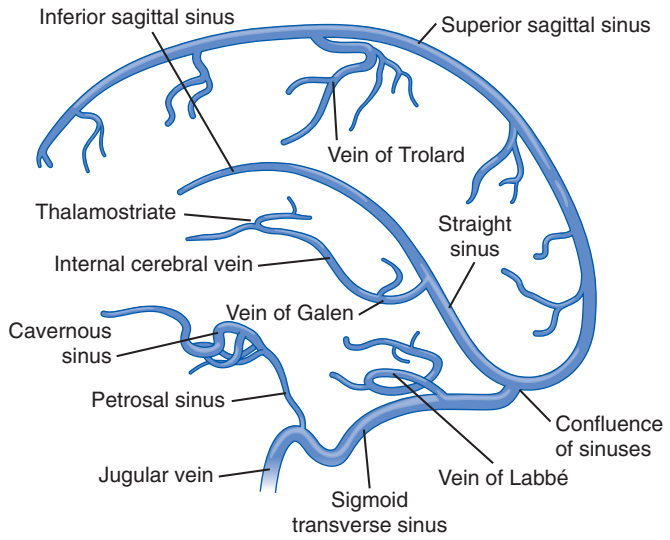
Regulation of Cerebral Blood Flow

The adult brain represents about 2% of total body weight (1350 g), but receives almost 15% of cardiac output. This high blood flow:mass ratio reflects the significant metabolic demand of the brain. At rest, it consumes oxygen at an average rate of 3.5 mL/100 g of brain tissue per minute, or 50 mL/min overall. This represents nearly 20% of total body oxygen utilization. Normal values for cerebral blood flow (CBF), cerebral metabolic rate (CMR), and other physiologic variables are provided in Table 9.1.

TABLE 9.1 Normal Cerebral Physiologic Variables

Cerebral Blood Flow	
Global	45–55 mL/100 g per minute
Cortical (mostly gray matter)	75–80 mL/100 g per minute
Subcortical (mostly white matter)	20 mL/100 g per minute
Cerebral metabolic rate of oxygen ($CMRO_2$)	3–3.5 mL/100 g per minute
Cerebral venous Po_2	32–44 mm Hg
Cerebral venous So_2	55%–70%
Intracranial pressure (supine)	10–15 mm Hg

Po_2, Partial pressure of oxygen; *So_2*, oxygen saturation.
Adapted with permission from Patel P, Drummond JC. CNS physiology and effects of anesthetic drugs. In: Miller RD, Eriksson LI, Fleisher LA, et al., eds. *Miller's Anesthesia.* 7th ed. Philadelphia: Elsevier; 2009.



• **Fig. 9.3** Cerebral venous anatomy. The venous drainage of the brain is composed of an interconnected system of superficial and deep veins and sinuses that return blood to the central circulation. Superficial veins, such as the vein of Trolard (most often found in the postcentral sulcus), typically empty into the superior sagittal sinus. The vein of Labbé is a superficial vein of the temporal convexity with drainage toward the transverse/sigmoid sinus. Many of the deep veins, including the inferior sagittal sinus, internal cerebral vein, and the vein of Galen, are directed toward the confluence of sinuses via the straight sinus. Flow from the confluence is directed through the transverse sinus, sigmoid sinus, and internal jugular vein before reaching the right atrium. The petrosal sinus provides drainage of the cavernous sinus directly into the sigmoid sinus.

Approximately 60% of cerebral energy consumption is used to support electrophysiologic function in the form of maintenance and restoration of ionic gradients as well as the synthesis, transport, and reuptake of neurotransmitters.[2] This *functional* component of cerebral energy consumption is reflected as electrical activity on electroencephalography (EEG) and is reduced by most anesthetic drugs. Maintenance of cellular homeostasis, which includes synthesis and transport of cellular components, accounts for the remainder of oxygen consumption. This *basal* component of neuronal energy consumption related to basic cellular housekeeping function is independent of electrophysiologic activity but is responsive to temperature manipulation.[3]

Glucose is the primary substrate of brain metabolism. In the presence of adequate oxygen delivery, glucose is metabolized to pyruvate by oxidative phosphorylation. In the absence of sufficient oxygen delivery, glucose is anaerobically metabolized, resulting in insufficient adenosine triphosphate (ATP) production and subsequent energy failure. Therefore the brain's considerable metabolic demands must be met by adequate and continuous delivery of both oxygen and glucose. There are elaborate mechanisms in place for regulating CBF to ensure these demands are met. The various mechanisms, which include chemical, myogenic, and neurogenic factors, are listed in Table 9.2.

TABLE 9.2 Factors Influencing Cerebral Blood Flow

Chemical/Metabolic/Humoral
Cerebral metabolic rate[a]
Anesthetics
Temperature
Arousal/seizures
$Paco_2$
Pao_2
Vasoactive drugs
Anesthetics
Vasodilators
Vasopressors
Myogenic
Autoregulation[b]
Rheologic
Blood viscosity
Neurogenic[c]
Extracranial sympathetic and parasympathetic pathways
Intraaxial pathways

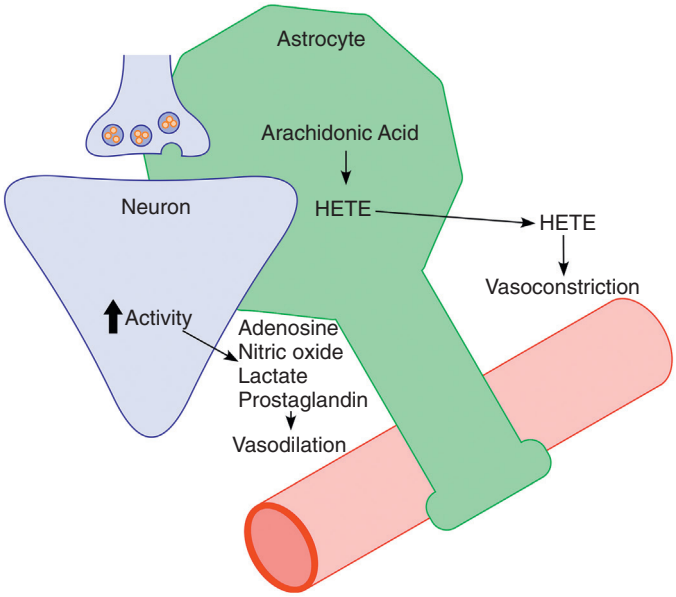
Pao_2, Alveolar oxygen partial pressure; *$Paco_2$*, partial pressure of carbon dioxide in arterial blood.
[a]Cerebal metabolic rate influence assumes intact flow-metabolism coupling.
[b]The autoregulation mechanism is fragile, and in many pathologic states cerebral blood flow is regionally pressure-passive.
[c]The contribution and clinical significance is poorly defined.
Adapted with permission from Patel P, Drummond JC. CNS physiology and effects of anesthetic drugs. In: Miller RD, Eriksson LI, Fleisher LA, et al., eds. *Miller's Anesthesia.* 7th ed. Philadelphia: Elsevier; 2009.

Chemical Regulation of Cerebral Blood Flow

A number of factors, by altering the biochemical milieu of the brain, modulate CBF; these include CMR, partial pressure of carbon dioxide in arterial blood ($PaCO_2$), and alveolar oxygen partial pressure (PaO_2).

Cerebral Metabolic Rate

CMR is directly proportional to neuronal activity.[4] Although the mechanism is not entirely understood, an increase in neuronal activity and CMR is tightly coupled to increased CBF.[3,4] This physiologic process, wherein blood flow and metabolism are matched, is referred to as *flow-metabolism coupling.* The cellular mechanisms involved continue to be investigated, but likely involve



• **Fig. 9.4** Cerebral flow-metabolism coupling. Neuronal activity results in metabolic by-products such as adenosine, lactate, nitric oxide, and prostaglandin that may influence local vessel resistance and cerebral blood flow. More recent data suggest the role of astrocytes both in modulating neuronal synaptic activity and serving and a conduit of this activity to the vascular endothelium. *HETE*, Hydroxyeicosatetraenoic acid.

processes mediated by a combination of neuronal activity and metabolic by-products, glial integration and modulation of neuronal synaptic activity, and vascular factors. Specific by-products of metabolism considered influential in this process include potassium ions (K^+), hydrogen ions (H^+), calcium ions (Ca^{2+}), lactate, adenosine, ATP, and nitric oxide (NO).[5–7] Glia are in direct contact with both neurons and capillaries, and mounting data highlight the role of glia as a likely conduit for coupling neuronal activity with regional blood flow (Fig. 9.4).[8] Cerebral vessels are also densely innervated, and peptidergic neurotransmitters released by nerves also contribute to vascular regulation and flow-metabolism coupling.[9] In the neurosurgical and critical care environments, CMR is influenced by the functional state of the nervous system, anesthetic agents, and temperature.

Functional State

CMR decreases during sleep and increases during sensory stimulation, mental tasks, or arousal of any cause. CMR is markedly increased during epileptic activity and substantially reduced in coma.

Anesthetic Agents

In general, with the exception of ketamine and nitrous oxide (N_2O), anesthetics suppress CMR. Specifically, the component of CMR related to electrophysiologic function is reduced.[10] With several agents, including barbiturates, isoflurane, sevoflurane, desflurane, propofol, and etomidate, increasing plasma concentrations cause progressive suppression of EEG activity with a concomitant reduction in CMR.[10–14] However, increasing the plasma level beyond that required to achieve suppression of the EEG results in no further CMR reduction. The component of CMR related to basic cellular homeostatic activities is unaffected by anesthetics (Fig. 9.5).

Temperature

CMR decreases by 6% to 7% per degree Celsius of temperature reduction, and can cause complete suppression of the EEG at about 18°C to 20°C.[15] In contrast to anesthetic agents, temperature reduction beyond that at which EEG suppression first occurs does produce a further decrease in CMR. This occurs because hypothermia decreases the rate of energy utilization associated with both electrophysiologic function and basal maintenance of cellular integrity (Fig. 9.6). These decreases were once assumed to be proportional, but subsequent data demonstrate preferential suppression of the basal component (with mild hypothermia).[2] The global cerebral metabolic rate of oxygen ($CMRO_2$) at 18°C is less than 10% of normothermic control values, which likely accounts for the brain's tolerance of circulatory arrest for moderate periods at these temperatures.

Hyperthermia leads to substantial increases in CMR and CBF.[16] However, above 42°C a dramatic reduction in $CMRO_2$ occurs, possibly owing to neuronal injury and protein denaturation.

$Paco_2$

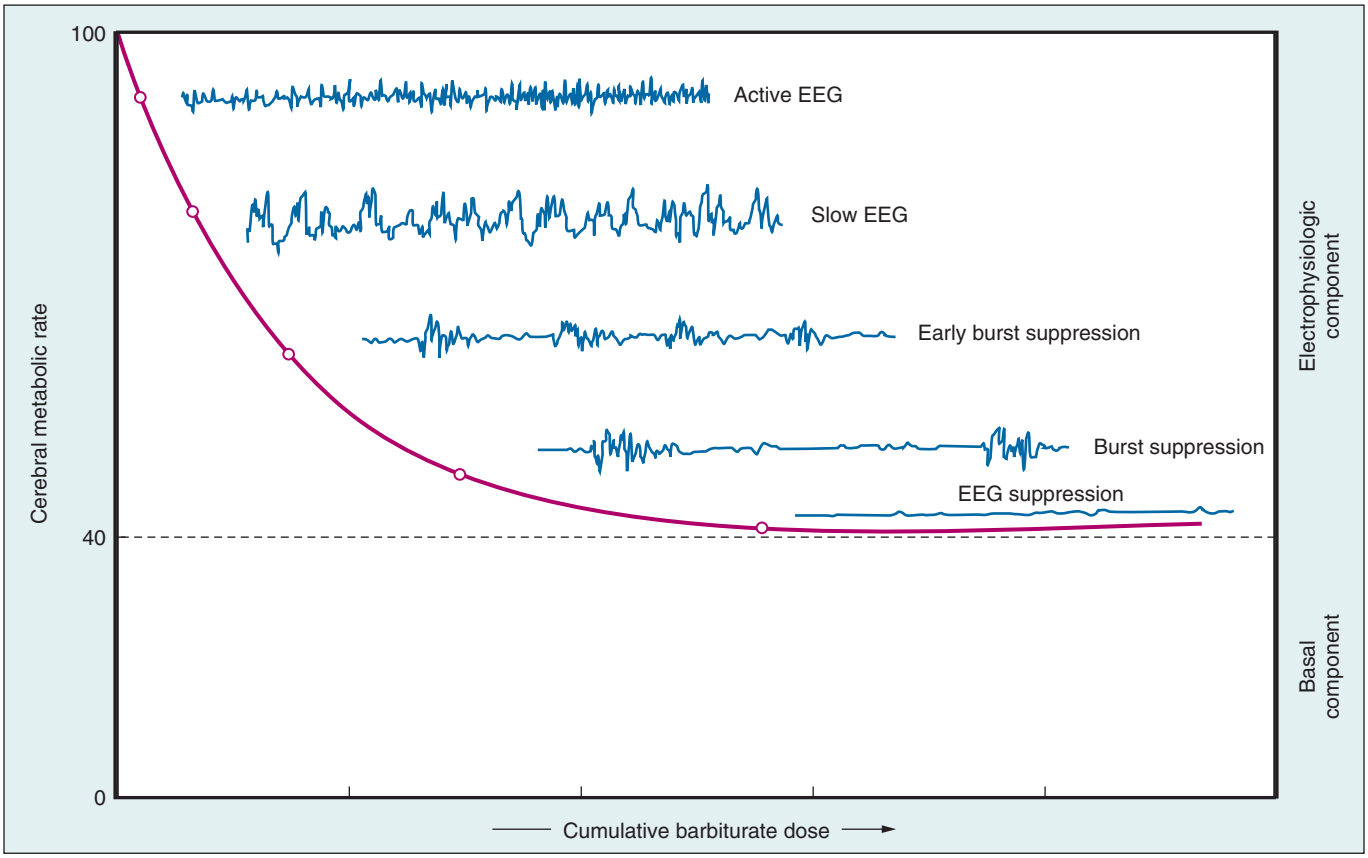
CBF varies directly with $PaCO_2$ (Fig. 9.7). For each change of 1 mm Hg in $PaCO_2$ from normal values, CBF changes 1 to 2 mL/100 g per minute.[17] This response is attenuated outside the physiologic range of about 20 to 80 mm Hg and is sensitive to the baseline CBF. For example, hyperventilation causes a greater reduction in CBF when the resting CBF is high (as can occur with volatile anesthetics), an effect that is attenuated with lower resting CBF. Therefore anesthetic agents have the capacity to alter CO_2 responsiveness of the cerebral circulation by changing basal CBF.

The changes in CBF caused by $PaCO_2$ depend on the pH in the extracellular fluid of the brain.[17,18] Extracellular pH and CBF changes occur rapidly after $PaCO_2$ adjustments because CO_2 (neutral charge) diffuses freely across the cerebrovascular endothelium. In contrast, acute systemic *metabolic* acidosis has little immediate effect on CBF because the blood-brain barrier (BBB) excludes H^+ from the perivascular space.

Although changes to CBF induced by $PaCO_2$ are rapid, they are not sustained. Despite maintenance of increased arterial pH (through hyperventilation), CBF returns toward baseline over 6 to 18 hours because CSF pH gradually normalizes through bicarbonate extrusion (Fig. 9.8).[19,20] Therefore patients with sustained periods of hyperventilation or hypoventilation deserve special consideration. Acute normalization of $PaCO_2$ results in a significant CSF acidosis (after hypocapnia) or alkalosis (after hypercapnia). The former results in increased CBF with a concomitant increase in intracranial pressure (ICP), depending on the prevailing intracranial elastance. The latter conveys the theoretical risk of ischemia.

Pao_2

The effects of PaO_2 on CBF are minimal within the normal physiologic range (PaO_2 from 60 to more than 300 mm Hg). Below a PaO_2 of 60 mm Hg, CBF increases rapidly (see Fig. 9.7). The mechanisms mediating cerebral vasodilation during hypoxemia remain elusive, but they appear to be influenced by metabolites produced by nonvascular cerebral tissue (e.g., NO), hypoxic effects directly influencing cerebral vascular endothelium and smooth muscle (e.g., hypoxia-induced hyperpolarization of smooth muscle), and stimulation of the receptors in the rostral ventrolateral medulla.[21,22] The response to hypoxemia is synergistic with hypercarbia-induced hyperemia.



• **Fig. 9.5** Barbiturate-induced suppression of cerebral metabolism. Administration of various intravenous anesthetic agents results in a dose-related reduction in the electrophysiologic component of cerebral metabolic rate (CMR) and thus cerebral blood flow through flow-metabolism coupling. Anesthetic induced-reductions are maximal at the point of electroencephalographic silence. At this point, additional drug administration does not result in a further reduction of the cerebral metabolic rate of oxygen. The basal component of CMR responsible for maintaining cellular homeostasis is not altered. *EEG,* Electroencephalogram.

Myogenic Regulation (Autoregulation) of Cerebral Blood Flow

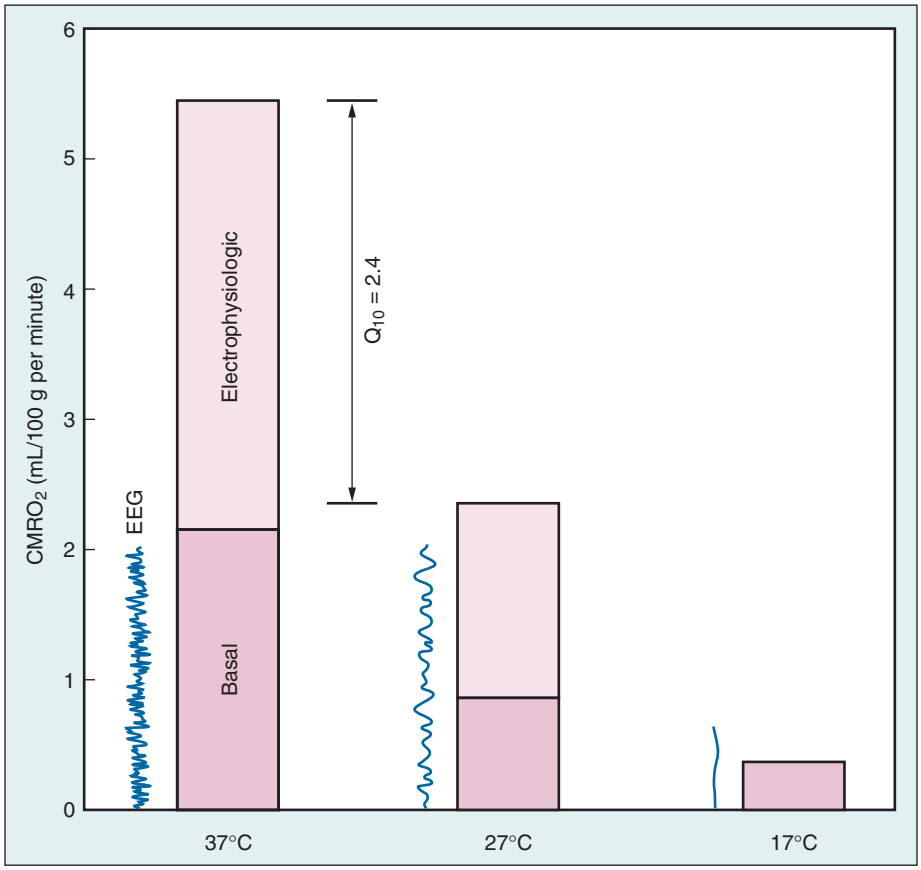
Autoregulation refers to the capacity of the cerebral circulation to alter vascular resistance to maintain a relatively constant CBF over a range of mean arterial pressure (MAP). Although animal models suggest a lower limit of autoregulation (LLA) near a MAP of 50 mm Hg, available human data suggest a higher threshold (with considerable interindividual variation).[23] In normal nonanesthetized humans, the limits of autoregulation occur near MAPs of approximately 70 and 150 mm Hg (see Fig. 9.7).[22] These limits are shifted toward the right in patients with poorly controlled, longstanding hypertension.[24] Note that the units used on the *x*-axis of "autoregulation curves" will influence the correct inflection points of the curve. When the *x*-axis is MAP, the normal average LLA is near 70 mm Hg. Cerebral perfusion pressure (CPP) is the ideal independent variable. However, ICP is usually not measured in normal subjects, so CPP (MAP-ICP) is rarely available. Assuming a normal ICP in a supine subject of 10 to 15 mm Hg, an LLA of 70 mm Hg MAP corresponds to 55 to 60 mm Hg expressed as CPP. Above and below the autoregulatory limits, CBF becomes pressure-dependent (pressure-passive) and varies linearly with CPP. The autoregulatory response to a change in arterial pressure occurs over the course of 1 to 2 minutes, such that a rapid change in arterial pressure will transiently alter CBF even within the normal autoregulatory range.[25]

The mechanisms governing autoregulation are unclear. According to the myogenic hypothesis, changes in CPP directly influence alterations in vascular smooth muscle tone independent of extrinsic factors. However, autonomic innervation of cerebral blood vessels might also contribute to autoregulation (discussed in later text).

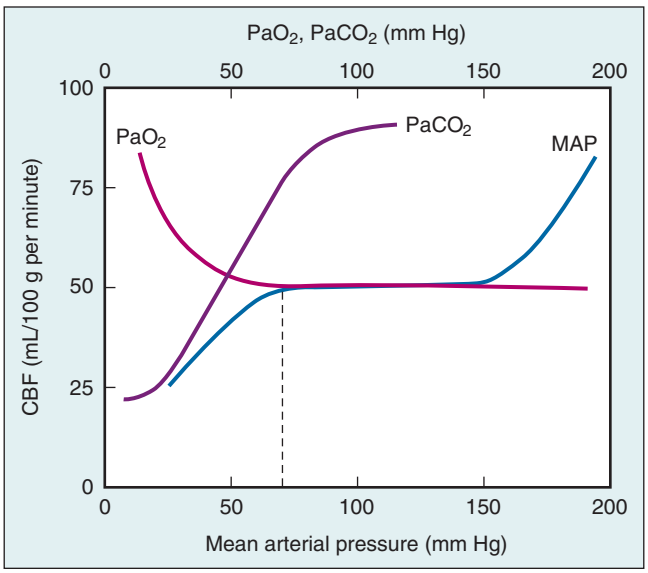
Autoregulatory mechanisms may be absent or significantly attenuated in pathologic conditions, such as cerebral ischemia, traumatic brain injury, and subarachnoid hemorrhage (Fig. 9.9). In addition, volatile anesthetics dose dependently attenuate autoregulation, an effect attributable to direct vasodilation.

Neurogenic Regulation of Cerebral Blood Flow

The cerebral vasculature is extensively innervated; the density of this innervation declines with decreasing vessel size.[26] Innervation includes cholinergic (parasympathetic and nonparasympathetic), adrenergic (sympathetic and nonsympathetic), serotonergic, and vasoactive intestinal polypeptide (VIP)ergic systems of both extraaxial and intraaxial (e.g., fastigial and dorsal raphe nucleus) origin.[27–31] Animal studies have established both extracranial sympathetic and



• **Fig. 9.6** Temperature-induced suppression of cerebral metabolic rate. Hypothermia reduces both components of cerebral metabolic activity: that associated with neuronal electrophysiologic activity and that associated with the maintenance of cellular homeostasis (*Basal*). This is in contrast to anesthetic agents that alter only the electrophysiologic component. The ratio of CMR at 37°C to that at 27°C, the Q_{10} ratio, is shown in the graph. *$CMRO_2$,* Cerebral metabolic rate for oxygen; *EEG,* electroencephalogram. (Adapted from Michenfelder JD. *Anesthesia and the Brain: Clinical, Functional, Metabolic, and Vascular Correlates*. New York: Churchill Livingstone; 1988.)

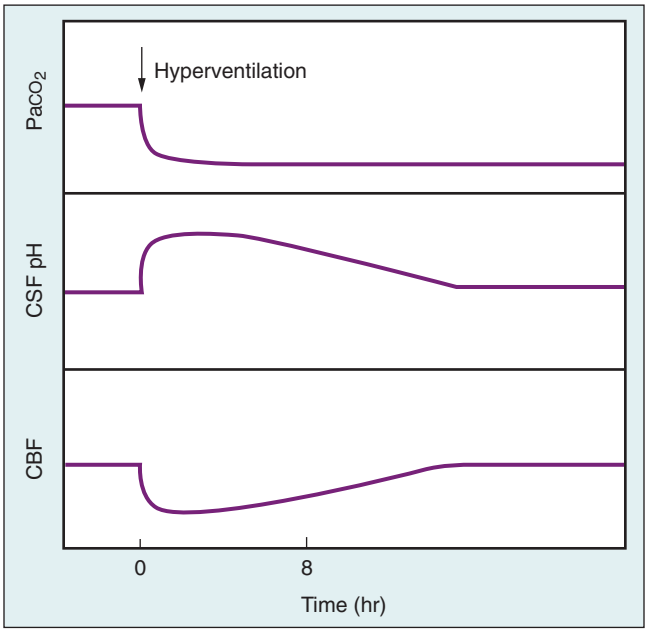


• **Fig. 9.7** Cerebral autoregulation. Changes in cerebral blood flow *(CBF)* caused by independent alterations in $PaCO_2$, PaO_2, and mean arterial pressure *(MAP). PaO_2,* Alveolar oxygen partial pressure; *$PaCO_2$,* partial pressure of carbon dioxide in arterial blood.

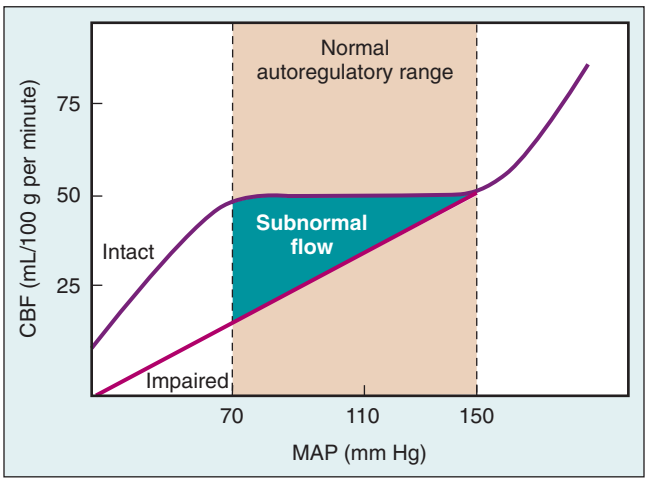
parasympathetic influence on CBF autoregulation.[27,29] In experimental animals, activation of sympathetic fibers shifts the autoregulation curve to the right. Beyond the upper limit of autoregulation, sympathetic activation is considered to be protective in that cerebral vasoconstriction limits the increase in CBF and reduces injury to the BBB. By contrast, in hemorrhagic shock, sympathetic activation may further limit CBF. In humans, stellate ganglion blockade in the setting of subarachnoid hemorrhage increases CBF considerably.[32] The role of parasympathetic innervation on human CBF is less clearly defined. However, in animals, parasympathetic activation can be induced by stimulation along its pathway (sphenopalatine ganglion, facial nerve) and results in increased cerebral blood flow independent of cerebral metabolic activity.[33]

Viscosity Effects on Cerebral Blood Flow

Blood viscosity variation, primarily determined by hematocrit, likely influences CBF modestly in healthy subjects (hematocrit range 33%–45%).[34] The benefit of improved CBF resulting from reduced viscosity appears relevant in the setting of focal cerebral ischemia when vasodilation in response to impaired oxygen delivery is probably already maximal.[35] In this setting, a hematocrit of 30% to 34% probably results in optimal oxygen delivery; however,



• **Fig. 9.8** Effect of sustained hyperventilation on cerebrospinal fluid pH and cerebral blood flow. Sustained hyperventilation results in almost immediate pH change in cerebrospinal fluid *(CSF)*/brain extracellular fluid and cerebral blood flow *(CBF)* as indicated in this nonquantitative graph. These changes are relatively brief, with return toward baseline over a period of 6 to 18 hours. *$PaCO_2$,* partial pressure of carbon dioxide in arterial blood.



• **Fig. 9.9** Impaired cerebral autoregulation. The *"impaired" curve* indicates a pressure-passive condition in which cerebral blood flow *(CBF)* varies directly with cerebral perfusion pressure. This curve is drawn to indicate subnormal CBF *(teal area)* despite mean arterial pressures within the typical autoregulatory range. This has been demonstrated following various central nervous system insults such as traumatic head injury and subarachnoid hemorrhage. The potential for even modest hypotension to cause ischemia is apparent. *MAP,* Mean arterial pressure.

manipulation of viscosity in patients with acute ischemic stroke has not been shown to reduce cerebral injury.[36]

Vasoactive Agents

A number of pharmacologic agents have cerebrovascular effects (Table 9.3). Paramount in the care of patients with intracranial pathology are anesthetic agents (see Chapters 10 and 11) and vasoactive drugs used specifically for hemodynamic manipulation (see Chapters 25 and 26).

TABLE 9.3 Vasoactive Agents and Their Effects on Cerebral Metabolic Rate and Blood Flow

Systemic vasodilators (e.g., nitroglycerine, nitroprusside, nicardipine)	Increase CBF/CBV[a]
Catecholamine agonists/antagonists	
α_1 agonist	Minimal direct effect on CBF
β agonist (BBB intact)	Minimal direct effect on CBF
β agonist (BBB disrupted)	Increase CMR/CBF
β antagonist	Minimal effect; can reduce CMR/CBF
Dopamine	Poorly defined; minimal increase in CBF at low dose?
Intravenous anesthetics	
Ketamine	Increase rCBF; global effects minimal when coadministered with other sedatives/controlled ventilation[b]
Others	Decrease CMR/CBF
Inhaled anesthetics	Decrease CMR/variable effect on CBF[b]

BBB, Blood-brain barrier; *CBF,* cerebral blood flow; *CBV,* cerebral blood volume; *CMR,* cerebral metabolic rate; *rCBF,* regional cerebral blood flow.
[a]Most systemic vasodilators result in cerebral vasodilation and increased CBF/CBV. The notable exception is enalapril, which does not cause cerebral vasodilation.
[b]See text for discussion.

Systemic Vasodilators

The majority of the drugs used to lower systemic blood pressure (including sodium nitroprusside, nitroglycerin, hydralazine, adenosine, and calcium channel blockers) also induce cerebral vasodilation. Agents that vasodilate both the cerebral and systemic circulations can increase cerebral blood volume (CBV), and therefore ICP, by two mechanisms: direct cerebral vascular smooth muscle relaxation and autoregulation-mediated vasodilation. The result is either increased CBF or maintenance of CBF despite inducing systemic hypotension. The hypotensive threshold at which CBF begins to decrease is lower if hypotension is induced with a cerebral vasodilator compared with hypovolemia or a noncerebral vasodilator. In contrast to direct cerebral vasodilators, the angiotensin-converting enzyme inhibitor enalapril has no significant impact on CBF.[37]

Adrenergic Receptor Agonists/Antagonists

Numerous drugs with activity at adrenergic receptors (α_1, α_2, β, and dopamine) have effects on cerebral physiology that depend on basal blood pressure, the systemic blood pressure change induced, the autoregulatory capacity, and the status of the BBB. A given agent can have direct effects on cerebral vascular smooth muscle and/or indirect effects mediated by cerebral autoregulation. When autoregulation is preserved, increases in systemic pressure increase CBF only if arterial pressure is below or above the limits of autoregulation. When the basal pressure is within the normal autoregulation range, systemic pressure changes do not significantly affect CBF as a result of cerebral vasodilation or vasoconstriction. When autoregulation is defective, CBF varies in direct relation to the systemic pressure (see Fig. 9.9).

α_1-Receptor Agonists

A frequent clinical concern is that the administration of agents with α_1-agonist activity (phenylephrine/norepinephrine) will reduce CBF by direct cerebral vasoconstriction. However, when used in the typical clinical dose ranges, neither intraarterial nor intravenous injection of potent α_1 agonists significantly affects CBF.[38,39]

Increases in CBF attributable to norepinephrine can occur when autoregulation is defective or MAP is beyond the limits of autoregulation. Agonists of β-adrenergic receptors (such as norepinephrine and epinephrine) can also increase cerebral metabolism with a coupled increase in CBF. This effect is most apparent in the presence of a defective BBB, which allows greater access to the brain parenchyma.[38,40]

β-Receptor Agonists

In low doses, β-receptor agonists have little direct effect on the cerebral vasculature. In large doses, particularly in the presence of a defective BBB, they can cause an increase in CMR accompanied by an increase in CBF.[38,40] These effects are likely mediated by the β_1 receptor.[41]

β-Receptor Blockers

β-Blockers have been reported to either reduce CBF or have no effect on CBF (and/or CMR). Catecholamine levels at the time of β-blocker administration and/or the status of the BBB may influence these findings. Adverse effects caused by β-blocker administration to patients with intracranial pathology are unlikely, apart from effects related to changes in perfusion pressure.

Dopamine

The effects of dopamine on CBF and CMR have not been defined with certainty. The available data suggest slight vasodilation with minimal change in CMR when administered in low doses with normal cerebral vasculature and the absence of cerebral vasoconstriction in high doses (100 μg/kg per minute).

Intravenous Anesthetics

In general, the intravenous anesthetic agents (propofol, etomidate, lidocaine, barbiturates, benzodiazepines, dexmedetomidine) produce parallel reductions in CMR and CBF.[42] With controlled ventilation and maintenance of normocapnia, it is likely that opioids have relatively little effect on CBF and CMR in the normal, unstimulated nervous system. Many investigations involving ketamine suggest that it increases CBF, particularly within the anterior cingulate cortex possibly through dilation of medium/large-sized intracranial vessels.[43] This has the potential to increase ICP; based on this concern, it has been suggested to avoid ketamine for neurosurgical anesthesia. More recent data, however, suggest that ketamine does not increase ICP when patients are sedated and ventilation is controlled.[44,45] In fact, ICP can be effectively reduced in patients with increased ICP that is refractory to conventional management.[46] Nonetheless, caution should be exercised with ketamine as the sole anesthetic in patients with impaired intracranial elastance.

Intravenous anesthetic-induced changes in CBF largely reflect coupling between CMR reduction and CBF. In addition, variable direct effects on cerebral vascular smooth muscle make minor contributions to the net CBF:CMR ratio. In general, autoregulation and $PaCO_2$ responsiveness are preserved.

Volatile Anesthetics

All volatile anesthetics, in a manner similar to intravenous sedative-hypnotic agents, suppress cerebral metabolism in a dose-related manner.[11] In contrast, they also directly affect vascular smooth muscle, resulting in cerebral vasodilation.[47] The net effect on CBF is a balance between reduction caused by CMR suppression and augmentation caused by direct cerebral vasodilation. Although the data vary depending on the agent (isoflurane vs. desflurane vs. sevoflurane), method/location of measuring CBF, and level to which systemic pressure is maintained, they may be best conceptualized in the following way in patients with preserved cognitive function. At low doses (about 0.5 MAC), the CMR-reducing effect likely predominates over direct vasodilation, resulting in a net decrease in CBF compared with the awake state. In an intermediate range (roughly 0.5–1.0 MAC), direct cerebral vasodilation offsets the effects of CMR suppression, and CBF is relatively unchanged compared with the awake state. In high doses (>1.0 MAC), the direct vasodilatory effect can predominate and CBF can be increased.

Although the available data suggest that volatile anesthetics have minimal effect on intracranial pressure dynamics when intracranial elastance is normal, they have the potential to induce increases in CBV and ICP in certain clinical scenarios (intracranial hypertension significant enough to produce changes in the level of consciousness). Furthermore, when near-maximal reduction of CMR has occurred because of antecedent drug administration or significant electrophysiologic suppression has occurred as the result of CNS pathology, introduction of a volatile agent may have a predominantly vasodilating effect even at relatively low doses.

The cerebrovasculature responsiveness to $PaCO_2$ is well maintained during anesthesia with all volatile anesthetic agents.[17] By contrast, increasing a volatile anesthetic dose progressively impairs autoregulation of CBF. At high doses, autoregulation is abolished and CBF becomes pressure-passive.

Age

Aging, from childhood to late adulthood, is associated with progressive reduction of CBF and $CMRO_2$. This may reflect the progressive reduction in gray matter volume that occurs with increasing age. The precise mechanism underlying this reduction is not clear; loss of neurons, loss of dendritic spines and synapses, and shrinkage of dendritic spines may play a role.[48]

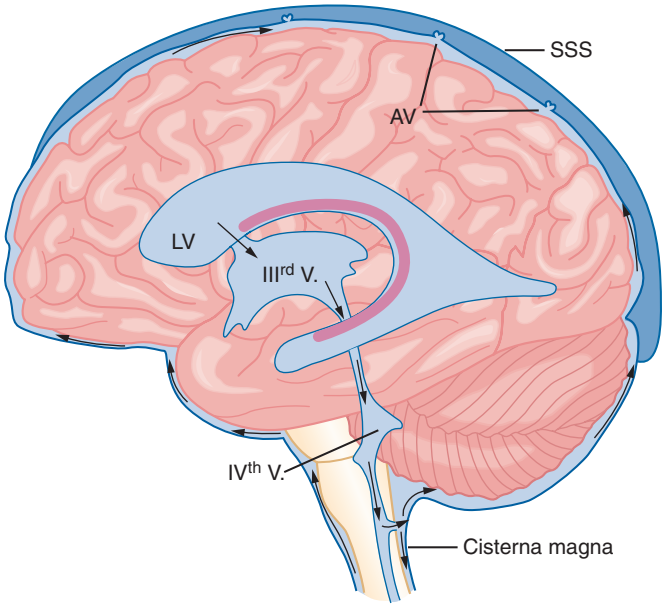
Cerebral Spinal Fluid Dynamics

Production

The volume of CSF in human adults is about 150 mL, half of which resides within the cranium and the other half in the spinal subarachnoid space. Approximately 70% is produced by the choroid plexus, and the remainder is largely a product of transependymal diffusion from the brain interstitium. The choroid plexus refers to a vascular proliferation with ependyma-lined epithelium found in the third and fourth ventricles as well as the medial walls of the lateral ventricles. The vasculature of the choroid plexus is characterized by relatively large-diameter capillaries with thin fenestrated walls. Although various drugs are capable of altering the rate of CSF formation, total CSF volume is typically turned over three to four times per day.

Circulation

CSF circulates primarily from sites of production in the lateral and third ventricles toward the fourth ventricle (by way of the aqueduct of Sylvius). CSF then exits the fourth ventricle, located between the brainstem and cerebellum, by way of paired lateral



• **Fig. 9.10** Cerebrospinal fluid (CSF) flow. The overall flow of CSF is demonstrated by *black arrows*. At the level of the cisterna magna, CSF can flow upward around the cerebral hemispheres or downward into the spinal subarachnoid space. The overall direction of flow in the spinal subarachnoid space is caudal posteriorly and rostral anteriorly. CSF is primarily absorbed into the superior sagittal sinus *(SSS)* through small arachnoid protrusions called arachnoid villi *(AV)*. *LV,* Lateral ventricle; *IIIrd V,* third ventricle; *IVth V,* fourth ventricle.

TABLE 9.4 Normal Composition of Cerebrospinal Fluid and Serum

	CSF	Serum
Osmolarity (mOsm/L)	295	295
Sodium (mEq/L)	138	138
Potassium (mEq/L)	2.8	4.5
Chloride (mEq/L)	119	102
Bicarbonate (mEq/L)	22	24
Phosphorus (mg/dL)	1.6	4.0
Calcium (mEq/L)	2.1	4.8
Magnesium (mEq/L)	2.3	1.7
Iron (g/dL)	1.5	15
Uric acid (mg/dL)	0.25	5.5
CO_2 tension (mm Hg)	47	41
pH	7.33	7.41
O_2 (mm Hg)	43	104
Glucose (mg/dL)	60	90
Lactate:pyruvate ratio	26	17.6
Protein (mg/dL)	35	7000

CSF, Cerebrospinal fluid; *CO_2,* carbon dioxide; *O_2,* oxygen.
Adapted from Fishman RA. *Cerebrospinal Fluid in Disease of the Nervous System.* 2nd ed. Philadelphia: WB Saunders; 1992.

openings (foramina of Luschka) and a single midline opening (foramen of Magendie) into the cisterna magna. From the cisterna magna, CSF fluid flows superiorly in the subarachnoid space bathing the cerebral hemispheres or inferiorly toward the spinal subarachnoid space (Fig. 9.10). Caudal movement of CSF in the spinal subarachnoid space occurs primarily posterior to the spinal cord, whereas the overall direction of flow ventral to the cord is cephalad. Movement for circulation of CSF is provided by hydrostatic pressure created at the sites of production, coordinated ciliary movement on the surface of ependymal cells, and ventricular excursion created by respiratory variation and vascular pulsations. CSF is absorbed primarily through arachnoid villi into the superior sagittal sinus and returned to the central circulation.

Function

The CSF functions both as a supportive and protective cushion for the CNS and as an excretory system for unwanted and potentially harmful substances. The buoyancy afforded the brain by the specific gravity difference between the brain and CSF acts to reduce the effective weight of the brain to approximately 4% of its mass. The CSF may also help provide the brain parenchyma a stable biochemical environment essential for proper function. Differences in composition between plasma and CSF (Table 9.4) are maintained by the BBB.

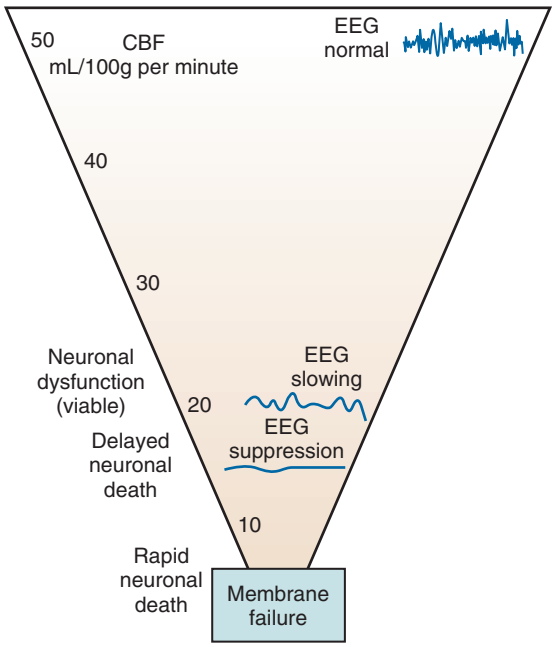
Blood-Brain Barrier

Most capillary beds contain fenestrations between endothelial cells that are approximately 65 Ångstroms in diameter. In the brain, with the exception of the choroid plexus, pituitary, and area postrema, tight junctions reduce this pore size between endothelial cells to approximately 8 Ångstroms. This significantly limits the passage of solutes (including pathogens) from the blood into the brain. As a result, most drugs primarily cross into the brain by transmembrane diffusion, which is influenced by characteristics such as molecular weight, the presence of ionic charge, and lipid solubility.

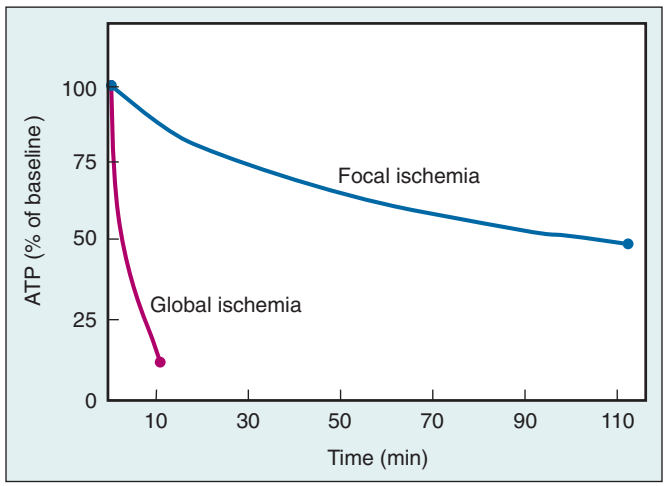
Pathophysiology of Cerebral Ischemia

Critical CBF Thresholds

The brain has a high demand for metabolic substrate (oxygen and glucose) and is quite vulnerable to interruptions in substrate supply. With declining CBF, and therefore oxygen delivery, neuronal function deteriorates in a progressive fashion (Fig. 9.11).[49] Normal CBF typically provides a substantial reserve in energy substrate delivery; it is not until CBF reaches 20 mL/100 g per minute that clinical and EEG evidence of ischemia are evident. Further reduction in CBF to about 15 mL/100 g per minute results in complete cessation of cortical electrical activity as indicated by a suppressed (flat) EEG. When CBF reaches about 6 mL/100 g per minute, indicators of irreversible membrane failure occur (elevated extracellular K^+, loss of the direct cortical response).[50] Between 15 and 6 mL/100 g per minute there is a progressive decrease in energy supply that will result in membrane failure and death over the time course of hours on one end and minutes on the other.[49] Regions of brain within this intermediate flow range, termed the



• **Fig. 9.11** Relationships between cerebral blood flow *(CBF),* electrophysiologic dysfunction, and neuronal viability. As CBF decreases, there is a progressive deterioration in electrophysiologic function, which is perhaps best demonstrated with electroencephalogram *(EEG)* recordings. Evidence of electrophysiologic dysfunction manifests in the form of EEG slowing at CBF less than 20 mL/100 g per minute. CBF in the range of 6 to 15 mL/100 g per minute provides insufficient metabolic substrate delivery to support electrophysiologic function (EEG suppression), but is adequate to prevent immediate membrane failure and neuronal death. When CBF is reduced below 6 mL/100 g per minute, irreversible and rapid membrane failure ensues, resulting in rapid neuronal death.



• **Fig. 9.12** Relative rates of ischemic energy failure. Energy failure rates following experimental global (decapitation) and focal ischemia (middle cerebral artery occlusion). In the presence of residual cerebral blood flow, energy failure is substantially delayed. *ATP,* Adenosine triphosphate.

ischemic penumbra, encompass tissue with potentially reversible dysfunction that will progress to neuronal death if flow is not restored.[51]

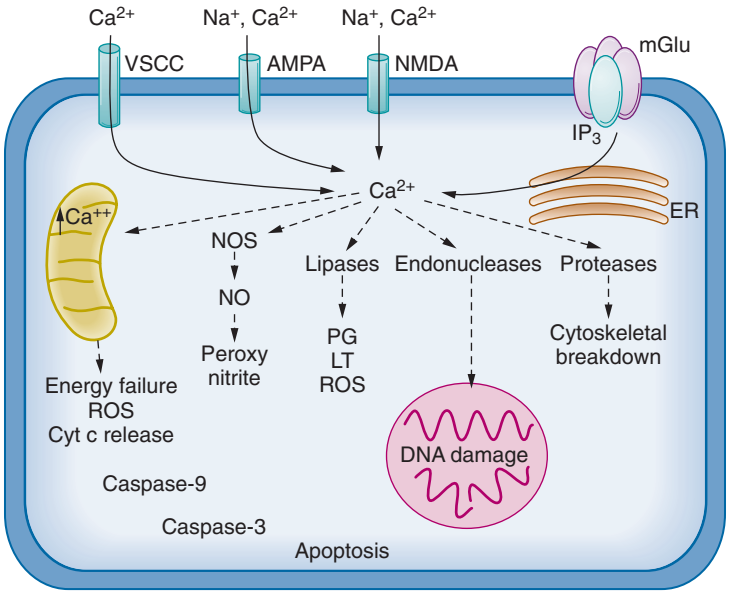
Cerebral ischemia can occur as a result of complete global ischemia (e.g., cardiac arrest) or focal ischemia from reduced flow within a specific vascular territory. With the former, there is cessation of CBF and there is a rapid reduction in cellular ATP.[52] In focal ischemia, the severity of ischemia is greatest within the core of the ischemic territory and irreversible cell injury is rapid. Surrounding the core is a region (the penumbra) in which ischemia is severe enough to abolish electrical activity but in which the neurons are viable for short periods of time. From a clinician's perspective, the difference is that incomplete ischemia can allow adequate ATP generation to stave off the catastrophic irreversible membrane failure that occurs within minutes during normothermic complete global ischemia (Fig. 9.12).[52,53] The duration of the period of potential viability in the penumbra region is dependent on residual CBF through the feeding vessel and the extent of collateral circulation. Importantly, autoregulation is abolished in the penumbra and collateral perfusion is critically dependent on cerebral perfusion pressure. Hypotension can dramatically increase the size of the penumbra, whereas modest increases in perfusion pressure may reduce the extent of injury.

Energy Failure and Excitotoxicity

Central to the pathophysiology of cerebral ischemia is energy failure. ATP supply is critical for maintaining normal membrane ion gradients within neurons. Energy failure therefore is rapidly associated with membrane depolarization and influx of Na^+ and Ca^{2+} with subsequent activation of voltage-gated Ca^{2+} channels, which further increase intracellular $[Ca^{2+}]$.[54] Depolarization also results in release of massive quantities of excitatory neurotransmitters, particularly glutamate, into the synaptic cleft from presynaptic terminals. Postsynaptic activation of glutamate receptors then further augments Na^+ and Ca^{2+} influx.[55] Activation of metabotropic glutamate receptors leads to the release of stored Ca^{2+} from endoplasmic reticulum via inositol 1,4,5-triphosphate receptors. Ionic influx is accompanied by water and results in neuronal swelling, called *cytotoxic* edema.[56] Neuronal injury that is augmented by excessive glutamate receptor activation is referred to as *excitotoxicity*.

Ca^{2+}, a ubiquitous second messenger, is required for the activation of a number of enzyme systems. The rapid, uncontrolled increase in cytosolic Ca^{2+} concentration initiates a number of cellular processes that contribute to neuronal injury (Fig. 9.13). Activated proteases degrade cytoskeletal proteins and other proteins. Lipases hydrolyze cellular lipids and thus cause damage to cellular membranes. Phospholipase A_2 releases fatty acids such as arachidonic acid that are metabolized into prostaglandins and leukotrienes by cyclooxygenase and lipoxygenase with the subsequent generation of superoxide free radicals. The latter, in combination with other free radicals generated in response to mitochondrial injury, can lead to lipid peroxidation and further membrane injury. Prostaglandins and leukotrienes evoke an inflammatory response and are powerful chemotactic agents. Platelet activation within cerebral microvessels, as well as inflammatory cell adhesion and infiltration into damaged areas, aggravates ischemic injury through microvasculature occlusion.

DNA damage is also an important consequence of ischemic neuronal injury (see Fig. 9.13). Generation of free radicals from arachidonic acid metabolism, from injured mitochondria, and from the production of peroxynitrite (from nitric oxide) leads to oxidative DNA injury. Ischemia-induced activation of endonucleases also produces DNA strand breaks. Under normal circumstances, these breaks are repaired through activation of poly-adenosine diphosphate ribose-polymerase (PARP), a DNA



• **Fig. 9.13** Pathophysiology of neuronal energy failure. During ischemia, inadequate neuronal adenosine triphosphate (ATP) supply, required for maintenance of ionic gradients, leads to presynaptic depolarization and the subsequent excessive unregulated release of excitatory neurotransmitters, especially glutamate. Activation of voltage-gated calcium ion *(Ca^{2+})* channels and excessive stimulation of ligand-gated ion channels result in rapid Ca^{2+} entry. Stimulation of metabotropic glutamate receptors *(mGlu)* generates inositol 1,4,5-triphosphate *(IP_3),* which causes endoplasmic reticulum *(ER)* release of Ca^{2+}. Activation of the α-amino-3-hydroxy-5-methyl-4-isoaxolepropionic acid *(AMPA)* receptor-gated subtype of glutamate receptors also permits excessive entry of sodium ions *(Na^+).* Excessive free Ca^{2+} results in activation of numerous enzymes detrimental to the neuron: protease activation causes cytoskeleton breakdown; lipases damage plasma membrane lipids and release prostaglandins *(PG),* leukotrienes *(LT),* and reactive oxygen species *(ROS);* activation of nitric oxide synthase *(NOS)* leads to formation of nitric oxide *(NO)* and the generation of peroxynitrite, a highly reactive free radical; and activated endonucleases cleave DNA. Mitochondrial injury leads to energy failure, *ROS,* and mitochondrial release of cytochrome c *(Cyt c);* the latter is one of the means by which neuronal apoptosis is initiated. *LT,* Leukotrienes; *NMDA,* N-methyl-D-aspartate; *NOS,* nitric oxide synthetase; *PG,* prostaglandins; *VGCC,* voltage-gated Ca^{2+} channels.

repair enzyme. However, with excessive DNA injury, depletion of the PARP substrate nicotinamide adenine dinucleotide (NAD) limits the capacity for DNA repair. NAD is an important coenzyme in energy metabolism and its depletion further exacerbates energy failure.

Lactate formation is an additional component to the pathophysiologic process of energy failure. Lactic acid is formed as a result of anaerobic glycolysis that takes place after oxygen supply failure. The associated pH decline contributes to the deterioration of the intracellular environment. Increased preischemic serum glucose can exacerbate this process by providing additional substrate for anaerobic glycolysis and, indeed, it has been associated with increased ischemic neurologic injury.[57]

Collectively, the simultaneous and unregulated activation of a number of cellular pathways overwhelms reparative and restorative processes and ultimately leads to neuronal death.

The Nature of Neuronal Death

Neuronal death that occurs as a result of ischemia can be either necrotic or apoptotic depending on the ischemic insult duration or intensity as well as the cell type and its life cycle stage. The excitotoxic injury described previously characteristically leads to necrosis, which is associated with local inflammatory cell infiltration and considerable "collateral damage." Neuronal necrosis mediated by excitotoxic injury is characterized by rapid cellular swelling, condensation and pyknosis of the nucleus, and swelling of the mitochondria and endoplasmic reticulum.

Neuronal apoptosis, a form of programmed cell death or cellular suicide, has also been demonstrated in a variety of cerebral ischemia models. Apoptosis is characterized by chromatin condensation, involution of the cell membrane, swelling of mitochondria, and cellular shrinkage. In the later stages of apoptosis, neurons fragment into apoptotic bodies that are then cleared from the brain. The absence of a substantial inflammatory response to apoptotic death limits injury to surrounding neurons that have survived the initial insult. Neuronal injury in response to ischemia cannot easily be divided into necrosis or apoptosis, but encompasses a spectrum in which some neurons undergo necrosis or apoptosis while others undergo cell death that has features of both necrosis and apoptosis.

Timing of Neuronal Death

Initial concepts of ischemia-induced neuronal death were restricted to the time of ischemia and early reperfusion period. More recent data indicate that postischemic neuronal injury is a dynamic process extending for a long period after ischemic insult.[58–60] Delayed

neuronal death, which was first demonstrated in models of global cerebral ischemia, also occurs following focal ischemia.[60] The extent of delayed neuronal death depends on the severity of the ischemic insult. With severe ischemia, most neurons undergo rapid death. With more moderate insults, neurons that survive the initial insult may undergo delayed death, which contributes to the gradual expansion of cerebral infarction after focal ischemia. Evidence of cerebral inflammation, which theoretically can contribute to further injury, has been demonstrated even 6 to 8 months after the primary ischemic event.

Key Points

- The brain has a high metabolic rate and is dependent on elaborate mechanisms that ensure continuous and adequate metabolic substrate delivery.
- CBF is autoregulated such that flow is normally constant over a range of mean arterial pressures (70-150 mm Hg). CBF is pressure-passive below or above the limits of autoregulation.
- Autoregulation can be impaired or absent following insults such as traumatic brain injury or subarachnoid hemorrhage. In such cases, CBF is pressure-passive and may be reduced despite a normal mean arterial pressure.
- CBF is under chemical regulation: it varies directly with arterial carbon dioxide tension ($PaCO_2$) in the range of 20 to 80 mm Hg and inversely with arterial partial pressure of oxygen (PaO_2) below 60 mm Hg.
- CBF is tightly coupled to local cerebral metabolism. When cerebral activity in a particular brain region increases, a corresponding increase in blood flow to that region occurs. Conversely, reduced activity/metabolism leads to reduced blood flow.
- About 60% of brain energy consumption supports electrophysiologic functions; the remainder supports cellular homeostasis.
- Intravenous anesthetics such as barbiturates, propofol, and etomidate can decrease the electrophysiologic component CMR up to 60% and thus substantially reduce CBF through flow-metabolism coupling. The effect is maximal at the point of electroencephalographic silence.
- Hypothermia reduces both the functional and basal components of CMR; CMR decreases about 6% to 7% per degree Celsius temperature reduction.
- The net effect of volatile anesthetics on CBF is a reflection of the relative contribution of two opposing effects: CMR reduction versus direct cerebral vasodilation. At subanesthetic doses, reduced metabolic rate offsets direct cerebral vasodilation and CBF is not significantly altered. Above minimum alveolar concentration, direct cerebral vasodilation may exceed CMR reduction and thus increase CBF/CBV.
- Systemic vasodilators (nitroglycerin, nitroprusside, hydralazine, calcium channel blockers) cause cerebral vasodilation and, depending on the MAP, can increase CBF.
- Vasopressors such as phenylephrine, norepinephrine, ephedrine, and dopamine do not have significant direct cerebrovascular effects.
- Focal cerebral ischemia is better tolerated than global ischemia because collateral blood flow may be sufficient to stave off neuronal injury until CBF can be restored.

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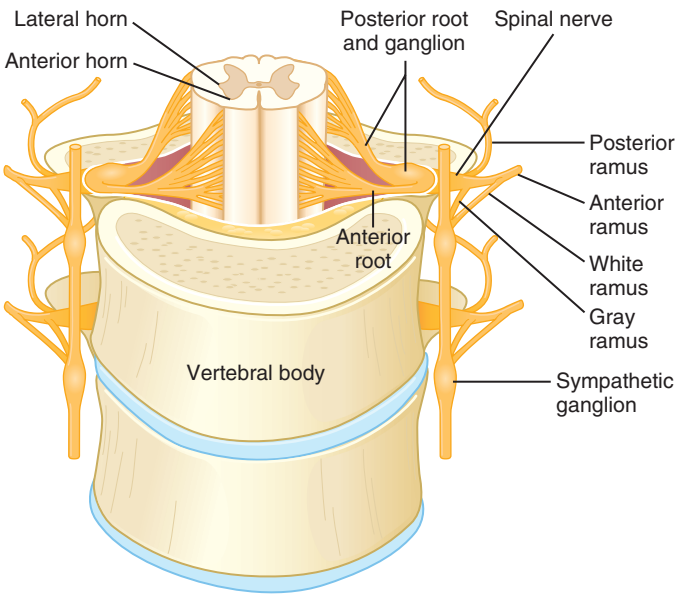
Anatomy and Imaging: The Nervous System

Nicholas Pierson, Sarah E. Stilwill, Elizabeth Ryals, and Jeffrey D. Swenson

This section outlines important anatomic structures and imaging techniques for the nervous system. Imaging techniques such as magnetic resonance imaging (MRI), computed tomography (CT), and plain radiography are presented to demonstrate their clinical roles.

Technical and clinical considerations exist for imaging in the acute care setting. For example, there are unique advantages and limitations for methods such as MRI and CT. Likewise, the decision to use contrast versus noncontrast techniques may vary based on the clinical setting. The choice of which imaging technology to use depends not only on the pathology in question but also on patient age, the speed at which the clinical question needs to be answered, the patient's clinical stability, the presence of surgical hardware, and any underlying comorbidities.

The effective use of all imaging techniques presupposes a knowledge of anatomy. For the nervous system, a fundamental structure is the spinal nerve and its relation to the spinal cord and surrounding vertebral structures (Fig. AI1.1). **Anterior and posterior spinal roots** carry motor and sensory fibers, respectively. These roots combine to form the **spinal nerve**. The **posterior root** is unique in that it includes a **ganglion** made up of the cell bodies of sensory nerves. By contrast, motor cell bodies are in the **anterior horn** of the spinal cord. Each **spinal nerve** gives rise to an **anterior** and **posterior ramus,** which carry both motor and sensory fibers.

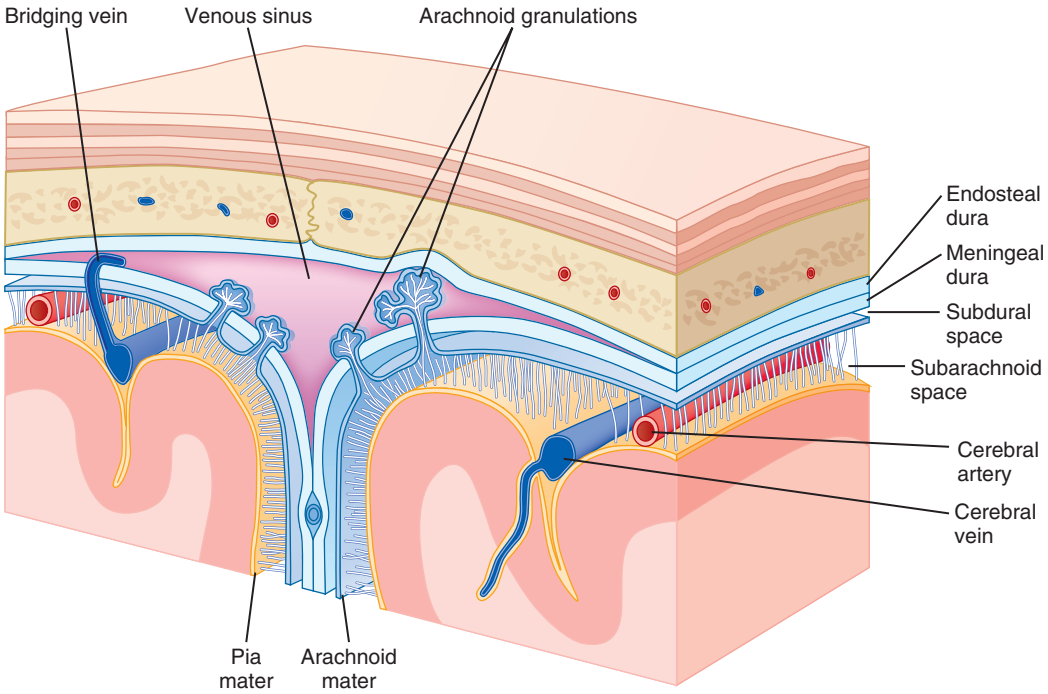


• **Fig. AI1.1** Anatomy of the spinal nerves, spinal cord, and vertebral body in an idealized anatomic drawing.

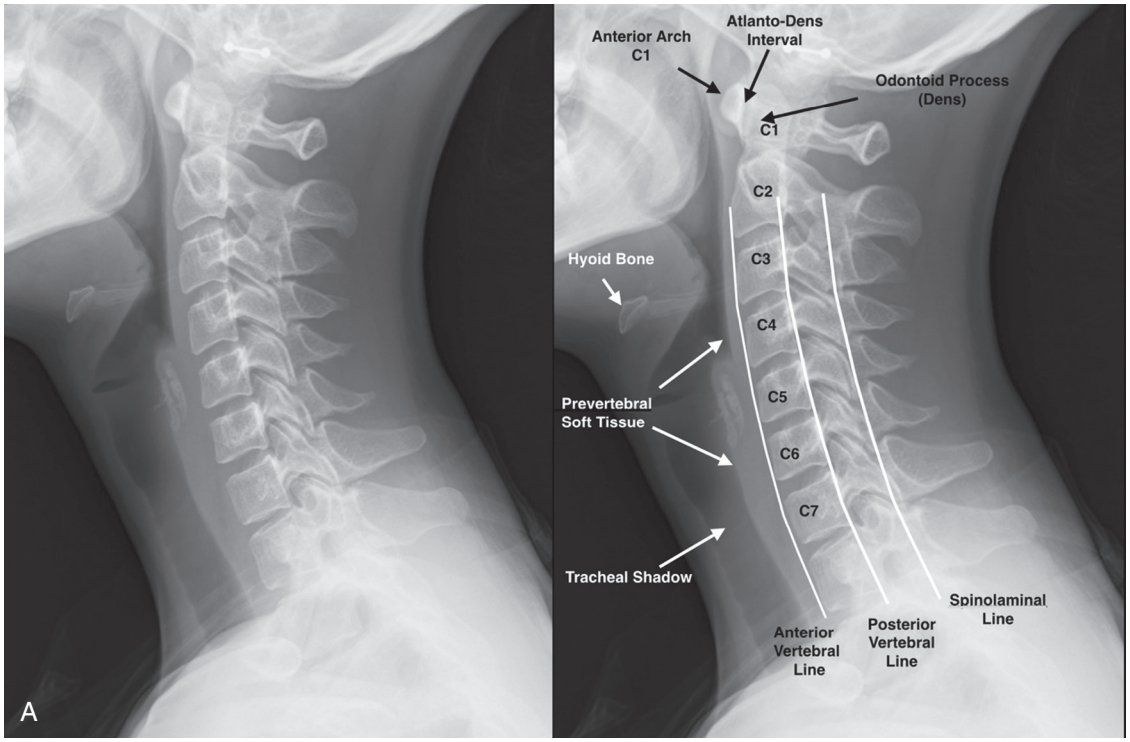
White rami connect presynaptic sympathetic fibers (whose cell bodies are in the **lateral horn** of the spinal cord) from the **anterior rami** to the **sympathetic ganglia**. **White rami** are present between the first thoracic and second lumbar levels of the spinal cord**. Gray rami** carry postganglionic sympathetic fibers at all levels from the **sympathetic ganglia** to **spinal nerves**.

Important vascular and meningeal structures of the head are displayed in a coronal plane (Fig. AI1.2). The **venous sinus** is formed by a separation of the **dura** into **endosteal** and **meningeal** layers. **Venous sinuses** are unique in that they have no valves or muscular tissue. They receive cerebral spinal fluid (CSF) through **arachnoid granulations**, which are projections of the **arachnoid mater** into the **venous sinuses** through which CSF enters the bloodstream. **Bridging veins** cross from the **subarachnoid space** to the **venous sinus**. Subdural hematoma can result from disruption of bridging veins in the subdural space. **Cerebral arteries and veins** are visible in the **subarachnoid space** overlying the **pia mater**. Hemorrhage in the **subarachnoid space** may result from cerebral artery aneurysm or trauma.

Advances in imaging of the nervous system can be demonstrated in the cervical spine. The upper left panel (A) of Fig. AI1.3 is a lateral radiograph of the cervical spine. The right panel shows the same radiograph with key anatomic structures labeled. The lower panels of Fig. AI1.3 show computed tomography (CT) and magnetic resonance imaging (MRI), which have now become standards in evaluation of cervical trauma. Although CT imaging is recognized as a standard for initial evaluation of cervical trauma, **MRI** is very sensitive for detection of spinal cord, ligamentous, and soft tissue injuries. The left panel is a **noncontrast CT** midline image showing a flexion-distraction injury at C6–C7. There is a burst fracture of C7, subtle traumatic anterior listhesis of C6 (*horizontal arrow*) and posterior interspinous space widening (*vertical arrow*). In the right panel, a **sagittal midline MRI** clearly shows fracture-related marrow edema within the **C7** and **T1** vertebral bodies, C6–C7 interspinous ligamentous edema (*paired white arrows*) and extensive posterior supraspinous soft tissue edema (*paired yellow arrows*) consistent with trauma soft tissue injury. **CT** is superior for cortical fractures, whereas **MRI** is more sensitive for detection of soft tissue injuries. Fig. AI1.4 compares CT and computed tomography angiography (CTA) in the setting of subarachnoid hemorrhage. The left panel shows a standard noncontrast CT image with extensive subarachnoid hemorrhage diffusely filling the basal cisterns (*double arrows*). The upper right panel shows a midline sagittal CTA image with a large bi-lobed aneurysm (*white arrow*) arising from the anterior communicating artery (ACOM). In the lower right panel, conventional angiography identifies the aneurysm (*white arrow*) prior to coil embolization.



• **Fig. AI1.2** Anatomy of the meninges and its vasculature in an idealized anatomic drawing.



• **Fig. AI1.3** (A, B) The anatomy of cervical bony structures and soft tissues is visualized using plain radiography (A), computed tomography (B, left), and magnetic resonance imaging (B, right). (From Goradia D, Linnau KF, Cohen WA, et al. Correlation of MR imaging findings with intraoperative findings after cervical spine trauma. *AJNR Am J Neuroradiol*. 2007;28:209–215.)

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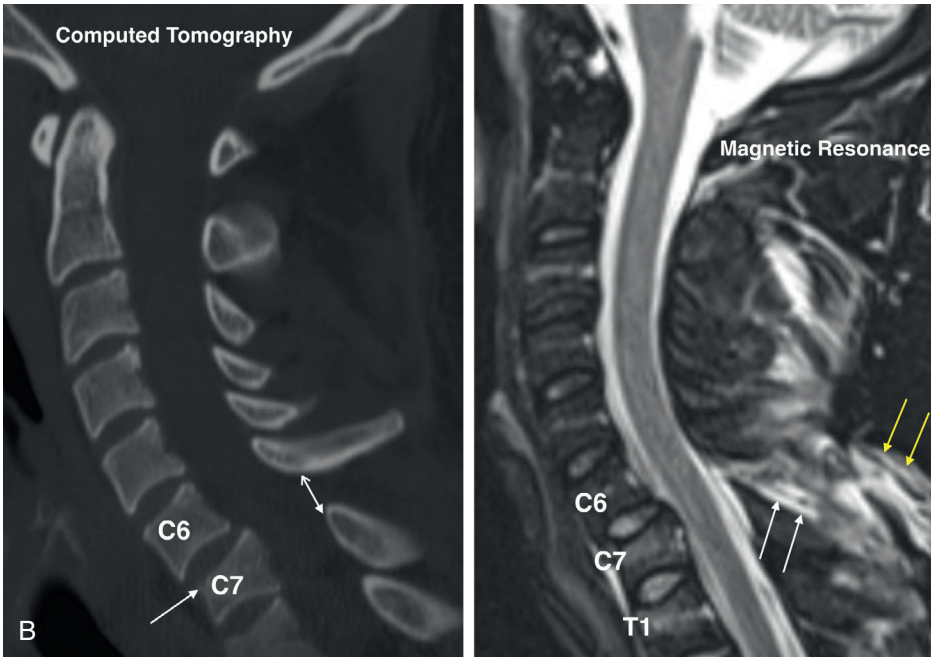
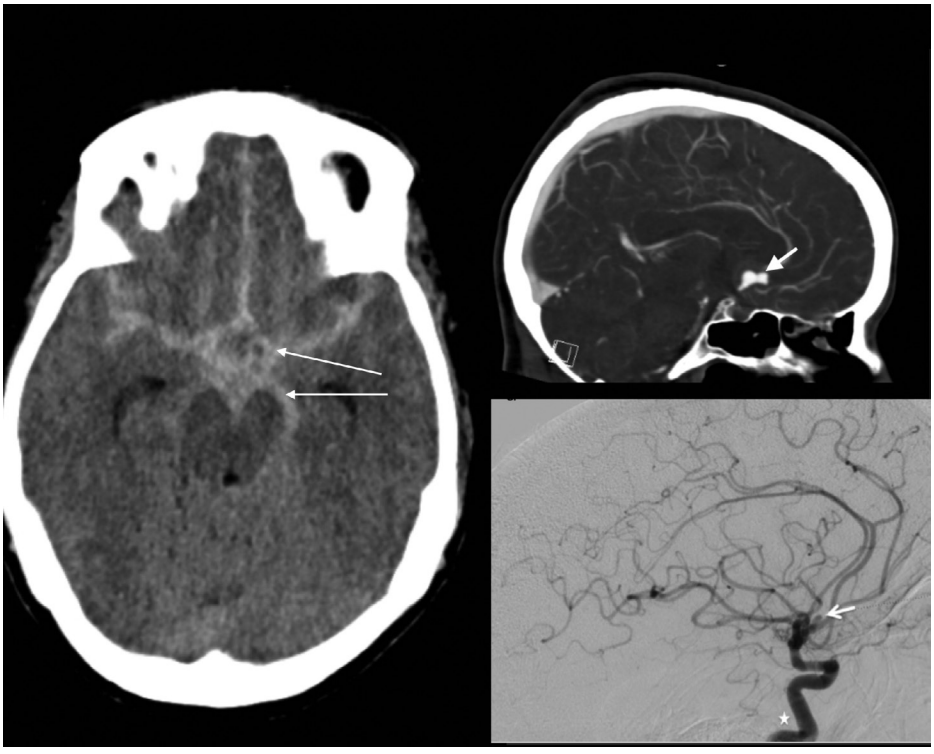
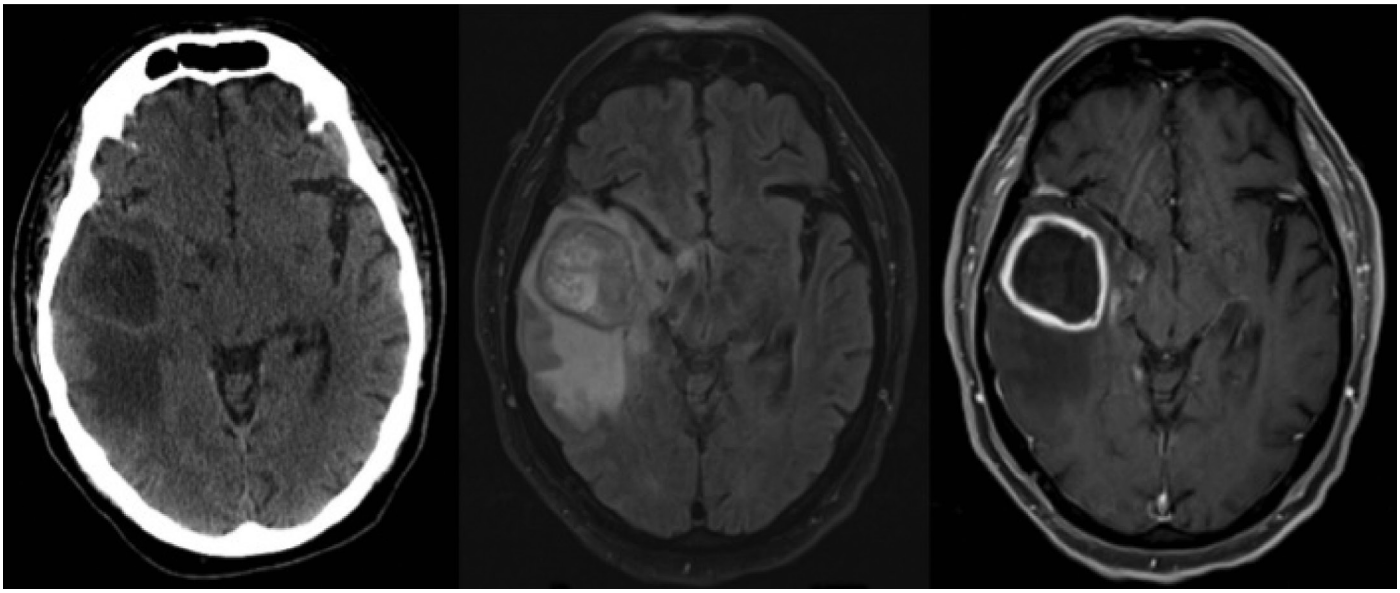


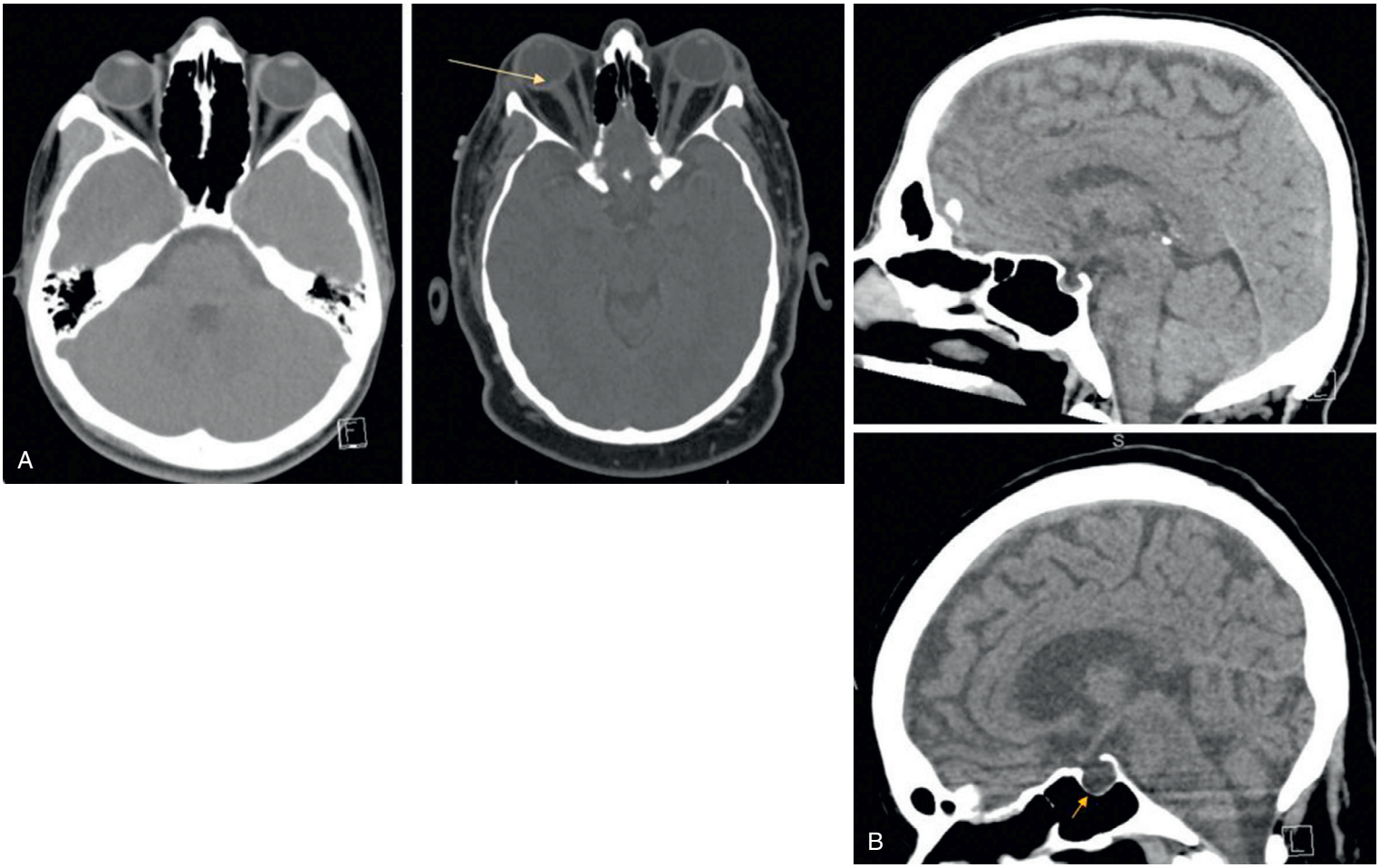
• **Fig. AI1.3, cont'd**



• **Fig. AI1.4** Anatomic changes associated with subarachnoid hemorrhage as visualized by computed tomography, computed tomography angiography, and cerebral angiography. (From McKinney AM, Palmer CS, Truwit, et al. Detection of aneurysms by 64-section multidetector CT angiography in patients acutely suspected of having an intracranial aneurysm and comparison with digital subtraction and 3D rotational angiography. *AJNR Am J Neuroradiol*. 2008;29:594–602.)



• **Fig. AI1.5** Anatomic changes associated with an intracranial mass lesion as visualized by standard magnetic resonance imaging, contrast-enhanced magnetic resonance imaging, and computed tomography. (From Smirniotopoulos JG, Murphy FM, Rushing EJ, Rees JH, Schroeder JW. Patterns of contrast enhancement in the brain and meninges. *Radiographics* 2007;27(2):525–551.)



• **Fig. AI1.6** Image findings associated with increased intracranial pressure.

Aneurysms are an important cause of subarachnoid hemorrhage. Noninvasive CTA provides highly accurate detection of aneurysms in addition to delineation of intracranial vascular anatomy. CTA has largely replaced conventional angiography for diagnostic evaluation of traumatic and atraumatic vascular pathology, including aneurysms, pseudo-aneurysms, dissection, uncontrolled hemorrhage, and vessel occlusion or stenosis. Additionally, CTA provides an anatomic road map for vascular anatomy and is applicable to pregnant and breast-feeding patients.

Fig. AI1.5 illustrates the advantage of **contrast-enhanced MRI** in comparison to **noncontrast MRI** and **CT** in the setting of an intracranial mass lesion. Gadolinium contrast–enhanced MR imaging improves the detection of both extra-axial and intra-axial infections compared to CT. Blood–brain barrier breakdown leads to increased vascularity/permeability and therefore contrast enhancement at sites of infection and inflammation. *Left panel:* A noncontrast CT image through the temporal lobe demonstrates a poorly defined space-occupying mass lesion with surrounding vasogenic edema and mass effect. *Middle panel:* Routine noncontrast MR image through the temporal lobe shows a well-defined circular mass lesion with extensive surrounding vasogenic edema and mass effect on the adjacent midbrain structures. *Right panel:* Contrast-enhanced MR image through the lesion demonstrates classic "ring-like" enhancement of this intracranial abscess with surrounding nonenhancing edema.

The CT images in Fig. AI1.6 show findings of the orbit and skull base associated with increased intracranial pressure. In Fig. AI1.6A, the left panel is an axial image at the level of the orbit showing a normal globe and optic nerve. In the right panel, an arrow highlights intraocular protrusion of the optic nerve consistent with elevated intracranial pressure. In Fig. AI1.6B, the top panel shows a sagittal image of a normal-appearing sella turcica. In the bottom panel, an arrow highlights flattening of the sella turcica (otherwise known as the "empty sella sign") secondary to increased intracranial pressure.

10

Pharmacology of Intravenous Anesthetics

PAUL S. GARCÍA, MATTHEW K. WHALIN, AND PETER S. SEBEL

CHAPTER OUTLINE

History of Intravenous Anesthesia
- General Anesthesia by Intravenous Agents
- Intravenous Anesthesia Mechanisms and Theory

Pharmacologic Targets of Intravenous Anesthetics in the Central Nervous System
- $GABA_A$ Receptors
- $GABA_A$ Insights from Mutagenic Studies
- N-Methyl-D-Aspartate Receptors
- Other Molecular Targets

Individual Agents
- Barbiturates

Benzodiazepines
- Etomidate
- Propofol
  - *Pharmacology*
  - *Formulation and Preparation*
  - *Metabolism, Redistribution, Clearance, and Elimination*
  - *Advantages and Disadvantages of Propofol as an Induction Agent*
  - *Clinical Features of Anesthesia Maintenance With Propofol*
  - *Fospropofol*
- Ketamine
- Dexmedetomidine

Emerging Developments
- High-Tech Delivery Systems
- Novel Sedatives
- Reversal of General Anesthesia

History of Intravenous Anesthesia

The concept of blood delivery of medication can be traced to the middle of the 17th century soon after Harvey described the function of the vascular system. Not only did Sir Christopher Wren study blood transfusions in dogs, but he also experimented with intravenous delivery of injected opium solution into these animals via a feather quill.[1] In the mid-19th century, technologic advancements in needle and syringe manufacturing led to injectable morphine for analgesia, but attempts to produce general anesthesia through intravenous drugs came later. Initial attempts with agents such as diethyl ether, chloral hydrate, magnesium sulfate, barbituric acid, and ethyl alcohol were stalled by prolonged side effects and limited techniques for ventilatory support.[2] Local anesthetics were also tested as intravenous agents for general anesthesia in the early 20th century before their primary clinical application in regional anesthesia was established.[3] The major historical developments in intravenous agents for general anesthesia lagged behind those of the inhaled anesthetics until Lundy and Waters began using barbiturates in the 1930s.[4]

General Anesthesia by Intravenous Agents

For the pedagogic purposes of this chapter, *intravenous anesthetic* is defined as a clinically available substance that when administered directly to the patient via the bloodstream can be used to induce or maintain a state of general anesthesia. Many injectable substances, such as antihistamines or antipsychotics (see Chapter 12), have obvious effects on the central nervous system (CNS) and can depress cognitive status and induce sleep. These drugs are potentially useful for several perioperative situations where sedation is required, but they are neither appropriate nor safe as primary agents for producing general anesthesia. Similarly, medications like the benzodiazepines can be classified as intravenous anesthetics yet are currently used primarily in the perioperative setting for premedication and sedation, not anesthesia. The intravenous opioids (see Chapter 17) form the backbone of modern surgical analgesia yet are not considered true intravenous anesthetics because awareness and recall can occur despite very high doses that produce deep sedation.[5]

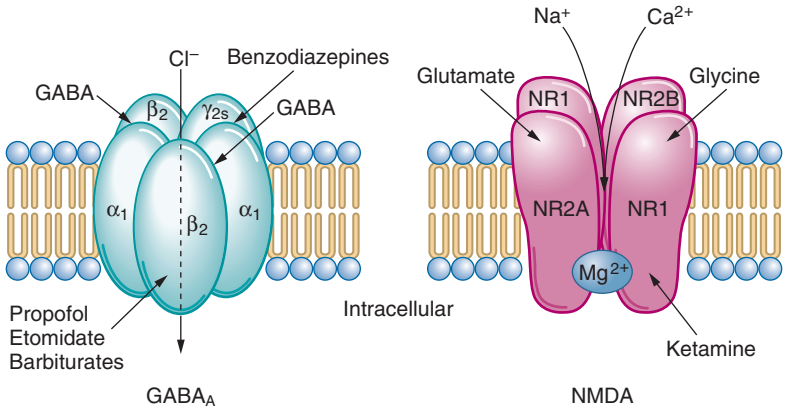
The concept of balanced anesthesia was originally used by Lundy to describe premedication and light sedation as adjuncts to regional anesthesia,[6] but the term was almost universally adopted when nitrous oxide anesthetics supplemented with thiopental and d-tubocurarine grew in popularity in the middle of the 20th century. At present, it is usually accepted that the state of general anesthesia can best be described as a delicate balance of the following effects: unconsciousness, analgesia, amnesia, suppression of the stress response, and sufficient immobility. The relative importance of each of these separate components varies for each case depending on specific surgical and patient factors; anesthesiologists must tailor combinations of intravenous drugs to match these priorities.

Abstract

Recent advances in molecular pharmacology and neuroscience have led to a greater understanding of how anesthetic chemicals can alter the function of the nervous system. Anesthesia through intravenous agents is a clinical state in which multiple behavioral endpoints are caused by a structurally diverse group of drugs. Certain membrane proteins possess specific binding sites that interact with injectable drugs currently used for clinical anesthesia. This chapter explores what is known and touches on what is unknown regarding the clinical use and neuropharmacologic mechanism of intravenous anesthetics.

Keywords

$GABA_A$
receptors
benzodiazepines
propofol
ketamine
dexmedetomidine



• **Fig. 10.1** Key targets of intravenous anesthetics. $GABA_A$ receptors are critical targets for benzodiazepines, barbiturates, etomidate, and propofol. Although it is possible for the drugs and ligands to interact with this protein in multiple areas, it is generally agreed that the endogenous ligand GABA binds to the receptor in a pocket between the α and β subunits. Many of the intravenous anesthetics have their main influence on the activity of this protein in the transmembrane portion of the β subunit, whereas the benzodiazepines modulate the protein through interactions with transmembrane amino acids between the α and γ subunits near the intracellular side. NMDA receptors are activated by the agonist glutamate and co-agonist glycine only when voltage changes displace Mg^{2+} from the ion channel pore. Ketamine also acts primarily by a pore-blocking mechanism. *Ca^+,* Calcium ion; *Cl^-,* chloride ion; *GABA,* gamma-aminobutyric acid type A; *Mg^{2+},* magnesium ion; *NMDA,* N-methyl-D-aspartate.

Intravenous Anesthesia Mechanisms and Theory

Modern anesthetic techniques have transformed surgery from a traumatic and barbaric affair to an acceptable, routine, and essential part of modern medicine. Despite the technologic advances made in perioperative medicine and surgical techniques, the drugs administered by anesthesiologists to render patients unconscious continue to be used without a clear understanding of how they produce anesthesia. Fortunately, through recent advances in molecular pharmacology and neuroscience, clinicians and investigators understand better than ever before how anesthetic chemicals can alter the function of the nervous system.

The elucidation of general anesthetic mechanisms was not accessible to traditional pharmacology methods; anesthesia is a clinical state in which multiple behavioral endpoints are caused by a structurally diverse group of drugs. Nevertheless, it appears that certain membrane proteins (Fig. 10.1) possess binding sites that interact with many of the currently used anesthetics (Table 10.1).[7,8] In general, the halogenated volatile anesthetic agents (see Chapter 11) exhibit less specificity for molecular targets than the intravenous agents.

At the cellular and network levels, intravenous anesthetics alter signaling between neurons by interacting directly with a small number of ion channels. Under normal conditions, these specialized membrane proteins are activated by chemical signals or changes in the membrane environment. Upon activation, channels modify the electrical excitability of neurons by controlling the flow of ions across the cell membrane via channels coupled with specific receptors that sense the initial signal (see Chapter 1).

The majority of intravenous anesthetics exert their primary clinical anesthetic action by enhancing inhibitory signaling via gamma-aminobutyric acid type A ($GABA_A$) receptors. Ketamine and dexmedetomidine are notable exceptions. From a neurophysiology perspective, unconsciousness can be considered as a disruption of the precisely timed cortical integration necessary to produce what is considered the conscious state.[7] It is interesting to note that the unconsciousness produced by ketamine is phenotypically different from that produced by the GABA-ergic agents (e.g., propofol, thiopental, or etomidate). Although many talented scientists worked diligently throughout the 20th century to discover a unifying mechanism by which diverse chemicals cause what is loosely defined as the anesthetic state, molecular investigations into the action of individual drugs have revealed that this one true "grail" does not exist. It should rather be interpreted that the anesthetized state (and its separate components) can be arrived at by any disruption of the delicately constructed and precisely timed neuronal networks that underlie the normal awake, unanesthetized state.

Pharmacologic Targets of Intravenous Anesthetics in the Central Nervous System

$GABA_A$ Receptors

GABA is the most abundant inhibitory neurotransmitter in the brain. $GABA_A$ receptors represent the most abundant receptor type for this ubiquitous inhibitory signaling molecule. $GABA_A$ receptors are broadly distributed in the CNS and regulate neuronal excitability.[9] They appear to mediate unconsciousness, arguably the most recognizable phenotype associated with general anesthesia.[9] There is also strong evidence that $GABA_A$ receptors are involved in mediating some of the other classic components of general anesthesia, including depression of spinal reflexes[10] and amnesia.[11] The contribution of $GABA_A$ receptors in mediating immobility and analgesia is less clear.

$GABA_A$ receptors are ligand-gated ion channels, more specifically members of the "Cys-loop" superfamily that also includes nicotinic acetylcholine, glycine, and serotonin type 3 (5-hydroxytryptamine type 3) receptors. Each of these receptors is formed as a pentameric combination of transmembrane protein subunits (see Fig. 10.1). This superfamily is named for the fixed loops formed in each of

TABLE 10.1 Comparison of Molecular Targets for Common Intravenous Anesthetic Agents

	$GABA_A$ Receptors	NMDA Receptors	2PK Receptors	Glycine Receptors	AMPA Receptors	5-HT Receptors
Thiopental	↑↑			↓	↓↓	↓
Benzodiazepines	↑↑			↑*	↓*	↑*
Etomidate	↑↑		↑	↑		
Propofol	↑	↓		↑↑	↓	↓
Ketamine	↑	↓	↑			↑
Dexmedetomidine (α_2 agonist)	↑*	↓*				
Isoflurane	↑	↓	↑↑	↑↑	↓↓	↑

AMPA, α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; *GABA,* gamma-aminobutyric acid type A; *5-HT,* 5-hydroxytryptamine; *NMDA,* N-methyl-D-aspartate; *2PK,* two-pore domain potassium.

Data summarized from Key References.

*Asterisks indicate a complex relationship between drug and receptor—either evidence for direct allosteric interaction between these drugs and receptors is suspected but has yet to be found, or receptor activity and/or expression is known to be influenced through administration of the drugs. Isoflurane is also shown for comparison.

the subunits by a disulfide bond between two cysteine residues. In 2014, the protein crystallization of a human $GABA_A$ receptor was reported.[12] Binding pockets for neurotransmitters are located at two or more extracellular interfaces: in the case of $GABA_A$ receptors, the endogenous ligand GABA binds between the α and β subunits. Thus far, 19 genes have been identified for $GABA_A$ receptor subunits (α1-6, β1-3, γ1-3, δ, ε, θ, π, ρ1- 3).[13] Although millions of subunit arrangements are possible, only a subset of receptor configurations is expressed in significant amounts in the CNS. Preferred subunit combinations distribute among different brain regions and even among different subcellular domains.[14] Each type of $GABA_A$ receptor exhibits subtly distinct biophysical and pharmacologic properties that in turn have diverse influences on synaptic transmission and synaptic integration.

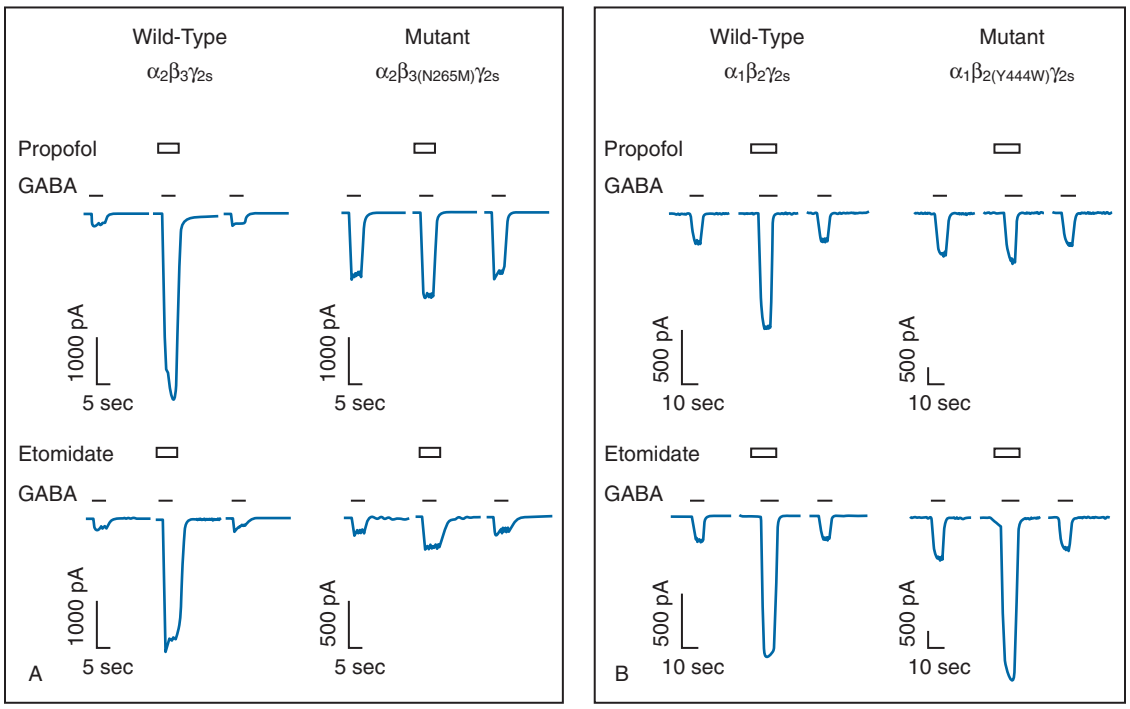
Specific behavioral effects of drugs have been linked to different subunit assemblies present in different brain regions. For example, benzodiazepines are thought to interact with $GABA_A$ receptors between the α and γ subunits[15] (see Fig. 10.1) and specific clinical effects have been linked to receptors containing specific α and β subunits. Propofol,[16] etomidate,[17] and barbiturates[18] interact with $GABA_A$ receptors within, or proximal to, β subunits. The β subunits show less specific subcellular localization compared to α subunits, and the distribution of β subunits in mammalian brain does not share the same clear distinctions as α subunits.[19] Therefore distinguishing specific differences between the GABA-mediated anesthetic effects of non-benzodiazepine intravenous anesthetics has been more elusive. However, research involving genetically manipulated mice has suggested that the sedation produced by etomidate can be primarily associated with activity at the β_2 subunit[20] while unconsciousness produced by the same drug can be associated with β_3 subunits (see "$GABA_A$ Insights from Mutagenic Studies").[21] Subtle pharmacodynamic differences between intravenous anesthetics (e.g., effects on postoperative nausea and vomiting) might also be mediated by interactions with targets in addition to $GABA_A$ receptors.

Almost all general anesthetics enhance $GABA_A$ receptor–induced chloride currents by enhancing receptor sensitivity to GABA, thereby inhibiting neuronal activation. Most of these drugs, at high concentrations, also directly open the channel as an agonist in the absence of GABA. By virtue of the specific distribution of these receptors in the cerebral cortex and other brain regions, in addition to being involved in producing anesthesia, $GABA_A$ receptors function in thalamic circuits necessary for sensory processing and attention, hippocampal networks involved in memory, and thalamocortical circuits underlying conscious awareness. Computational neuronal modeling studies have been important in revealing the impact of propofol and etomidate on dynamic changes in these networks.[22,23]

$GABA_A$ Insights From Mutagenic Studies

The critical role of the $GABA_A$ receptor in the pharmacodynamics of anesthetic drugs has been established through laboratory experimentation using genetic modifications of this protein. In the early 1990s, in vitro studies aimed at determining the interactions of the endogenous ligand GABA with its receptor revealed that specific amino acid substitutions in the $GABA_A$ receptor conferred the sensitivity of the channel to agonist or allosteric modulator activity.[24–26] By 1995, several functional domains of the $GABA_A$ receptor associated with binding of agonists and allosteric modulators were identified (reviewed by Smith and Olsen[27]). Following the discovery of the site of benzodiazepine action, investigators discovered that mutation of a pair of transmembrane amino acids on the α subunit of $GABA_A$ renders the receptors insensitive to inhaled anesthetics.[25,28] That same year, a corresponding area on the β_3 subunit was determined to be critical for the action of etomidate.[29] Further studies have determined this location to be essential to the actions of other intravenous agents such as propofol and pentobarbital.[18,30] A different amino acid residue appears to be involved with the specific actions of propofol only (Fig. 10.2).[16]

The strategy behind these discoveries was to examine the subtle differences among the amino acid sequences in receptor isoforms known to have different sensitivities to anesthetics. Originally receptor chimeras of unnatural subunit configurations were used, eventually giving way to specifically modified subunits via site-directed mutagenesis. Potential residues and amino acid sequence domains that mediate anesthetic sensitivity can be anticipated by



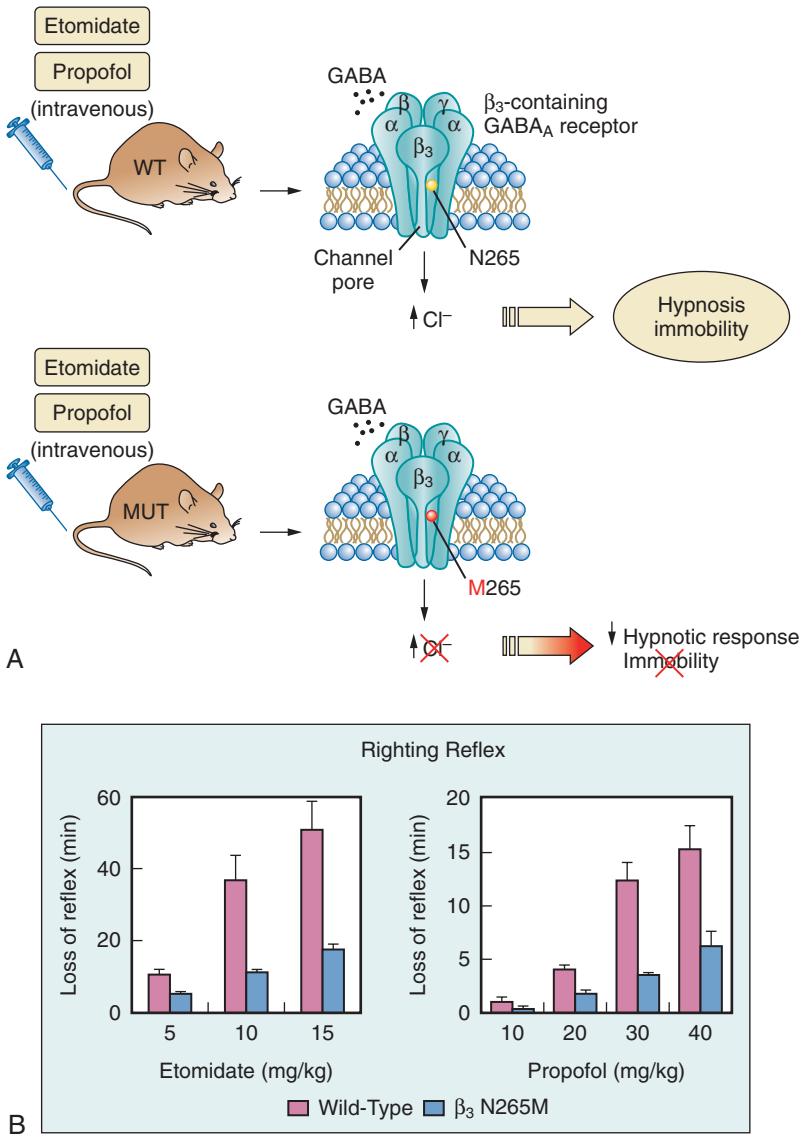
• **Fig. 10.2** Site-directed mutagenesis elucidates specific amino acid residues involved in anesthetic actions at the $GABA_A$ receptor in patch clamp experiments. Treatment with GABA (duration shown with *black line*) alone or in combination with anesthetics (indicated by *white box*) triggers depolarization of wild-type and mutant receptors. A, The substitution of a methionine (M) residue for an asparagine (N) residue in the 265th position on the β_3 subunit (β_3 N265M mutation) renders that $GABA_A$ receptor immune to enhancement of chloride current via etomidate and propofol administration. B, In a similar study of the β_2 subunit, substitution of tryptophan (W) for the native tyrosine (Y) blocks propofol enhancement but the receptor remains sensitive to etomidate. *GABA,* Gamma-aminobutyric acid type A. (A, Adapted from Siegwart R, Jurd R, Rudolph U. Molecular determinants for the action of general anesthetics at recombinant $\alpha_2\beta_3\gamma_2$ $GABA_A$ receptors. *J Neurochem*. 2002;80:140–148; B, Adapted from Richardson JE, Garcia PS, O'Toole KK, et al. A conserved tyrosine in the beta2 subunit M4 segment is a determinant of gamma-aminobutyric acid type A receptor sensitivity to propofol. *Anesthesiology.* 2007;107:412–418.)

comparing data among different mutated and chimeric receptors. Typically, functional studies are carried out in vitro by virally transfecting this DNA into living cells, which results in expression of these receptors on their cell surface. Immortal cells derived from human embryonic kidney cells and the eggs of the amphibian *Xenopus laevis* (oocytes) have been invaluable as conduits for this type of research; establishing electrical access in these cells using the conventional patch-clamp technique is relatively straightforward and measurements of their chloride currents in response to opening of the $GABA_A$ channel is robust (see Fig. 10.2).

By now a great body of literature exists in which anesthetic sensitivity has been mapped to specific point mutations on $GABA_A$ receptors.[8] Some of these point mutations, so-called silent mutations, do not affect the natural function of the receptor but only its modulation by specific anesthetics. The introduction of mutations such as these into genetically modified mice can be used to determine the importance of this receptor to the production of certain qualities of an anesthetic in vivo.[31] In vivo experimentation on animals possessing these "knock-in" point mutations has advantages over traditional gene knockout studies. Specifically, if the receptor is unaltered except with respect to its response to exogenous anesthesia, there exists less potential for compensatory changes that could influence the results of in vivo experiments. Mouse geneticists have successfully bred mice with attenuated sensitivity to benzodiazepines as well as etomidate and propofol.[17,31–33]

By creating a point mutation that confers anesthetic selectivity in a single specific subunit, the phenotypic effects attributable to that drug and that subunit can be dissected (Fig. 10.3). For example, the substitution of a methionine (M) residue for an asparagine (N) residue in the 265th position on the β_3 subunit (β_3 N265M mutation) results in a phenotypically normal animal that is essentially immune to the hypnotic effects of propofol and etomidate while maintaining its sensitivity to inhaled anesthetics.[17] Similarly, substituting an arginine (R) for the histidine (H) residue in the 101st position on the α_1 subunit (α_1 H101R mutation) essentially renders that $GABA_A$ receptor unresponsive to benzodiazepines.[31] By making analogous substitutions in the other α subunits, scientists have been able to map particular behavioral effects from benzodiazepines to specific subunits. For example, the α_1 subunit appears to mediate the sedative, amnestic, and anticonvulsant actions of some benzodiazepines, whereas benzodiazepine muscle relaxation and anxiolysis are mainly mediated via α_2 and α_3 subunits.[31,32,34,35]

These amino acid substitutions (in vitro and in vivo) alter the molecular environment in the anesthetic binding cavity by reducing the number of favorable interactions between the receptor and the



• **Fig. 10.3** Genetic manipulation of $GABA_A$ receptors in mice facilitates the study of behavioral effects of different anesthetic drugs. A, In this schematic diagram, intravenous anesthetics (e.g., propofol and etomidate) are administered to a mouse with normal or wild-type *(WT)* $GABA_A$ receptors and, as expected, general anesthesia ensues. When these same drugs are administered to an animal with a specific knock-in mutation at the 265th position on the β_3 subunit, the effects of these drugs are mitigated. B, Quantitative data comparing the effect of propofol and etomidate on wild-type and β_3 N265M knock-in mutants in the loss of righting reflex test, an animal correlate of unconsciousness. *Cl^-,* chloride ion; *GABA,* gamma-aminobutyric acid type A. (Adapted from Jurd R, Arras M, Lambert S, et al. General anesthetic actions in vivo strongly attenuated by a point mutation in the GABA(A) receptor beta3 subunit. *FASEB J.* 2003;17:250–252.)

anesthetic molecule, thus reducing the efficacy of that anesthetic drug on enhancing GABA-ergic transmission. Although this work has greatly increased insight into anesthetic mechanisms, a complete description of the biophysical interactions between specific residues and specific anesthetics remains as incomplete as understanding of the spike-coded pattern of neuronal network activity responsible for the transitions between consciousness and unconsciousness.

N-Methyl-D-Aspartate Receptors

Whereas augmentation of endogenous inhibitory chemical signaling is important to mechanisms of anesthesia, mitigation of excitatory signaling also depresses neuronal activity. Of the many excitatory chemical signals in the CNS, blockade of the N-methyl-D-aspartate (NMDA)-type glutamate receptor appears to be most relevant to mechanisms of anesthesia. There are two broad categories of excitatory synaptic receptors that use the amino acid L-glutamate as their chemical messenger: NMDA receptors and non-NMDA receptors.[36] The latter group, which mediates fast excitatory postsynaptic currents, can be subdivided into α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors and kainate receptors. Neither AMPA nor kainite receptors have a clear effect on anesthetic-induced unconsciousness,[37] but the role of AMPA receptors in "off-target" effects of anesthetics is being actively

explored (see "Emerging Developments"). NMDA receptors, by contrast, mediate excitatory postsynaptic currents of relatively prolonged duration. NMDA receptors are found presynaptically, postsynaptically, and extrasynaptically[38]; they are important targets for xenon, nitrous oxide, and the dissociative anesthetic ketamine.[39]

NMDA receptors are tetramers consisting of four subunits arranged circumferentially around a central ion channel pore (see Fig. 10.1).[36] All NMDA receptors contain an obligatory NR1 subunit and at least one of four types of NR2 subunits (A–D). Other subunits (NR3) and numerous splice variants exist that translate to considerable variability in the kinetic and pharmacologic profile of each receptor isoform.[40] In contrast to non-NMDA glutamate receptors, which are selective for sodium ions (Na^+), the pore of NMDA receptors permits entry of both monovalent and divalent cations (Na^+ and calcium ions [Ca^{2+}]) into the cell upon activation. The Ca^{2+} flux is important for activating Ca^{2+}-dependent processes in the postsynaptic cell such as long-term potentiation, a form of synaptic plasticity thought to play an important role in memory.[41]

NMDA receptors are unique among ligand-gated ion channels in that their probability of opening depends not only on presynaptic release of neurotransmitter but also on the voltage across the membrane containing the receptor. Until membrane depolarization occurs, magnesium ions (Mg^{2+}) block the channel pore if agonist is present. High-frequency excitatory input causes membrane depolarization, so NMDA receptors play a significant role in CNS functions that require activity-dependent changes in cellular physiology such as learning and processing of sensory information.[42] In the nociceptive circuitry of the spinal cord, repeated peripheral nerve stimulation results in an increase in response to subsequent stimuli through activation of NMDA receptors. This "windup" phenomenon is associated with hyperalgesia, and both knockout and knockdown of NR1 block inflammatory pain in animals.[43,44] This, combined with their ability to modify opioid tolerance, makes NMDA receptor antagonists promising treatments for chronic pain.[45]

NMDA antagonists are classified by their mechanism of action. Volatile anesthetics may exert some of their effects as competitive antagonists by displacing the coagonist glycine from NMDA receptors.[46] The intravenous NMDA antagonists in current clinical use are primarily channel blockers that bind to the pore only in its open confirmation. They are considered uncompetitive antagonists and, because their binding requires prior activation by agonist, they are termed *use-dependent*.[36] Blockers such as ketamine, which remain bound after channel closure, cause prolonged disruption of the associative aspects of neuronal communication. High concentrations of ketamine cause sedation and loss of consciousness with a significant incidence of dysphoric effects. This may reflect a lack of selectivity among various NMDA isoforms or activity at other receptors (see Table 10.1). Noncompetitive antagonists, which bind to allosteric sites with some NMDA receptor subunit specificity, may have more specific clinical effects and a better side effect profile.[36]

Other Molecular Targets

Other receptors, such as glycine receptors, voltage-gated Na^+ channels, and two-pore domain potassium (2PK) channels, deserve attention as they probably contribute to certain components of the balanced anesthetic state with intravenous anesthetics. Glycine receptors colocalize with $GABA_A$ receptors near the cell body. Propofol, etomidate, and thiopental all have some positive modulation of the glycine receptors, but ketamine does not. Glycine receptors have an inhibitory role, particularly in the lower brainstem and spinal cord. They are likely major contributors to anesthetic immobility, especially that produced by the volatiles. An investigation of spinal neurons estimated that propofol's effects on immobility were mediated almost entirely via GABA receptors, whereas the immobility caused by sevoflurane was predominantly mediated by glycine receptors.[47] Propofol inhibits some subtypes of voltage-gated Na^+ channels, which could contribute to its antiepileptic activity.[48] In high doses, ketamine can also block Na^+ channel activity.[49]

2PK Channels modulate neuronal excitability through control of the transmembrane potential. There are 15 different 2PK isoforms, and functional channels are formed from homomeric or heteromeric dimers. Genetic deletion of several members of this channel family (TREK1, TREK2, TASK1, TASK3, and TRESK) in animal models reduces the immobilizing effect of intravenous and volatile general anesthetics, which suggests a contribution to their anesthetic mechanisms.[50]

Hyperpolarization-activated cation channels (HCN channels) are important in mediating coordinated neuronal firing between the thalamus and cortex. These channels play an important role in setting the frequency of thalamocortical rhythms critical for high-order cognitive processing and are also important for controlling burst firing in the hippocampus, thalamus, and locus coeruleus.[51] Amnesia and hypnosis are produced upon disruption of signaling in these brain areas via inhaled and intravenous anesthetics.[52,53] Some anesthetics like dexmedetomidine exert their sedating effects by activating α_2 receptors in the locus coeruleus.[54]

Novel techniques may identify a host of other targets for anesthetic drugs. For example, azipropofol is an analog that becomes covalently linked to a binding partner when exposed to light. Tadpoles given this drug had prolonged anesthesia when exposed to light and proteomic analysis of the linked molecules identified novel potential targets of propofol.[55]

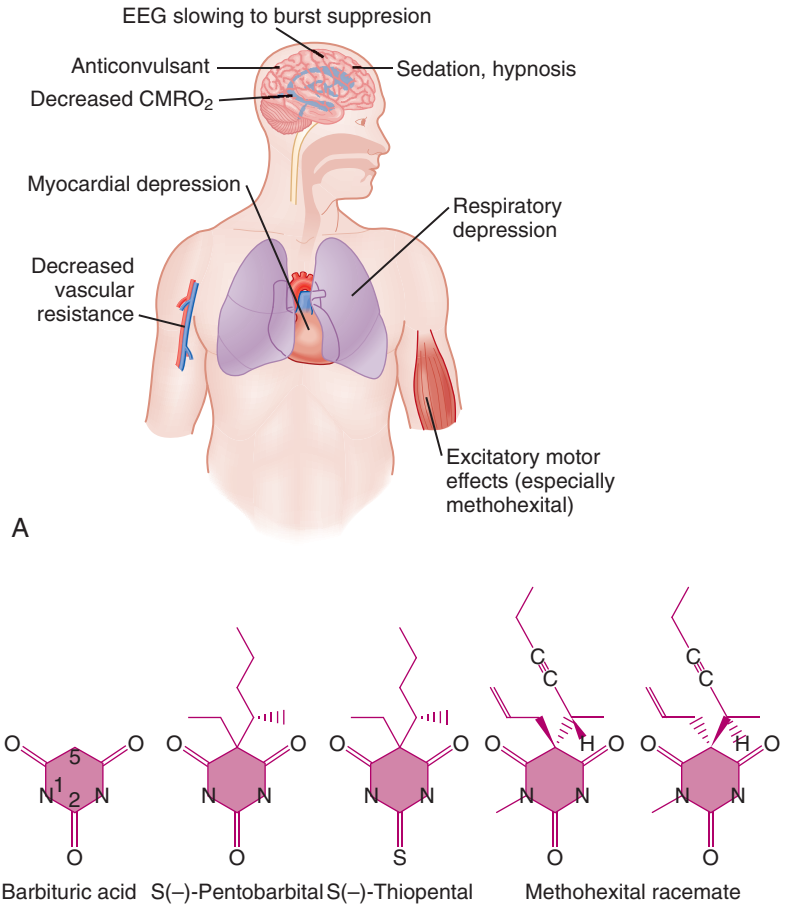
Individual Agents

Barbiturates

In 1864, some 20 years after Morton and Long independently discovered inhaled anesthesia, von Baeyer synthesized barbituric acid, which eventually led to the development of intravenous anesthesia. Barbituric acid is pharmacologically inert, but substitutions at the C5 position impart hypnotic activity. The clinical use of barbiturates as hypnotics began in 1904 with 5,5-diethyl-barbituric acid, but their adaptation to anesthesia was pioneered in the late 1920s by Bumm in Germany and Lundy in the United States.[4,56] Lundy's investigations included pentobarbital, also known as nembutal (sodium [N] 5-ethyl-5-[1-methylbutyl]) substituted barbituric acid). Thionembutal, the sulfur substitution of this compound better known as sodium thiopental, became the dominant intravenous induction agent of the next 60 years.

Thiopental was popularized by Lundy but might have been first used in a patient several months earlier in 1934 by Waters in Wisconsin. It was used in short procedures and early use was limited by the lack of reliable equipment to maintain intravenous access. Over time it evolved from a sole agent to a means of inducing anesthesia without breathing the pungent vapors of that era (e.g., ether).

Both pentobarbital and thiopental are supplied as racemic mixtures (see Chapter 2), with the S(−) isomer exhibiting roughly



• **Fig. 10.4** A, Selected effects of barbiturates. B, Structures of clinically important barbiturates. Pentobarbital and thiopental are supplied as racemic mixtures but only their more potent isomers are shown. Methohexital has two chiral centers and both of the isomers in the commercial formulation are shown. *$CMRO_2$,* Cerebral metabolic rate for oxygen; *EEG,* electroencephalography.

double the potency of the R(+) form. Methylation of the ring nitrogen of methohexital creates a second chiral center and a total of four stereoisomers. Early animal work at Eli Lilly revealed that the potent β isomers had more excitatory side effects so methohexital is marketed as a racemate of the α isomers.[57] The α-dextrorotatory form is roughly three times more potent than the α-levorotatory ($S_\alpha R_\beta$) isomer and recent stereochemical synthesis suggested that the latter is responsible for the residual excitatory effects of commercial methohexital (Fig. 10.4B).[58]

Methohexital found use in electroconvulsive therapy and pentobarbital was used as a pediatric premedication, but thiopental was the mainstay for the intravenous induction of anesthesia before the introduction of propofol. American production of thiopental ceased in 2010 and plans to import the drug from Europe stalled over the political controversy associated with thiopental's use for lethal injection in the U.S. penal system. Like etomidate, thiopental enhances $GABA_A$ receptor function in a stereoselective manner.[59] This is also true for other barbiturate sedatives/hypnotics such as hexobarbital and pentobarbital. Thiopental directly gates $GABA_A$ receptors at high concentrations (like propofol and etomidate). Thiopental discriminates between synaptic and extrasynaptic $GABA_A$ receptors in the hippocampus, suggesting a possible role for the δ subunit in barbiturate enhancement of this channel.[60] The β subunit has also been implicated as a molecular site of action of barbiturates at $GABA_A$ receptors.

In addition to $GABA_A$ receptors, barbiturates modulate a variety of ligand-gated ion channels in vitro. They block the action of the excitatory neurotransmitter glutamate at AMPA and kainate receptor subtypes, but not at NMDA receptors. They also inhibit neuronal nicotinic acetylcholine receptors. The relevance of these receptors to the clinical action of barbiturates remains unclear. Several clinical effects appear to be modulated by allosteric augmentation at $GABA_A$ receptors. Transgenic mice carrying a point mutation (N265M) of the $GABA_A$ β_3 subunit are resistant to the immobilizing effects of pentobarbital.[18] However, this mutation had no effect on the pentobarbital-induced respiratory depression and intermediate blunting of hypnotic and cardiovascular effects. Future studies are needed to determine whether these effects are mediated by some other $GABA_A$ receptor subtype, ionotropic glutamate receptors, or other receptors.

Barbiturates produce dose-dependent CNS depression with characteristic effects on electroencephalography (EEG), progressing from a low-frequency, high-amplitude pattern to isoelectric periods of increasing duration. The cerebral metabolic rate for oxygen ($CMRO_2$) is decreased to a widely quoted maximal extent of 55%, and both cerebral blood flow and intracranial pressure (ICP) are decreased as a result of flow-metabolism coupling. These factors led to widespread use of barbiturates for neuroprotection, although large trials and metaanalyses have failed to show substantial clinical benefit in humans. Thiopental and pentobarbital have anticonvulsant

effects in the setting of prolonged high-dose administration, whereas prolonged use of methohexital leads to epileptiform discharges.

Barbiturates cause venodilation with consequent decreases in preload and cardiac output. This effect is particularly pronounced in hypovolemic patients.[60] There is in vitro evidence for direct myocardial depression at doses much higher than those used for anesthesia. Selected effects of barbiturates are summarized in Fig. 10.4.

Barbiturate sodium salts require a pH greater than 10 to remain in aqueous solution and precipitate readily when mixed with nonbasic solutions such as normal saline solution. They also precipitate when combined in high concentrations with certain weak bases such as the neuromuscular blockers, forming a "conjugate salt" (e.g., sodium thiopental and rocuronium bromide precipitate to form sodium bromide). In the plasma, barbiturates are readily protonated and become quite lipophilic, which leads to unconsciousness 30 to 60 seconds after bolus injection. Kinetic modeling of bolus administration reveals a rapid peak in effect site (CNS) concentration (Fig. 10.5A). The subsequent decline in concentration results primarily from redistribution to other tissues rather than metabolism and elimination (see Chapter 2). Repeated bolus dosing or continuous infusions lead to very prolonged recovery times as depicted by plots of the context-sensitive half-time (see Fig. 10.5C).[61] When given in very high doses, thiopental can even exhibit "zero-order kinetics," wherein metabolic capacity is saturated, grossly prolonging the duration of action.

Thiopental is highly protein bound (75%–90%) in the plasma, primarily to albumin. Decreased albumin levels such as those seen in chronic renal or hepatic disease can markedly increase free drug levels and may warrant decreased dosing.[62] Thiopental undergoes some desulfurization to form its parent drug pentobarbital. This "metabolite" is likely relevant only to prolonged high-dose administration of thiopental. Both drugs are deactivated by poorly characterized pathways in the liver to form inactive carboxylic acid and alcohol derivatives. Thiopental causes some cytochrome P450 induction but this is generally of no clinical consequence when used as an induction agent. An active porphyric crisis could be exacerbated by this mechanism, but triggering an event in a patient with latent porphyria is reported to be unusual.[63] Even so, it is prudent to avoid even potential triggers in patients with porphyria.

Benzodiazepines

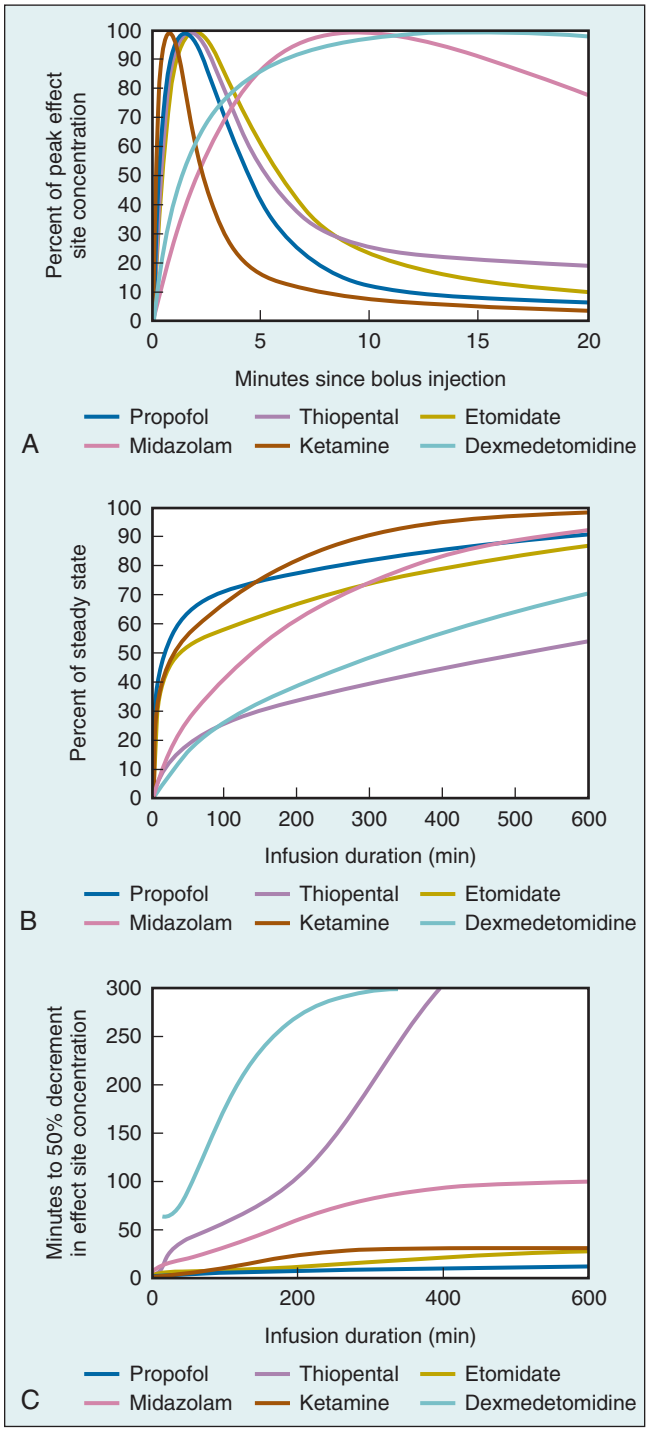
Benzodiazepines were introduced into clinical use in the 1960s and rapidly gained popularity as anxiolytics with a wider safety margin than barbiturates.[64] Diazepam, lorazepam, and midazolam are three of the most important class members in the practice of anesthesia. Diazepam and lorazepam are lipophilic and are traditionally formulated in propylene glycol because they are not soluble in water. These formulations are associated with pain on injection and long-term infusions in the intensive care unit (ICU) can lead to glycol toxicity. The imidazole ring of midazolam allows the preparation of acidic aqueous solutions, which cause minimal pain on injection.[65] Once at physiologic pH, midazolam assumes a more lipophilic ring conformation and can gain rapid access to the CNS (Fig. 10.6B).

Benzodiazepines act on a subset of $GABA_A$ receptors containing γ subunits to potentiate chloride conductance upon GABA binding. This modulatory mode of action is postulated to create a "ceiling effect" that limits CNS depression, although when combined with other drugs, benzodiazepines can lead to dangerous respiratory depression.[66] Even when respiratory drive is preserved, midazolam increases the likelihood of airway obstruction, and caution is advised in patients with obstructive sleep apnea or advanced age.[67,68] The binding pocket appears to be at the interface of the α and $\gamma 2$ subunits in receptors containing α_1, α_2, α_3, or α_5 subunits. Recent elegant studies of mutant $GABA_A$ subunits in transgenic mice have raised the possibility of dissecting the effects of the benzodiazepines at a molecular level (see earlier "$GABA_A$ Insights from Mutagenic Studies").

Benzodiazepines have anxiolytic, sedative, hypnotic, amnestic, and anticonvulsant properties in the CNS. In animals, they may either promote or block hyperalgesia depending on the model studied.[69,70] The α subunit of the $GABA_A$ receptor appears to differentially mediate the CNS effects of benzodiazepines. For example, α_2-containing receptors play an important role in anxiolysis, anti-hyperalgesia, and centrally mediated muscle relaxation, whereas α_1-containing subunits are important mediators of the sedative, amnestic, and anticonvulsive effects of benzodiazepines.[71] Although benzodiazepines can be used for the induction of anesthesia, the high doses required delay emergence unless the surgery is of prolonged duration. Combining midazolam with another induction agent can offer improved hemodynamic stability without affecting emergence. Other selected effects of benzodiazepines are depicted in Fig. 10.6.

Oral midazolam in children has an onset of action within 10 minutes and peaks in 20 to 30 minutes; its effects begin to dissipate 45 minutes after administration. This kinetic profile requires some planning to get the child to the operating room within the window of efficacy. As shown in Fig. 10.5A, intravenous midazolam does not reach peak effect site concentration until nearly 10 minutes after administration. When titrating midazolam, one must therefore be patient to avoid "stacking" the doses and oversedating the patient. The onset of intravenous diazepam is more than twice as rapid as that of midazolam, but its use is limited by an extremely long duration of action. Not only is the elimination half-life 10 times longer than that of midazolam, but about half of the parent drug is metabolized to the active compound desmethyldiazepam, which has an even longer elimination half-life. Both midazolam and diazepam are metabolized by cytochrome P450 enzyme 3A (CYP3A) family members in the liver and are subject to interactions with erythromycin and antifungal medications. Diazepam is also metabolized by CYP 1A2 and CYP 2C19.

Premedication is currently the main role of benzodiazepines in anesthesia; a majority of U.S. practitioners surveyed in the 1990s used intravenous midazolam for adults (>70%) and oral midazolam for children (80%).[72] For patients requiring long-term mechanical ventilation, combinations of an opioid and benzodiazepine have been the traditional method of sedation but the latest Society of Critical Care Medicine (SCCM) guidelines encourage use of nonbenzodiazepine alternatives.[73] Although midazolam is often considered a short-acting benzodiazepine, prolonged infusions in critically ill patients lead to markedly delayed awakening in part owing to accumulation of its active metabolite 1-hydroxymidazolam (see Fig. 10.5B and C). For this reason, the SCCM sedation guidelines recommend limiting midazolam use to 2 to 3 days.[74] For longer periods of sedation, the benzodiazepine of choice is lorazepam, but some formulations of lorazepam are formulated in a glycol-based vehicle and prolonged infusions lead to glycol toxicity. An emerging body of literature links benzodiazepine use to delirium in critically ill patients.[75,76] Because delirium increases time on mechanical ventilation, length of stay, and morbidity and mortality, there has been some movement toward other sedatives in the ICU.



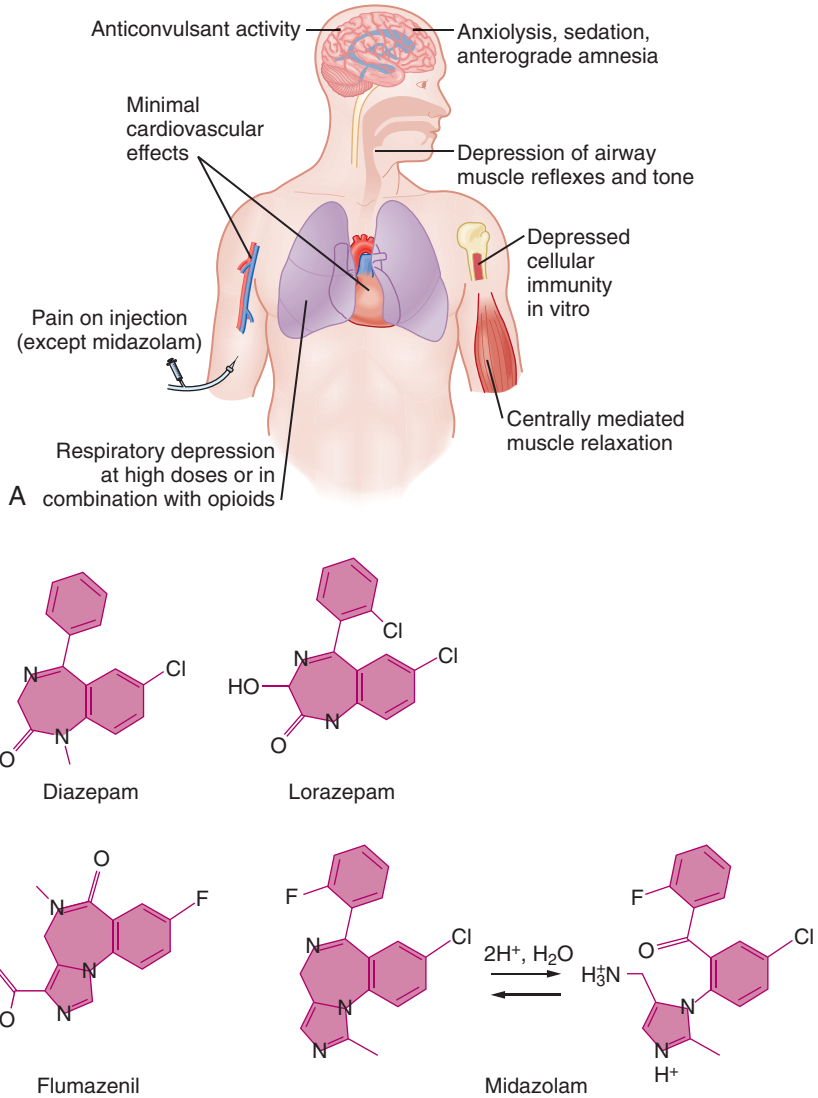
• **Fig. 10.5** A, Bolus front- and back-end kinetics comparing the time courses of effect site concentrations after bolus injection based on the pharmacokinetics and rate of plasma effect site equilibrium. The curves have been normalized to the peak effect site concentration, permitting comparison of the relative rate of rise (and fall) independent of dose. B, Infusion front-end kinetics expressed as a percentage of eventual steady-state effect site concentration. After 10 hours, no intravenous anesthetic has reached steady-state concentration. C, Infusion back-end kinetics (i.e., the context-sensitive half-times) of intravenous anesthetics based on the pharmacokinetics and rate of plasma effect site equilibrium. (Simulations courtesy of Dr. Shinju Obara, Fukushima University, Japan, performed with PKPDtools [www.pkpdtools.com].) Note that dexmedetomidine is not approved for bolus dosing, but the curve was derived from the data of Dyck et al.,[168] using PKPDtools with an assumed time to peak effect of 15 minutes. Pharmacokinetics of the intravenous anesthetics derived from studies of propofol, thiopental, etomidate, midazolam, ketamine, and dexmedetomidine. Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology*. 1998;88:1170–1182; Stanski DR, Maitre PO. Population pharmacokinetics and pharmacodynamics of thiopental: the effect of age revisited. *Anesthesiology*. 1990;72(3):412–422; Arden JR, Holley FO, Stanski DR. Increased sensitivity to etomidate in the elderly: initial distribution versus altered brain response. *Anesthesiology*. 1986;65:19–27; Greenblatt DJ, Ehrenberg BL, Gunderman J, et al. Pharmacokinetic and electroencephalographic study of intravenous diazepam, midazolam, and placebo. *Clin Pharmacol Ther*. 1989;45:356–365; Buhrer M, Maitre PO, Hung O, et al. Electroencephalographic effects of benzodiazepines. I. Choosing an electroencephalographic parameter to measure the effect of midazolam on the central nervous system. *Clin Pharmacol Ther*. 1990;48:544–554; and Domino EF, Domino SE, Smith RE, et al. Ketamine kinetics in unmedicated and diazepam-premedicated subjects. *Clin Pharmacol Ther*. 1984;36:645–653.)

Benzodiazepines also have some immunomodulatory effects on monocytes and T cells in vitro.[77,78] There are several studies linking outpatient benzodiazepine use to increased infection, but it is unknown whether brief perioperative use carries any risk.[79]

An important and unique feature of the benzodiazepines compared to the other GABA-ergic sedative hypnotics is that a competitive antagonist for the reversal of benzodiazepine effects is available. As an intravenous rescue agent, flumazenil can rapidly reverse the CNS depression associated with benzodiazepine intoxication. Routine administration of flumazenil to patients presenting to the emergency department with the suspicion of overdose can lead to seizures via precipitating acute withdrawal in chronic benzodiazepine users.[80] But there is some evidence that flumazenil has anticonvulsant properties suggesting that this drug may have mixed or partial agonist effects on the $GABA_A$ receptor, even in the absence of benzodiazepine administration.[81] In support of this phenomenon is the potential for high doses of flumazenil to potentiate the hypnosis of other positive GABA modulators such as propofol.[82] Its use to augment recovery from general anesthesia is being explored with mixed results (see "Emerging Developments"). Although flumazenil can be lifesaving in cases of benzodiazepine overdose, its short-acting kinetic profile creates the possibility of resedation after the effects of flumazenil dissipate.

Etomidate

Etomidate is a rapidly acting intravenous agent that was introduced into clinical practice in the 1970s. Compared with other induction agents, it has minimal effects on the cardiovascular system.[83] Because of its association with nausea and prolonged suppression of adrenocortical synthesis of steroids, its main clinical use is for inductions in which hemodynamic stability is essential.[84] The R(+) isomer has much greater hypnotic effects (Fig. 10.7), and it is formulated as a single enantiomer. Like propofol, etomidate interacts with $GABA_A$ receptors in a stereoselective manner.[85] Its enhancement of GABA-mediated current is smaller on receptors containing the β_1 subunit.[86] Of all the clinically used intravenous anesthetics, etomidate exhibits the greatest selectivity for $GABA_A$ receptors and has the fewest relevant interactions with other ion channels (see Table 10.1).



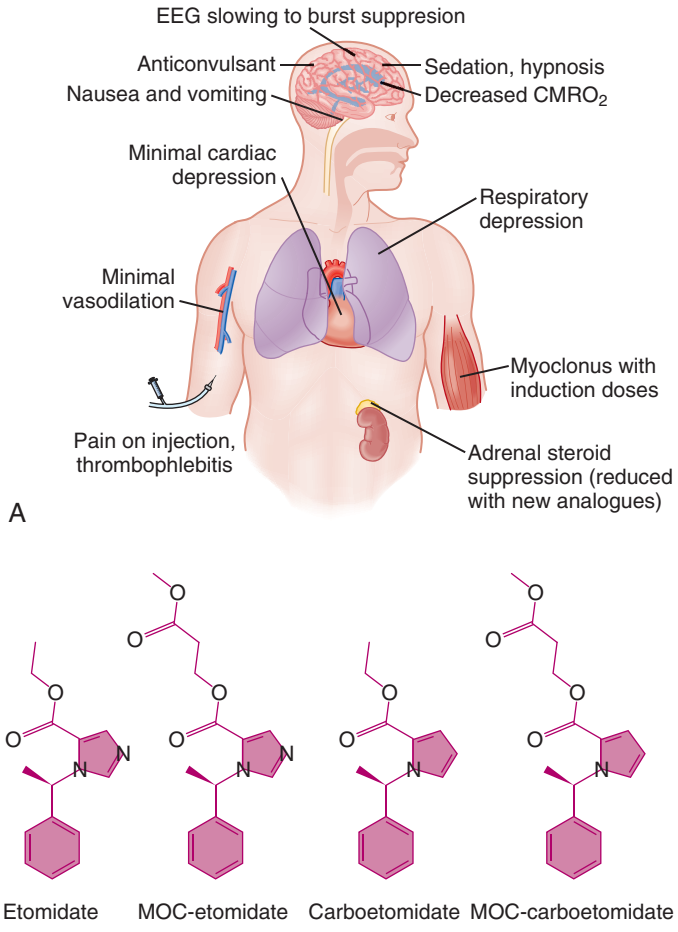
• **Fig. 10.6** A, Selected effects of benzodiazepines. B, Structures of clinically important benzodiazepines, including both the hydrophilic prodrug *(right)* and lipophilic *(left)* conformations of midazolam. Flumazenil is generally considered a benzodiazepine antagonist but has demonstrated some partial agonist effects (see text). *H^+,* Hydrogen ion.

Following intravenous injection, etomidate is tightly bound to plasma proteins such as albumin. The uncharged drug is highly lipophilic so etomidate rapidly penetrates the blood-brain barrier; peak brain levels are achieved within 2 minutes of injection (see Fig. 10.5A). Etomidate is metabolized in the liver by ester hydrolysis to a pharmacologically inactive metabolite.

The effects of etomidate on the CNS are similar to those of propofol and the barbiturates. Induction doses are associated with a high incidence of myoclonus, possibly via a loss of cortical inhibition during the transition from consciousness to unconsciousness. Although this myoclonic activity could be mistaken for generalized tonic-clonic seizures, etomidate has anticonvulsant activity in several experimental models. Epileptic attacks occur less frequently during etomidate anesthesia, but it is likely that propofol and thiopental possess greater anticonvulsant effects; etomidate is therefore a viable option for electroconvulsive therapy.

Etomidate causes less depression of ventilation compared with the barbiturates (see Fig. 10.7).[87,88] Despite its favorable hemodynamic profile, it should be noted that patients with high sympathetic tone such as those with shock, intoxication, or drug withdrawal can have a precipitous drop in blood pressure even when etomidate is used to induce anesthesia.

In 1983, investigators reported increased mortality in ICU patients sedated for days with etomidate.[89] The increased mortality was attributed to suppression of cortisol synthesis since etomidate is a potent inhibitor of the synthetic enzyme 11β-hydroxylase in the adrenal cortex. The original retrospective study has been criticized for failing to control for the severity of illness and for the potential role played by concurrent administration of adjuncts to ICU sedation (e.g., opioids) in those patients. Randomized controlled trials in elective cardiac surgery and critically ill patients verified the adrenal suppression but did not show differences in clinical outcome.[84,90] A large retrospective study of cardiac surgery patients using propensity matching also found no link between etomidate use and increased length of stay or arrhythmia.[91] However, the same group found etomidate carried an odds ratio for death of



• **Fig. 10.7** A, Selected effects of etomidate. B, Structures of etomidate and its analogs. *$CMRO_2$,* Cerebral metabolic rate for oxygen; *EEG,* electroencephalography; *MOC,* methoxycarbonyletomidate.

2.5 in a retrospective, propensity-matched analysis of more than 7000 American Society of Anaesthesiologists (ASA) class III and class IV patients undergoing noncardiac surgery.[92] Another study of nearly 6000 patients (approximately 40% ASA class III and class IV) before and after increased etomidate use in the setting of the 2010 propofol shortage found no such association.[93] Although the most recent metaanalysis reported no statistically significant association between etomidate use and mortality in critically ill patients,[94] new etomidate analogs are currently under development to avoid endocrine disturbance (see "Emerging Developments").

Propofol

Propofol (Fig. 10.8) is the most widely used intravenous agent. While it is most often used for inducing anesthesia, it also is used for procedural/ICU sedation and for total intravenous anesthesia (TIVA). Since its introduction in the late 1980s TIVA use has dramatically increased. Propofol is listed as an essential medicine by the World Health Organization.

Pharmacology

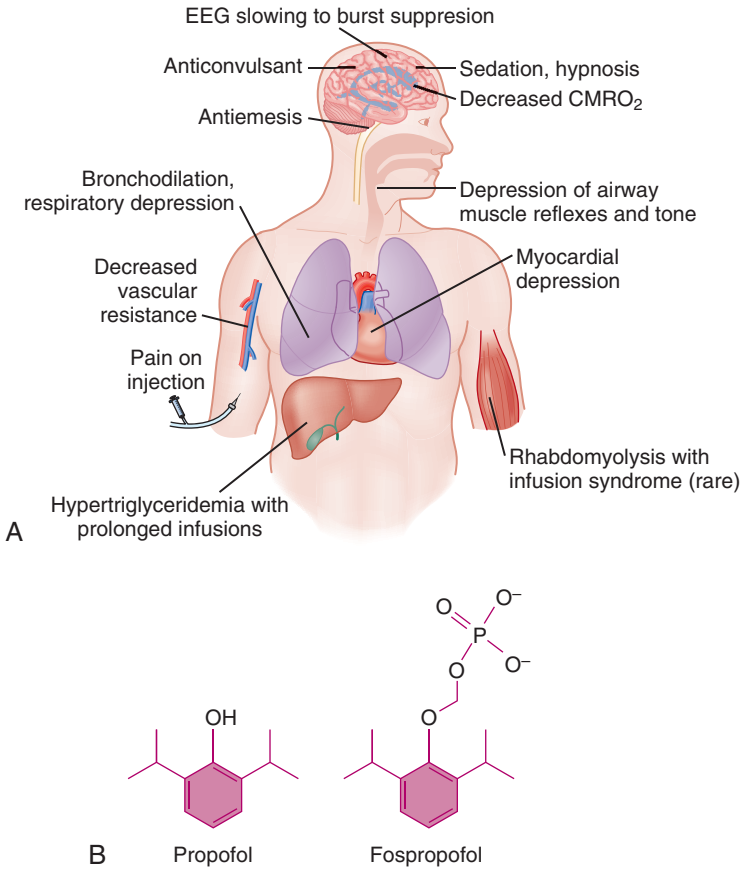
Propofol (2,6, diisopropylphenol) potentiates GABA-mediated responses in neurons and directly activates $GABA_A$ receptor function.[95] Other receptors respond to propofol in the therapeutic concentration range, but the majority of its clinical effects are likely mediated through GABA receptors. The specific interaction between propofol and $GABA_A$ receptors is not fully characterized, but likely involves residues in the transmembrane domains on β subunits.[16] Site-directed mutagenesis studies with recombinant $GABA_A$ receptors have contributed to precise knowledge regarding the molecular interactions between this drug and $GABA_A$ receptors. Initially, only the property of direct activation of the $GABA_A$ receptor by propofol was thought to depend on the β subunit, whereas the modulatory effects were considered to involve other subunits.[96] There is now evidence that α, β, and γ subunits all contribute to $GABA_A$ sensitivity to propofol.[97,98]

Formulation and Preparation

The necessity to formulate propofol in a lipid emulsion (because of its extremely poor water solubility) has some very important clinical implications. The original preparation of propofol used a polyethoxylated castor oil (Cremophor EL) in its formulation, but this mixture was abandoned because of concern for allergic reactions to the excipient.[99] The most commonly available propofol formulations today involve a mixture of soybean oil, glycerol, and purified egg phospholipid to solubilize the drug.[100] Despite initial concerns that the egg-derived lecithin might precipitate anaphylaxis in egg-allergic individuals, it appears that propofol can be safely used in egg-allergic patients.[101] Most egg allergies are related to egg albumin (in egg whites) as opposed to lecithin (primarily in the egg yolk), and a small study revealed no hypersensitivity to propofol in egg-allergic patients undergoing skin prick testing.[102]

Perhaps most important among concerns over the lipid formulation of propofol involves the promotion of rapid microbial growth. This issue received much attention after a high-impact epidemiologic investigation described unusual outbreaks of postoperative infections at seven hospitals.[103] In 2007 the U.S. Food and Drug Administration (FDA) mandated that all propofol emulsions in the United States contain an antimicrobial agent (ethylenediaminetetraacetic acid or sodium metabisulfite).[104,105] The FDA also recommended that, to minimize the potential for bacterial contamination, both the vial and prefilled syringe formulations must be used on only one patient, administration must commence immediately after the vial or syringe has been opened, and administration from a single vial or syringe must be completed within 12 hours of opening.[106] Failing to follow these practices and usual aseptic technique for intravenous administration of medication can lead to transmission of viral particles between patients and bacterial sepsis.[107–110]

Although pain on injection was a contributing factor to changing the initial formulation of propofol, the change to the current isotonic, emulsified, soybean-based formulation has not eliminated pain on injection of propofol. Pain on intravenous injection of any medication has multiple etiologies and can be influenced by the temperature of the drug, the site of administration, the size of the vein, the speed of injection, and the rate of infusion of the carrier fluid. Some common hyperosmolar formulations of diazepam and etomidate also cause pain on injection, and this pain is often reduced with formulations that are closer to blood in osmolarity.[111,112] However, the modern formulation of propofol is not hyperosmolar and has a pH in the physiologic range. It is thought that the pain on injection of propofol is related to its free aqueous concentration, because the pain on injection appears to be less when the propofol concentration is reduced in its current formulation.[111] From a mechanistic perspective, investigations of propofol-induced injection pain has focused on the transient receptor potential



• **Fig. 10.8** A, Selected effects of propofol. B, Structures of propofol and the water-soluble prodrug fospropofol. *$CMRO_2$,* Cerebral metabolic rate for oxygen; *EEG,* electroencephalography.

(TRP) family of ion channels. Multiple investigators have shown a role for TRPA1 as a mediator of propofol-induced pain and TRPV1 has been implicated in some studies but not in others.[113–115] Many strategies to reduce pain have been studied, but a metaanalysis concluded that use of an antecubital vein versus a hand vein and coadministration of lidocaine (either as a pretreatment or mixed with propofol) were most effective.[116] Administration of opioids prior to propofol injection is another important way to mitigate injection pain.

Metabolism, Redistribution, Clearance, and Elimination

The rapid effects of propofol on the brain make it a frequent choice for sedation in monitored anesthesia care settings and for induction and maintenance of general anesthesia. Its rapid metabolic clearance is useful in pediatric procedures like magnetic resonance imaging, in the critical care arena for sedation during mechanical ventilation, and in neuroanesthesia to temporarily reduce cerebral metabolic rate (i.e., burst suppression or isoelectric EEG).

Propofol is metabolized via conjugation into inactive metabolites; however its clearance (total body clearance estimated at 25 mL/kg per minute) exceeds that of hepatic blood flow and continues to some extent even during the anhepatic phase of liver transplantation; this argues for some extrahepatic metabolism of the drug.[117] Like most of the intravenous anesthetics, the offset of the hypnotic effect after bolus administration occurs mainly through redistribution of propofol from the brain to less well-perfused sites. Target plasma concentrations for inducing unconsciousness are 2 to 2.5 μg/mL and for maintenance of anesthesia are 2 to 6 μg/mL. The elimination half-life of propofol is prolonged because of the slow mobilization from adipose tissue. Regardless, obesity should not be considered a contraindication to its use for induction or maintenance.

Obesity does not drastically prolong recovery, and dose adjustments based on lean body weight have been suggested.[118] However, there is some controversy about this as some groups have demonstrated total body weight (TBW) as the best predictor of propofol pharmacokinetics.[119] One of the newest pharmacokinetic models for propofol by Eleveld et al. used TBW and was superior to previous models in obese patients.[120] Another group validated the Eleveld model in an independent group of obese patients and found that the older Schnider and Marsh models performed better when TBW was replaced with adjusted body weight (defined as ideal body weight + 0.4 × [TBW − ideal body weight]).[121]

Moderate hepatic or renal impairment has little effect on the duration of clinical effect. The dose requirement for propofol is reduced in the elderly because of reduced metabolic clearance of drugs and reduced relative volume of the central compartment. Dosing is increased in pediatric populations because relative central compartment volume is larger and clearance and metabolism are increased. Sex differences for the pharmacokinetics[122] and pharmacodynamics[123,124] of propofol have been reported, and men sometimes emerge more slowly from propofol total intravenous anesthesia. The mechanisms underlying this observation may involve sex-linked polymorphisms in liver microsomal enzymes.[122,125,126]

Advantages and Disadvantages of Propofol as an Induction Agent

Propofol has a number of advantages over other intravenous agents for induction. It depresses airway reflexes, reduces nausea, and does not induce adrenocortical suppression.[127] Simulations of bolus kinetics indicate that it is second only to ketamine in speed of onset and offset (see Fig. 10.5A).

The primary disadvantage of propofol is its depressive effect on the cardiovascular system. Patients who are hypovolemic, debilitated, or reliant on high sympathetic tone to maintain blood pressure require careful titration of propofol to avoid severe hypotension. Animal models of severe hemorrhagic shock suggest that the induction dose should be reduced by a stunning 80% to 90% of usual doses if given before fluid resuscitation and decreased 50% if given after resuscitation.[128,129] Use of propofol in patients with cardiac tamponade or critical aortic stenosis can result in hemodynamic collapse.

Mixtures of low-dose ketamine infusions (10–20 μg/kg per minute) with propofol infusions (100–200 μg/kg per minute) have been used to mitigate the cardiovascular effects of both drugs, especially in pediatric anesthesia.[130] A recent metaanalysis of this mixture in the emergency department suggested a reduced rate of respiratory side effects compared with propofol alone.[131] A reduction in induction dose (1–1.5 mg/kg) is recommended for patients older than 65 years of age; however, there is evidence that older patients often receive greater than this recommended dose.[132,133]

Clinical Features of Anesthesia Maintenance With Propofol

Early clinical trials in the late 1980s and early 1990s consistently reported faster time to eye-opening and other recovery criteria for propofol-based TIVA anesthetics compared with "traditional" regimens of thiopental and volatile agents such as enflurane or isoflurane. Until the development of propofol, TIVA for surgeries with planned extubation was rarely performed owing to prolonged emergences. Propofol maintains a short context-sensitive half-time even after prolonged infusion (see Fig. 10.5C). More recent studies comparing propofol-based techniques to newer inhaled agents with lower blood and tissue solubility (desflurane and sevoflurane) have either failed to show benefit or have shown only minimal benefits in speed of recovery, but there are environmental benefits to avoiding the greenhouse gas effects of volatiles.[134,135] The carbon footprint of TIVA is orders of magnitude lower than that of inhaled anesthetic techniques.[135] The updated consensus guidelines for nausea and vomiting recommend propofol-based TIVA as part of a multimodal approach for patients at high risk for nausea and vomiting.[136] In addition to its benefits for patients at high risk for malignant hyperthermia or postoperative nausea and vomiting, propofol appears to confer improved operating conditions for endoscopic sinus surgery and decreased postoperative pain.[137] For example, in gynecologic procedures postoperative pain and opioid administration were reduced in those receiving propofol TIVA.[138] Similar trends were observed in two recent metaanalyses of surgeries of varying types, but more research is needed to determine if this is a clinically meaningful effect.[139,140]

Anesthetic depth is an important consideration when comparing propofol-based TIVA techniques with volatile anesthesia. The concentration of expired anesthetic gases measured by modern anesthesia monitors correlates with the concentration of inhaled agent in the CNS.[141] Because propofol blood concentrations are not easily measured in the operating room, many practitioners choosing TIVA with propofol as their maintenance anesthetic attempt to control for individual variability in drug clearance through the use of an EEG-based depth of anesthesia monitor because it has been shown to decrease anesthetic use and facilitate postoperative recovery.[142] Favorable pharmacokinetic properties and effects on cerebral blood flow (CBF) and cerebral metabolic requirement for oxygen have made propofol popular for neuroanesthesia. In animal studies, reduction of CBF occurs even when mean arterial blood pressure is held constant, and propofol can reduce ICP even when cerebral perfusion pressure is fixed.[143] Cerebral autoregulation also appears to be preserved in the setting of propofol anesthesia.[144] In comparison, the volatile agents tend to increase ICP and at high doses compromise cerebral autoregulation. Although propofol and thiopental have similar effects on brain physiology, propofol might suppress apoptosis in models of ischemia in vitro (see Chapter 9).[145–147]

The latest Society of Critical Care Medicine sedation guidelines recommended the use of propofol when rapid or frequent interruptions of sedation are required, such as serial neurologic evaluations.[73] Awakening times were similar after 24-, 48-, 72-, and 96-hour constant rate infusions of propofol. Prolonged, high-dose infusions can lead to hypertriglyceridemia or a constellation of metabolic acidosis, rhabdomyolysis, renal failure, and hemodynamic instability, known as propofol infusion syndrome. These complications are not common, but patients should be monitored closely for propofol infusions greater than 48 hours. Although moderate-dose infusions (>40 μg/kg per minute) can increase triglyceride levels in critically ill patients after just 3 days, low-dose propofol infusions (<33 μg/kg per minute) showed no detectable increase in triglycerides after 2 weeks of constant infusion.[125]

It is difficult to imagine the practice of anesthesia without propofol. It is also essential outside the operating room in settings such as the ICU, pediatric imaging procedures, and endoscopy suites. Propofol has numerous advantages (see Fig. 10.8), but its depression of respiration makes it potentially dangerous in unskilled hands. Propofol appears to have greater relaxation effects on the pharyngeal musculature than thiopental and should be administered only by persons trained in the rescue of patients who experience deeper-than-intended sedation, including general anesthesia (and who are not involved in the conduct of the procedure).[106,127]

Currently, no widely accepted method is available to anesthesia providers in the United States that allows estimates of blood concentrations of intravenous drugs being infused for maintenance of anesthesia during TIVA. This presents a disadvantage of intravenous anesthetics compared with inhaled anesthetics, which are typically used in conjunction with monitors equipped with gas sampling for measurements of expired concentrations. Using computer-based models of drug pharmacokinetics, mathematical modeling of a drug's disposition can provide a convenient way to estimate these blood concentrations of intravenous agents.[148] Target-controlled infusion devices (e.g., Diprifusor) have been used successfully in maintaining anesthesia for both inpatient and outpatient surgery.[149] Despite obvious advantages of these devices in predicting blood concentrations, some controversy exists in regard to which pharmacokinetic model should be used.[150,151] Another impediment to widespread use of these devices has been the unfamiliarity of providers in targeting an actual blood concentration range, as it is more common to think in terms of infusion rates rather than blood concentrations for infusions of other medications in the hospital.[152] There have been some attempts to improve the adoption of these devices by targeting the calculated index from processed EEG devices used to estimate anesthetic

"depth" rather than targeting a desired blood concentration (see "Emerging Developments").[153]

Fospropofol

Circulating phosphatases metabolize the water-soluble prodrug, fospropofol, into propofol, formaldehyde, and a phosphate group (Fig. 10.12A).[154] It was envisioned during the drug development process that the slower onset of drug effect associated with the metabolism of the propofol prodrug would allow safe bolus administration in the setting of procedural sedation. However, the FDA product labeling ultimately recommended that fospropofol should be administered only by persons trained in general anesthesia as unanticipated transitions to general anesthesia remain a possibility. The formaldehyde levels measured after routine fospropofol administration are indistinguishable from baseline levels.[155] After administration of the drug, formaldehyde is rapidly metabolized to formate. Although high formate levels can lead to metabolic acidosis, there has been no reported formate toxicity from fospropofol. Other supposed advantages from this alternative formulation of propofol are decreased risk of bacteremia and decreased risk of hyperlipidemia. Fospropofol does not bind TRPA1[115] and has less pain on injection, although pruritus and perineal paresthesias are reported side effects of its administration.[156]

Ketamine

Ketamine, an arylcyclohexylamine related to phencyclidine, was developed in the 1960s and approved for use in the United States in 1970. Early test subjects described a sense of disconnection from their environment, leading to the term "dissociative anesthesia."[157] Its combination of hypnosis and analgesia showed great promise as a complete anesthetic with minimal effects on cardiovascular function, respiratory drive, and airway reflexes. Concern over psychologic side effects such as hallucinations and emergence delirium limited its clinical use as a primary anesthetic agent, but there is an increasing body of evidence supporting the use of subanesthetic doses for treatment of acute and chronic pain (see following text).

Ketamine was originally produced as a racemic mixture, and most commercial preparations continue to be a racemic mix of the R and S enantiomers (see Chapter 2). S(+) ketamine, a single-enantiomer formulation available in some areas of Europe and South America, is more potent in most clinical and experimental settings (Fig. 10.9).

Despite more than 40 years of clinical use, the key site or sites of ketamine action have not been fully elucidated. The diverse effects of ketamine are likely mediated by a variety of receptors and signaling pathways. Landmark studies in the 1980s identified ketamine as an NMDA receptor antagonist in the spinal cord and brain.[158,159] Ketamine binds uncompetitively within the ion channel pore in a use-dependent fashion, but there is some evidence for allosteric binding as well.[36,160] Experimental data support a role for NMDA receptors in mediating analgesia, but their role in ketamine anesthesia is unclear.[43,44] Ketamine also inhibits nicotinic acetylcholine receptors at clinically relevant concentrations, which could contribute to analgesia but does not appear to influence its sedative properties.[161] Ketamine has some local anesthetic properties on Na^+ channels and binds μ- and κ-opioid receptors.[162] Although blunted responses to ketamine have been noted in μ-opioid receptor knockout mice, the limited effect of naloxone on ketamine actions in humans suggests a limited role for these receptors. Finally, knockout of the HCN1 receptor in mice abolishes the hypnotic effect of ketamine and propofol but not of etomidate.[53] Further research is needed to confirm the significance of this pathway in humans.

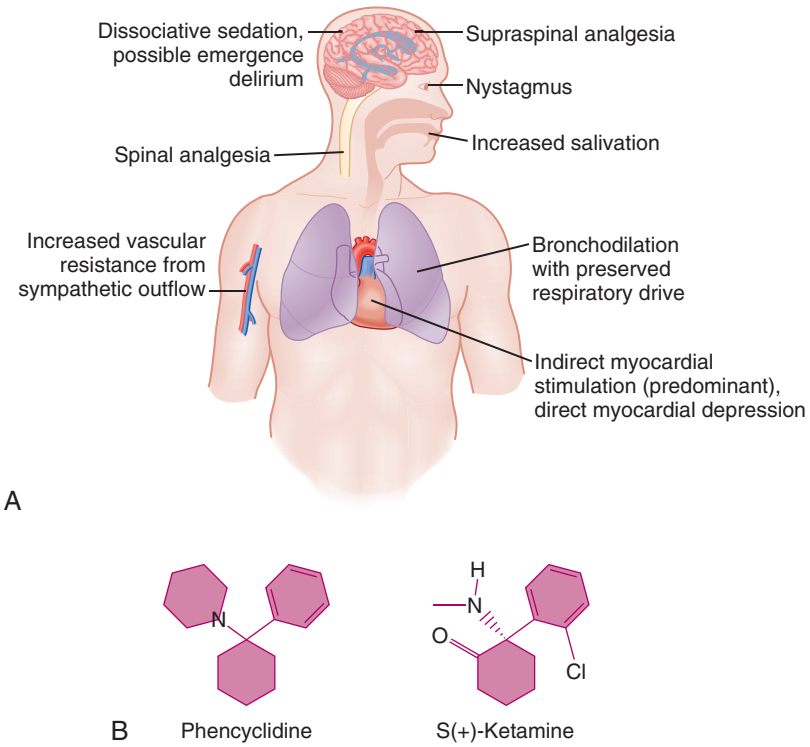
In the brain, ketamine has a unique profile combining depressed consciousness with increased sympathetic tone. This sympathetic activation leads to increases in cardiac output in patients with normal catecholamine stores, which can make ketamine a useful induction agent in patients with hypovolemia. In patients with shock and depleted catecholamine reserves, the inability to mount a sympathetic surge unmasks a direct myocardial depressant effect of ketamine.[163] Respiratory effects of ketamine include bronchodilation, preservation of respiratory drive, and maintenance of respiratory muscle tone.[164,165] It produces direct relaxation of airway smooth muscle ex vivo but may also cause bronchodilation indirectly through the modulation of vagal tone.[166,167] Ketamine has a number of other effects detailed in Fig. 10.9.

Compared with other intravenous anesthetics, ketamine has relatively low plasma protein binding. This, in conjunction with its lipid solubility, allows rapid accumulation in the CNS. Intravenous bolus administration leads to peak effect site concentration within a minute (see Fig. 10.5A). Peak effects for other routes of administration are 10 to 15 minutes for intramuscular injection and 15 to 30 minutes following oral administration. Hepatic cytochrome P450 enzymes (especially CYP 3A4) metabolize ketamine to norketamine by N-methylation in a perfusion-limited manner. Extensive first-pass metabolism leads to less than 20% bioavailability of orally administered ketamine. Norketamine is roughly one-third as potent as ketamine; its contribution to clinical effects appears relatively more significant in settings of long infusions or chronic use.

Concerns over side effects limited ketamine's use in developed nations for many years but recently there has been renewed interest in the drug. Low doses are frequently used to augment regional anesthesia during cesarean sections when the regional block is inadequate. Subanesthetic infusions may decrease postoperative pain in patients using opioids long periods. It can be used for inductions in patients with asthma or hypovolemia; in a randomized controlled trial of acutely ill patients requiring rapid sequence intubation it was as effective as etomidate.[84] Ketamine is sometimes used in critical care in cases of status asthmaticus as an adjunctive bronchodilator, and as an analgesic for dressing changes in the burn ICU.

The role of ketamine in patients with neurologic injury is controversial. Its blockade of NMDA receptors could attenuate excitotoxicity, but animal studies have demonstrated neurotoxic effects on the developing brain.[168] The trade-offs are presently unclear but recent German guidelines have outlined a role for ketamine in brain injured patients whose partial pressure of carbon dioxide in arterial blood is being controlled with mechanical ventilation.[169] The sympathomimetic properties of ketamine allow sedation with preserved or augmented blood pressure to improve cerebral perfusion. Ketamine has traditionally been avoided in neuroanesthesia (see Chapter 9) but that may be changing. Ketamine may confer some antiinflammatory effects and its coadministration has been associated with a reduction in postoperative delirium in high-risk patients.[170]

Ketamine's use as an opioid-sparing adjunct for decreasing postoperative pain has played a key role in its resurgence in modern operating rooms. Although ketamine has analgesic properties of its own, some of the benefits may come from the prevention of opioid-induced hyperalgesia. This effect has been shown for fentanyl[171] and remifentanil and may be mediated by NR2B subunit of NMDA receptors in the spinal cord.[172] A small clinical study



• **Fig. 10.9** A, Selected effects of ketamine. B, Structures of S(+) ketamine and its parent drug phencyclidine. Ketamine is usually supplied as a racemic mixture but the more active S(+) isomer is available in some countries.

reported the dose required to achieve the desired effect in 95% of the population for ketamine to prevent remifentanil-induced hyperalgesia was 0.33 mg/kg.[173] A review of intraoperative single-dose or low-dose infusions reported a 40% decrease in postoperative opioid consumption across numerous studies.[174] It has also been used postoperatively as an opioid adjunct in patient-controlled analgesia. A recent metaanalysis of this indication found that adding ketamine to the opioid decreased pain intensity, opioid consumption, and postoperative nausea and vomiting without a significant increase in hallucinations.[175]

In addition to its use for acute pain, ketamine may have some benefits to patients with chronic pain. In opioid-tolerant patients undergoing back surgery, intraoperative ketamine reduced pain scores and opioid consumption not only in the acute postoperative period, but also 6 weeks after the operation.[45] Post hoc analysis suggested that the greatest benefit was in those patients whose preoperative opioid consumption exceeded the equivalent of 0.55 mg/hr of intravenous morphine. Ketamine has been used in the treatment of complex regional pain syndrome, but a recent systematic review concluded that the current evidence to support its use is of moderate to low quality.[176] There has also been interest in the potential for ketamine to reduce the development of chronic postoperative pain. A metaanalysis suggested some benefit of intravenous ketamine over placebo, but it is likely that a multimodal approach is needed for this issue.[177]

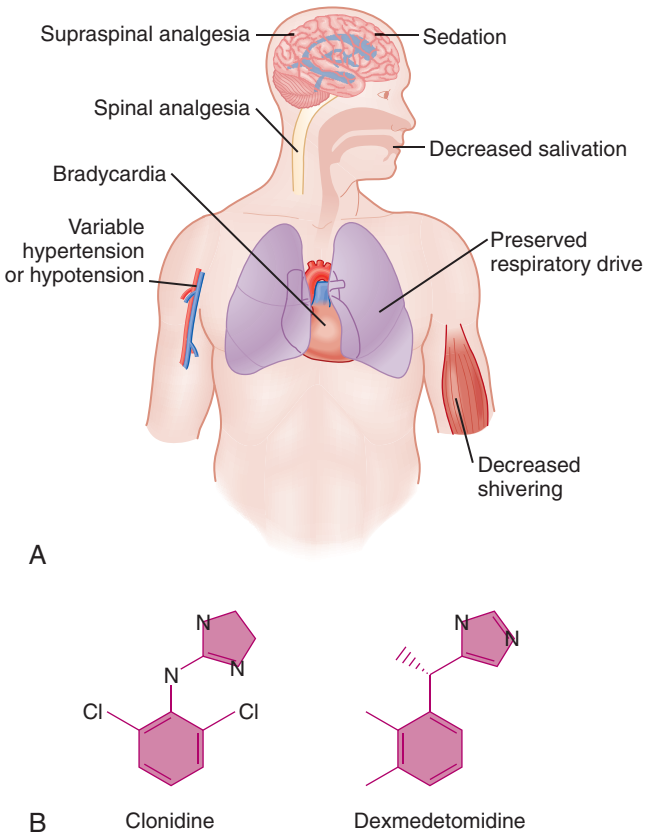
The analgesic properties of ketamine and preservation of respiratory drive are also useful for procedures in which it is critical to maintain spontaneous ventilation and preserve airway reflexes. These cases include patients with large anterior mediastinal masses who may sustain airway collapse if they become apneic or those patients whose airways must be secured while awake. Ketamine increases salivation and airway secretions that can impair visualization during fiberoptic intubation; dexmedetomidine has emerged as an alternative with antisialagogue effects.[178]

Dexmedetomidine

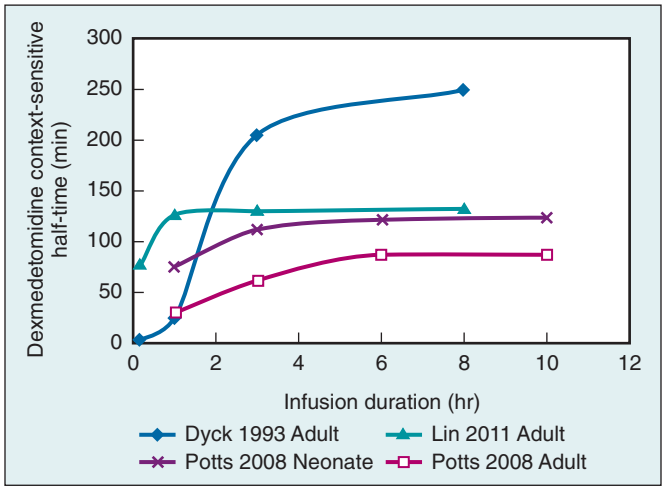
Evidence of analgesic effects of the α-adrenergic agonist clonidine emerged in animal studies in the 1970s and led to the development of agents with greater α_2 specificity. Medetomidine was developed in the 1980s and found to have an α_2/α_1 selectivity ratio of 1620, almost eight times higher than clonidine's ratio. The α-adrenergic effects were mediated exclusively by the d-enantiomer now known as dexmedetomidine (Fig. 10.10).[179] Even at high doses it does not produce general anesthesia but it is a valuable sedative in a number of settings.

Dexmedetomidine has effects both on the spinal cord and in the locus coeruleus. A number of elegant studies in transgenic mice suggest that the α_{2A}-subtype receptor mediates the majority of the analgesic and sedative effects on the CNS.[180] Dexmedetomidine leads to hyperpolarization via influx of potassium ions with a subsequent decrease in neuronal firing as well as reduced norepinephrine release mediated by inhibitory presynaptic autoreceptors. It also decreases cyclic adenosine monophosphate (cAMP) concentration by inhibiting adenylyl cyclase. Many of its effects stem from this decreased sympathetic outflow, but in some cases direct effects on peripheral α_{2B} and α_{2A} receptors predominate and blood pressure increases.[181] This hypertensive response is sometimes seen during loading doses and is the reason that dexmedetomidine should not be administered as a bolus.

The sedation produced by dexmedetomidine is different in that patients tend to be easily arousable. This feature, in combination



• **Fig. 10.10** A, Selected effects of dexmedetomidine. B, Structures of the α_2 agonists clonidine and dexmedetomidine.



• **Fig. 10.11** Context-sensitive half-times of dexmedetomidine reported in adults and neonates based on various pharmacokinetic models. (Modified from Dyck JB, Maze M, Haack C, et al. Computer-controlled infusion of intravenous dexmedetomidine hydrochloride in adult human volunteers. *Anesthesiology*. 1993;78:821–828; Potts AL, Warman GR, Anderson BJ. Dexmedetomidine disposition in children: a population analysis. *Paediatr Anaesth*. 2008;18:722–730; and Lin L, Guo X, Zhang MZ, et al. Pharmacokinetics of dexmedetomidine in Chinese post-surgical intensive care unit patients. *Acta Anaesthesiol Scand*. 2011;55:359–367.)

with its minimal effects on respiratory drive, allows continuation of infusions during weaning from mechanical ventilation and after extubation without the need for dose titration.[182] It has some analgesic qualities and augments the effects of opioids by both spinal and supraspinal mechanisms.[54,183] In contrast to other agents, dexmedetomidine has limited amnestic effect and so should be avoided as a sole agent in patients with neuromuscular blockade. Dexmedetomidine also reduces shivering in an additive fashion with meperidine, raising the possibility that effects of both are mediated by α_2 receptors.[184]

The sympatholytic effects of dexmedetomidine lead to decreased heart rate and blood pressure, which can be helpful, harmful, or of no clinical consequence. In many scenarios these effects are minimal and well tolerated. In patients with cardiac disease there is a potential benefit of decreased myocardial demand in response to painful stimuli, and in some studies this was associated with a mortality benefit.[185] Bradycardia can be dangerous in the setting of heart block and dexmedetomidine should be used with caution in this setting. Significant hypotension is more likely in patients with high sympathetic tone such as patients with diabetes, the elderly, and those with hypovolemia. Selected other effects are shown in Fig. 10.10.

Dexmedetomidine is metabolized in the liver primarily by glucuronidation with a small portion undergoing hydroxylation by CYP 2A6. The distribution half-life is 6 to 8 minutes and its lipophilicity leads to a high volume of distribution. The context-sensitive half-times range from 25 to 120 minutes for a 1-hour infusion to 87 to 250 minutes for infusions greater than 6 hours (Fig. 10.11).[186–188]

Dexmedetomidine sedation is increasingly used in the ICU and is associated with less delirium than benzodiazepine sedation.[189,190] Dexmedetomidine may reduce delirium in part because its sedation closely mimics physiologic sleep in adults and children.[191,192] This concept has been extended to the perioperative period, with a recent trial showing a decrease in postoperative delirium in elderly surgical patients.[193] The ability to extubate patients without weaning dexmedetomidine can facilitate earlier extubation in those patients who become agitated when sedation is held. In the United States, dexmedetomidine is approved for infusions up to 24 hours, but much longer infusions have been reported in the literature. There are case reports of withdrawal phenomena, including agitation, tachycardia, and hypertension, which may be treated with clonidine.[194]

Controversy over the use of propofol by nonanesthesiologists (see "Emerging Developments") has prompted a number of studies of dexmedetomidine as an alternative in sedation practice.[195] A small clinical trial suggested it was comparable to propofol but had longer recovery times; conventional doses up to 1 μg/kg per hour often require supplementation with other drugs. One group reported success of dexmedetomidine as a sole agent in more than 97% of pediatric magnetic resonance imaging scans by escalating the loading dose to 3 μg/kg and the infusion to 2 μg/kg per hour.[196]

Although initially approved by regulatory agencies only for ICU sedation, the clinical applications of dexmedetomidine have continued to expand since dexmedetomidine was approved for monitored anesthesia care sedation in the United States. The antisialagogue effect of dexmedetomidine represents an advantage over ketamine for awake fiberoptic intubations.[178] It has also been administered intranasally for premedication of children and adults.[197,198] The specific and distinctive mechanism of action of dexmedetomidine provides an important alternative amid ongoing uncertainty about short- and long-term cognitive effects of more established anesthetics in both young and old patients.[76]

Emerging Developments

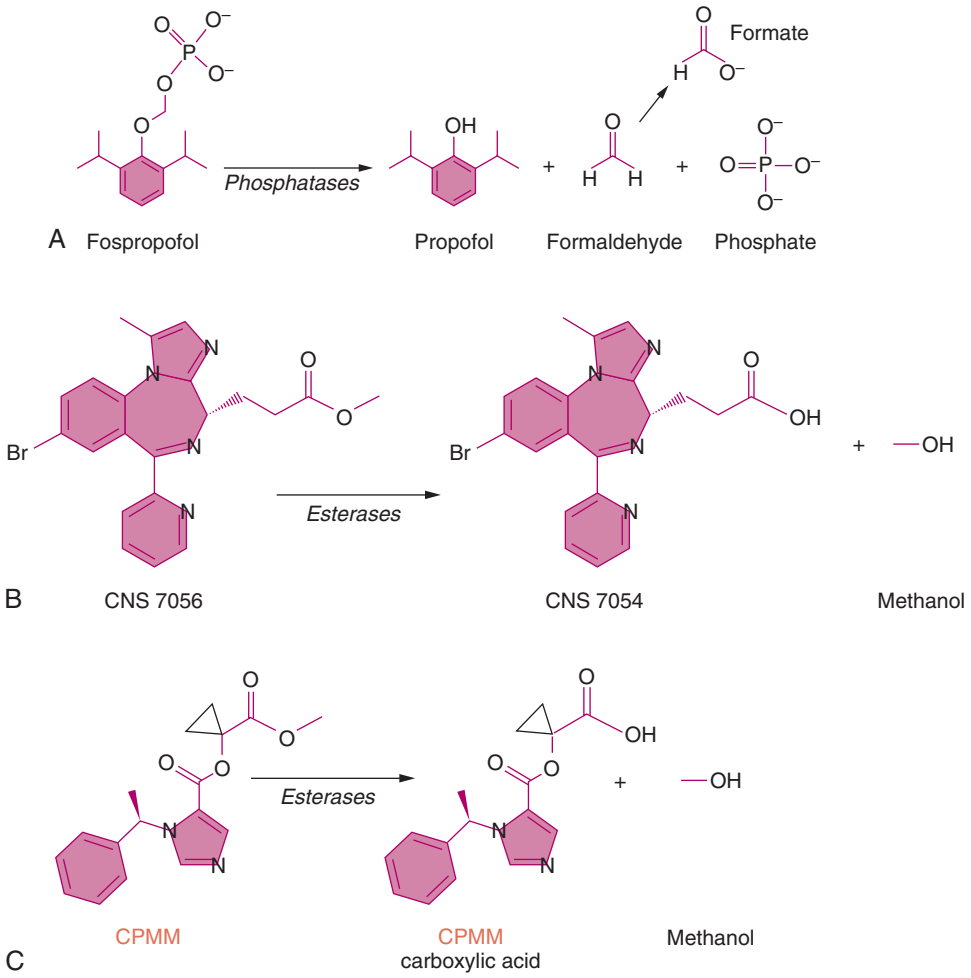
High-Tech Delivery Systems

The development of a computer-aided device that dynamically adjusts anesthetic administration based on measured physiologic parameters has been explored for both inhaled and intravenously administered drugs.[199–201] Commonly referred to as closed-loop anesthesia delivery systems, these devices are typically associated with feedback controls based on predicting depth of hypnosis via EEG analysis or other brain monitor (e.g., auditory evoked potentials).[202] A recent meta-analysis has shown some benefit to closed-loop anesthesia delivery systems over manual infusion rates and open-loop target-controlled infusions, but there is some controversy regarding their economic efficiency and the choice of physiologic parameters to which dosage is titrated.[203] The first FDA-approved device in the United States (Sedasys) was withdrawn by the manufacturer in 2016 for lack of market receptivity (the device performed as designed), but other devices are likely to follow.[204] Controversy surrounding the supervision of these automated devices for use in endoscopic and other office-based procedures will also necessitate discussions regarding the safety of traditional anesthesia drugs in the hands of nonanesthesiologists.

Novel Sedatives

The rapid growth in outpatient and office-based procedures has stimulated the development of several new drugs. Many so-called soft drugs have been designed to mimic the rapid, end-organ independent metabolism of drugs such as remifentanil.[205,206] The benzodiazepine CNS-7056, also known as remimazolam, undergoes ester hydrolysis to form a carboxylic acid metabolite that is 300 times less potent (Fig. 10.12B).[207] It may offer sedation with less postprocedure cognitive effects than midazolam and is now at an advanced stage of clinical development in humans.

A similar strategy has been applied to modify etomidate and reduce its adrenal suppression effects. Investigators have developed an ultrarapid metabolizing etomidate named methoxycarbonyl-etomidate (MOC-etomidate), which is broken down via nonspecific esterases.[208] The in vitro half-life of MOC-etomidate is approximately one-tenth that of its parent compound etomidate. The rapid metabolism of MOC-etomidate into a carboxylic acid metabolite, which has low affinity for 11β-hydroxylase, results in less adrenocortical suppression than its parent compound.[209] This compound, as well as carboetomidate (see Fig. 10.7), a pyrrole analog of etomidate specifically designed not to bind 11β-hydroxylase with



• **Fig. 10.12** Metabolism of next-generation intravenous anesthetics. Fospropofol (A) is a prodrug that is activated by phosphatases.[172] The benzodiazepine remimazolam/CNS-7056 (B) and the etomidate analog cyclopropyl methoxycarbonyl metomidate (C) are rapidly metabolized by esterases to carboxylic acid derivatives with very low activity.[212] *MOC,* Methoxycarbonyletomidate.

high affinity, both maintain the beneficial qualities of etomidate, including rapid induction of general anesthesia with significant hemodynamic stability in animal models.[210] MOC-carboetomidate combines rapid esterase metabolism with the minimal adrenal effects of carboetomidate.[211] Although metabolites of these etomidate analogs may have some sedative effects, it appears that the metabolites of cyclopropyl methoxycarbonyl metomidate (CPMM) (Fig. 10.12C) do not readily accumulate in the CNS.[212] Thus, CPMM emerged as the lead candidate molecule for clinical development among these short acting etomidate analogs. Unfortunately, the CPMM development program was complicated by the appearance of neuroexcitatory phenomenon in animal models and humans which resulted in cancellation of the program. Whether other short acting etomidate analogs related to CPMM will undergo clinical development is unclear. In terms of mechanism, all of these etomidate analogs modulate current through the $GABA_A$ receptor, like their parent compound.[213]

Recently ketamine analogs have been modified for ultrarapid metabolism.[214,215] These analogs appear to mediate a similar dissociative anesthesia appropriate for surgery in animal models.[215,216] The intent is that some of the negative psychological side effects can be mitigated with rapidly decreasing blood levels.

Reversal of General Anesthesia

Anesthesiologists have several intravenous "antidotes" for certain features of the anesthetized state at their disposal (e.g., neostigmine for neuromuscular blocking agents or naloxone for opioids). Since the arrival of flumazenil, reversal of general anesthesia or sedation has been investigated to facilitate and expedite recovery from benzodiazepine-based procedural sedation or general anesthesia.[217,218] Early studies showed little effect on recovery from enflurane or propofol anesthesia, but concurrent opioid administration may have contaminated the results.[219,220] More recent studies have shown improvements in the quality of recovery, including reduced shivering and expedited recovery endpoints, in unpremedicated patients receiving volatile anesthesia.[221,222] Interestingly, flumazenil may also find a role in reducing postoperative narcotic usage.[223] Although the $GABA_A$ receptor may play a prominent role in emergence and recovery, the partial agonist properties of this drug may make it difficult to study as a pure reversal agent of general anesthesia.[224] Studies investigating the role of dopamine in anesthesia recovery are also promising.[225]

Non-Anesthesia Uses of Intravenous Anesthetics

Intravenous ketamine has been shown to rapidly reverse symptoms of depression even in patients who have failed conventional therapy.[226] Several NMDA blocking drugs are in current human trials for treatment-resistant depression,[227] but preclinical data suggest that ketamine may exert some of its antidepressant effect through activation of AMPA receptors.[228] In addition to therapeutic applications, some intravenous anesthetics are being used for diagnostic purposes. Drug-induced sleep endoscopy has been used to aid in the diagnosis and evaluation of treatment options in obstructive sleep apnea.[229,230] Typically, propofol is given, but other regimens (e.g., dexmedetomidine) have been used. Recently administration of intravenous agents in the sedation range was shown to unmask focal neurologic deficits related to cranial tumors. Propofol and midazolam elicited stroke-like symptoms with greater frequency than dexmedetomidine.[231]

Key Points

- Intravenous anesthetics are used both to induce and maintain general anesthesia in the operating room, for sedation and anxiolysis preoperatively, for procedures outside the operating room, and in the ICU.
- Potentiation of the effect of the inhibitory neurotransmitter GABA at $GABA_A$ receptors is the most important mechanism of action for barbiturates, benzodiazepines, etomidate, and propofol.
- Ongoing molecular studies are dissecting not only the specific binding pockets for intravenous anesthetics but also the receptor subunit combinations that differentially mediate effects such as sedation, anxiolysis, and amnesia.
- Etomidate plays an important role in the induction of anesthesia in patients with significant cardiovascular comorbidities such as congestive heart failure or hemorrhagic shock.
- Propofol-based TIVA has advantages over anesthetic maintenance with volatile anesthetics in some patient populations.
- Ketamine blocks glutamate signaling at NMDA-type glutamate receptors, but its clinical effects are broader and more profound than those of more specific NMDA receptor antagonists.
- Subanesthetic doses of ketamine are useful adjuvants for patients with chronic pain; its combination of low cost, analgesia, and preserved respiratory drive make it an important anesthetic, especially in developing nations.
- Dexmedetomidine is a highly specific α_2-adrenergic receptor agonist that produces sedation with preserved respiratory drive. Dexmedetomidine has seen an increasing role in perioperative and ICU sedation.
- The combination of intravenous anesthetics can be tailored for each patient and procedure to optimize the key aspects of the anesthetic and minimize toxicity.

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Pharmacology of Inhaled Anesthetics

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CHAPTER OUTLINE

Historical Perspective
- Discovery of Inhaled Anesthetics
- Development of Modern Inhaled Anesthetics

Structure-Activity Relationships
- Meyer-Overton Correlation
- Stereoselectivity

Mechanisms of Action
- From Lipid-Based to Protein-Based Mechanisms
- Diversity of Molecular Targets
- Multiple Behavioral Endpoints
- Molecular and Cellular Sites of Action
- Drug Class Effects

Nonanesthetic Effects
- Bronchodilation
- Neuromuscular Effects
- Analgesia and Neuroprotection

Adverse Effects
- Respiratory Depression
- Cardiovascular Depression
- Cardiac Dysrhythmias
- Neurophysiologic Effects
- Immunomodulatory Effects
- Hepatotoxicity
- Nephrotoxicity
- Malignant Hyperthermia
- Postoperative Nausea and Vomiting
- Metabolic Effects

Unique Features of Individual Agents
- Agents With Prominent $GABA_A$ Receptor Activity
  - *Halothane, Enflurane, Methoxyflurane*
  - *Isoflurane*
  - *Sevoflurane*
  - Desflurane
  - *Ether and Chloroform*
- Agents With Prominent NMDA Receptor Activity
  - *Nitrous Oxide*
  - *Xenon*
  - *Cyclopropane*
- Environmental Considerations

Drug Interactions
- Reduction in MAC by Anesthetic Adjuvants
- MAC Additivity
- Synergy With Opioid-Induced Respiratory Depression

Factors Influencing MAC
- Age
- Temperature
- Pharmacogenetic Effects on Potency

Common Clinical Indications and Considerations
- Induction and Maintenance of Anesthesia
- Neuroanesthesia and Neuromonitoring
- Cardiac Anesthesia
- Pediatric Anesthesia
- Obstetric Anesthesia
- Ambulatory Anesthesia
- Thoracic Anesthesia

Emerging Developments
- Developmental Neurotoxicity
- Anesthesia and Neurodegenerative Disease
- Neuroinflammation and Cognitive Dysfunction
- Inhaled Anesthetic Sensitivity: Triple Low
- Anesthetic Preconditioning
- Immunomodulation and Cancer
- Closed-Loop Anesthetic Delivery
- Accelerated Emergence

This chapter focuses on the pharmacology of the inhaled anesthetics, including their mechanisms of action and clinical effects (pharmacodynamics). Related pharmacokinetic principles of inhaled anesthetics are covered in Chapter 3.

Historical Perspective

Discovery of Inhaled Anesthetics

The German physician and botanist Valerius Cordus (1515–1544) described a method for preparing ether by combining sulfuric acid with alcohol, which he called *oleum dulci vitrioli* or "sweet oil of

Abstract

Inhaled anesthetics as single agents provide all of the essential features of general anesthesia, including amnesia, unconsciousness, and immobility. Each of these components results from agent-specific actions on distinct neuronal pathways in the central nervous system. The characteristic immobilizing effect of volatile anesthetics involves a site in the spinal cord. Amnesia and unconsciousness involve incompletely understood supraspinal mechanisms. The precise mechanisms by which inhaled anesthetics alter synaptic transmission have not been fully elucidated despite a number of promising candidate molecular targets. The typical anesthetic binding site is hydrophobic and amphipathic. In contrast to intravenous anesthetics, inhaled anesthetics can act at a number of membrane bound ion channels and receptors at clinically relevant effect-site concentrations. Volatile anesthetics have potentiating effects on inhibitory $GABA_A$ and glycine receptors and K^+ channels, and inhibitory effects on excitatory Na^+ and Ca^{2+} channels. The gaseous anesthetics nitrous oxide and xenon have predominant NMDA-type glutamate receptor blocking effects. Inhaled anesthetics have a diverse range of clinically significant effects on multiple organ systems, both beneficial and potentially adverse. Potentially beneficial effects include organ protection, while adverse effects include respiratory and cardiovascular depression. Inhaled anesthetics have agent-specific pharmacologic, pharmacokinetic, and side-effect profiles that determine their optimal clinical applications based on patient and procedure specific applications. Anesthetic-induced neurotoxicity occurs in animal models at critical periods in early brain development with unclear clinical significance.

Keywords

Meyer-Overton
anesthetic preconditioning
anesthetic neuroprotection
anesthetic neurotoxicity
binding site
ion channel
molecular mechanisms of anesthetic action
postoperative cognitive dysfunction

vitriol." Paracelsus (1493–1541), the father of toxicology, recognized the analgesic properties of ether:

> *[I]n diseases which are treated by allaying the pain, it cures all of the disorders, relieves all of the pains, reduces the fever, and prevents the disagreeable complications of all sicknesses.*[1]

Paracelsus was unknowingly close to the discovery of the anesthetic effects of ether. Two centuries later in the 18th century, despite flammability issues and the lack of appropriate delivery systems, Friedrich Hoffmann of Halle (1660–1742) recommended the introduction of ether into medicine.

In 1772 nitrous oxide (N_2O) was discovered by the English philosopher and chemist Joseph Priestley (1733–1804). He and other scientists such as Joseph Black (1728–1799) and Antoine Lavoisier (1743–1794) identified many other atmospheric gases, including oxygen, hydrogen, and carbon dioxide, pioneering the field of "pneumatic medicine" and elucidating the basic properties of gases. In 1799 Thomas Beddoes (1760–1808) established the Pneumatic Institution for Relieving Diseases by Medical Airs in England. Together with young assistant Humphry Davy (1778–1829), who ultimately became more successful than him, Beddoes experimented with N_2O. Davy performed numerous experiments on himself and discovered both the mood-enhancing effects, leading to the name *laughing gas,* and the analgesic effect of N_2O. Despite these pain-relieving effects and its potential use for surgical procedures, N_2O did not meet expectations as a cure for diseases, and the Pneumatic Institution soon closed.

Decades later Gardner Quincy Colton (1814–1898), a self-proclaimed professor of chemistry, went on tour with his (lucrative) "scientific exhibits" and public demonstrations of N_2O. In 1844 dentist Horace Wells (1815–1848) attended one of Colton's demonstrations of the effects of laughing gas and observed its analgesic effects in a fallen volunteer. The next morning, a fellow dentist removed one of Wells' molars with only little pain while Colton administered N_2O.[2] Wells saw potential in N_2O and scheduled a demonstration at Harvard Medical School in 1845 with help of his assistant William T.G. Morton (1819–1868). During the demonstration the patient cried out and moaned, probably owing to failure of continuous delivery of the gas, an incident that discredited N_2O as an anesthetic. Wells later committed suicide.

Morton was searching for another suitable substance to relieve pain during tooth extractions. He met Charles T. Jackson (1805–1880), a Harvard professor in chemistry who introduced him to ether. Morton's experiments on himself and on his pet animals were promising, and in September 1846 he performed a painless tooth extraction. This caught the attention of Harvard surgeon Henry J. Bigelow (1818–1890), who helped schedule a successful public demonstration at Massachusetts General Hospital on October 16, 1846, which is considered by many the beginning of the era of anesthesia. Morton did not reveal the identity of the substance he called *Letheon,* which was ether he masked with additional fragrances and colors. Most likely he saw a potential for profit and unsuccessfully attempted to patent Letheon. Under pressure from the hospital, Morton revealed the identity of the main ingredient ether, and after further procedures with ether followed, Bigelow published the results of ether as a suitable agent for use in surgical procedures.[3] The term *anesthesia* is derived from Greek *αn-* "without" and *aisthētikos* "perception" or "sensation."

Controversy regarding who first discovered anesthesia arose with contenders including Wells, Jackson, and especially Crawford W. Long (1815–1878), a physician in rural Georgia who had used ether anesthesia since 1842 but did not publish his work until after Bigelow's report.[4] Morton with his perseverance is generally credited with the discovery of anesthesia, although there are regional sentiments favoring Wells or Long. The use of both ether and N_2O was quickly adopted by many institutions, revolutionizing surgery and defining the field of anesthesia.

The science of anesthesia began with the introduction and development of chloroform as an anesthetic by John Snow (1813–1858) in England.[5] He conducted experiments on the physical and pharmacologic properties of chloroform and other inhaled anesthetics, developed methods for their administration by introducing the chloroform inhaler, studied their side effects and complications, and developed specific clinical applications. His work established the scientific basis of anesthesia by determining the relationships between anesthetic solubility, vapor pressure, and potency. He also described five stages of etherization in response to increasing doses, presaging Guedel's description, and the first dose-response relationship for an anesthetic. These are among the seminal foundation studies of inhalational anesthesia.[6]

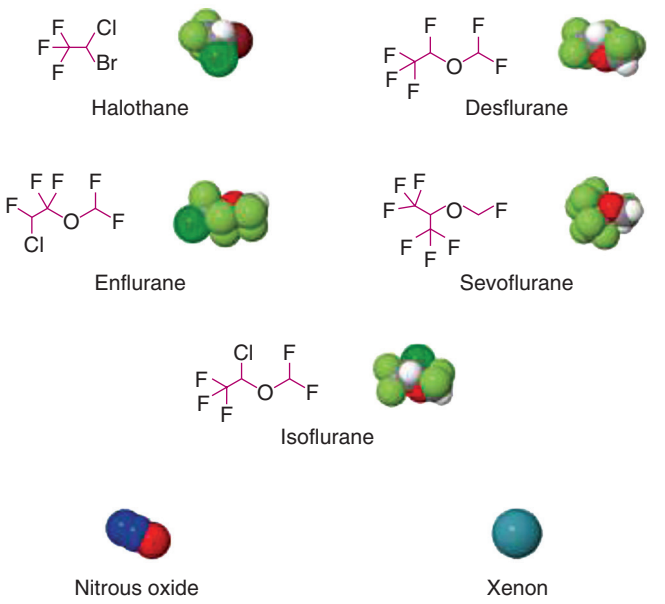
Development of Modern Inhaled Anesthetics

The development of the modern potent inhaled anesthetics was facilitated by developments in fluoride chemistry that accelerated with the atomic weapons program in the mid-20th century. This allowed the synthesis and testing of many fluorinated alkane and ether compounds that were safer and less combustible than ether or cyclopropane. Robbins demonstrated the potential of fluorinated hydrocarbons as nonflammable inhaled anesthetics with greater therapeutic ratios than ether or chloroform.[7] This work led to the synthesis and testing of the polyhalogenated alkane halothane, which showed outstanding anesthetic properties in animals and humans.[8] This was followed by the pioneering work of Ross Terrell (1925–2010) and colleagues who synthesized and evaluated more than 700 fluorinated compounds that included the essential agents of the past 40 years of modern inhalational anesthesia, the fluorinated methyl ethyl ethers: enflurane, isoflurane, sevoflurane, and desflurane (Fig. 11.1).[9]

Structure-Activity Relationships

Meyer-Overton Correlation

At the beginning of the 20th century, Meyer and Overton independently observed that the potency of volatile anesthetics for sedating tadpoles is closely correlated with their solubility in olive oil (Fig. 11.2A). Subsequent investigations confirmed that for a majority of anesthetic agents potency is proportional to lipid solubility as measured by the oil-gas partition coefficient. Remarkably, this correlation holds across multiple animal phyla from invertebrates to humans and spans over five orders of magnitude in potency. Another way of stating this correlation is that the product of the oil-gas partition coefficient and anesthetic potency defined as minimum alveolar concentration (MAC; see Chapter 3) is constant between anesthetics. This implies that at MAC the concentration of inhaled anesthetic molecules in the hydrophobic phase is approximately 50 mM. This observation formed the basis for a unitary hypothesis that argued that the mechanism of action of inhaled anesthetics was derived from their effects on bulk lipid membrane properties. A more modern, mechanistic form of the lipid-based hypothesis suggests that anesthetic-induced changes in the bilayer lateral pressure profile of lipids in the vicinity of membrane proteins alter their functional properties.[10,11]

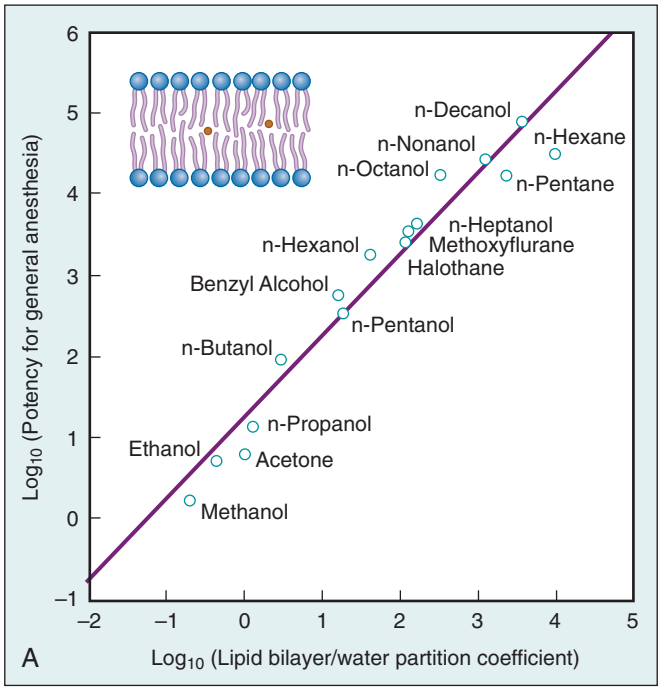


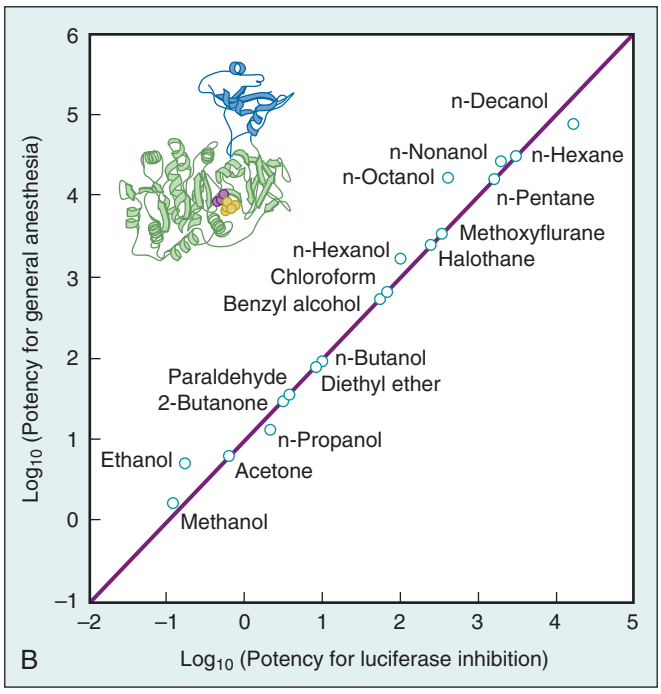
• **Fig. 11.1** Structure of representative inhaled anesthetics shown as two-dimensional and space-filling models. Note the similarities among the modern methyl ethyl ethers, in particular desflurane and isoflurane, which differ by a single substitution.

Despite its central position in mechanistic theories of anesthesia, the Meyer-Overton correlation had limitations. Although Meyer and Overton both used olive oil as their reference solvent, similar correlations have been obtained using other hydrophobic solvents that are more hydrophobic than olive oil, such as benzene, which do not produce as strong a correlation as olive oil. The amphipathic (having both hydrophobic and hydrophilic qualities) solvents methanol, octanol, and lecithin produce even better correlations than olive oil, correctly predicting that enflurane is less potent than isoflurane. However, lipid solubility alone does not predict anesthetic potency in that a number of chemically similar compounds with lipid solubilities comparable to known anesthetics lack anesthetizing capacity themselves. These so-called nonimmobilizers have been useful experimentally as a negative test in evaluating potential anesthetic targets.[12] Although the Meyer-Overton correlation does constrain the possible mechanisms of action of anesthetics (the site at which anesthetics bind must be hydrophobic, and likely amphipathic), in practice this is not a particularly restrictive constraint on possible anesthetic binding sites because lipid bilayers, membrane proteins, and most water-soluble proteins have amphipathic domains. Functional studies indicate that volatile anesthetics do not alter bulk lipid bilayer properties at clinically relevant concentrations that do modify ion channel function.[13,13a]

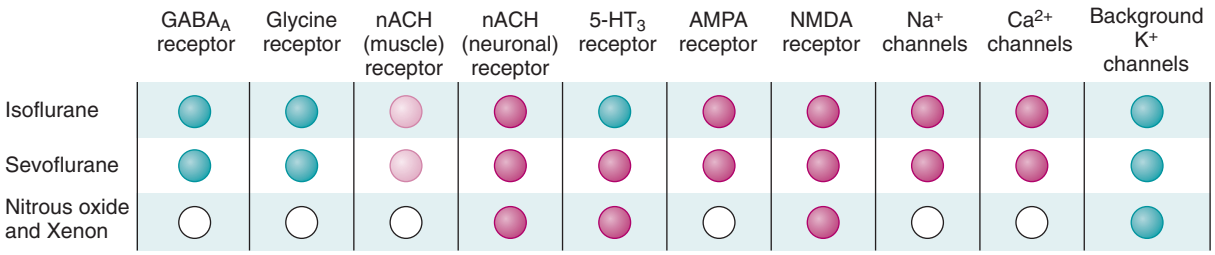
Stereoselectivity

Isoflurane, enflurane, halothane, and desflurane all have a chiral carbon atom, and thus they exist as racemic mixtures of enantiomeric pairs that are mirror images of each other, but with identical physical and chemical properties other than their ability to polarize light in opposite directions (see Chapter 1). While they are synthesized as racemic mixtures, separation of the enantiomers of isoflurane and halothane by gas chromatography allowed testing of the





• **Fig. 11.2** General anesthetics act by binding directly to proteins. A, The Meyer-Overton correlation (c. 1900) suggested that lipids were the principal target for anesthetics based on the correlation between anesthetic potency and lipid-water partition coefficients. B, General anesthetic potencies correlate equally well with their potency for inhibition of the soluble enzyme firefly luciferase. The crystal structure of luciferase is shown in the inset. (Reprinted with permission from Macmillan Publishers Ltd. *Nature* copyright 2007. Franks NP. Molecular targets underlying general anaesthesia. *Br J Pharmacol*. 2006;147[suppl 1]:S72–S81.)



• **Fig. 11.3** Ligand-gated and voltage-gated ion channels are thought to be among the most relevant targets for general anesthetics. The activities of representative inhaled anesthetics on these targets in vitro are summarized. A *dark green* or *pink spot* indicates significant potentiation or inhibition, respectively, by the anesthetic at clinically relevant concentrations; a *light pink* spot indicates some inhibition, and an *empty spot* indicates no effect at clinically relevant concentrations. This summary represents a synthesis of major effects, but important differences exist between various receptor and channel isoforms (not indicated here). *AMPA,* α-Amino acid-3-hydroxy-5-methyl-4-isoxazole; *CA^{2+},* calcium ion; *GABA,* gamma-aminobutyric acid; *K^+,* potassium ion; *nACh,* nicotinic acetylcholine; NMDA, N-methyl-D-aspartate; *Na^+,* sodium ion. (Modified from Rudolph U, Antkowiak B. Molecular and neuronal substrates for general anaesthetics. *Nat Rev Neurosci*. 2004;5:709–720.)

anesthetic properties of the individual enantiomers, which have identical lipid solubilities. Rats are about 1.5-fold more sensitive to the (+)enantiomer than the (–)enantiomer of isoflurane, while its lipid perturbing effects are equivalent (nonstereoselective).[14,15] A number of putative targets (see later text), including gamma-aminobutyric acid $(GABA)_A$ receptors and N-methyl-D-aspartate (NMDA) receptors, have demonstrated stereoselectivity in vitro, although not to the degree seen in vivo.[16,17] Interestingly, L-type calcium ion (Ca^{2+}) channels (which partially mediate the cardiodepressive effects of volatile agents) do not demonstrate stereoselectivity in vitro, suggesting that the more potent enantiomer should have an increased therapeutic ratio (reduced cardiovascular depression) compared with the racemic mixture.[18] Importantly, the stereoselectivity of anesthetic potency indicates that lipid solubility alone does not determine anesthetic potency.

Mechanisms of Action

From Lipid-Based to Protein-Based Mechanisms

The chemical diversity of the agents that can be used as general anesthetics historically favored a unitary mechanism to explain anesthesia. The Meyer-Overton correlation suggested that the effect sites of anesthetics were lipophilic or amphipathic. As a result, initial concepts of general anesthetic mechanisms favored effects on the bulk properties of lipid membranes, which allowed for the vast chemical diversity of agents found to produce an anesthetic state (see earlier text). However, no verifiable hypothesis of a lipid-based mechanism, which usually invoked effects on lipid membrane properties (e.g., bilayer fluidity, thickness, curvature, permeability), was developed. Moreover, comparable effects on membrane biophysical properties could be achieved by small changes in temperature that do not cause anesthesia. Subsequently, the nonimmobilizers were found to violate the basic Meyer-Overton correlation between potency and lipophilicity.[12] The improved correlation between anesthetic potency and solubility in amphipathic rather than purely hydrophobic solvents is consistent with a protein-based mechanism, or perhaps a lipid bilayer with phospholipoproteins. The proof of concept for a protein as an anesthetic target was provided by Ueda and extended unambiguously by Franks and Lieb who reported that the bioluminescent function of the protein luciferase was inhibited by a large range of anesthetic molecules with potencies predicted by the Meyer-Overton correlation (see Fig. 11.2B).[19,20] This concept was strengthened by demonstration of stereoselective anesthetic effects, which imply specific anesthetic chiral binding sites.[21]

Diversity of Molecular Targets

Anesthesia is a composite pharmacologic endpoint that is commonly defined as reversible amnesia, loss of consciousness, and immobility. It is not surprising then that these diverse effects result from multiple mechanisms, and that the relative potency and efficacy of various general anesthetics in producing each of these endpoints vary between specific anesthetics (Fig. 11.3). The prevailing view is that inhaled anesthetics have multiple, agent-specific effects on a number of molecular targets critical to neuronal communication and excitability, as summarized in Table 11.1.[22,23] These multiple actions work in concert or individually to produce the pleiotropic effects characteristic of inhaled anesthetics.[24]

Criteria for identifying the molecular targets of inhaled anesthetics are shown in Table 11.2. Volatile anesthetics at clinically relevant concentrations positively modulate inhibitory $GABA_A$ receptors and inhibitory glycine receptors, inhibit excitatory NMDA-type glutamate receptors and neuronal nicotinic acetylcholine receptors (nAChRs), activate certain two-pore domain potassium (K_{2P}) and leak potassium ion (K^+) channels, and inhibit multiple voltage-gated sodium ion (Na^+) channel (Na_v) and Ca^{2+} channel (Ca_v) subtypes. The gaseous inhaled anesthetics (cyclopropane, N_2O, xenon) at clinically relevant concentrations do not affect $GABA_A$ receptors but block NMDA receptors and activate K_{2P} channels.[25,26]

Putative anesthetic targets are not distributed evenly throughout the nervous system. For example, multiple subtypes of $GABA_A$ receptors exist, each with its own expression profiles at the regional, cellular, and subcellular levels. Specific receptor isoforms appear to mediate various anesthetic endpoints, as shown for certain intravenous anesthetics (see Chapter 9).

Multiple Behavioral Endpoints

Anesthesia is a drug-induced comatose state with multiple behavioral components, including the essential triad of unconsciousness,

TABLE 11.1 Overview of Putative Sites of Inhaled Anesthetic Action

Level	Site	Effect	Target(s)
Proteins	Amphipathic binding sites	Conformational flexibility, ligand binding	Ion channels, receptors, signaling proteins
Action potential	Nervous system	Small reduction in amplitude	Na^+ channels
	Cardiovascular system	Reduced amplitude, duration	Ca^{2+} channels, K^+ channels
Synaptic transmission			
Inhibitory	Presynaptic terminal	Enhanced transmitter release	
	Postsynaptic receptors	Enhanced transmitter effects	Glycine, $GABA_A$ receptors
Excitatory	Presynaptic terminal	Reduced transmitter release	Na^+ channels, Ca^{2+} channels, K_{2P} channels
	Postsynaptic receptors	Reduced transmitter effects	NMDA receptors, nicotinic acetylcholine receptors
Neuronal networks	Neuronal circuit	Altered long-term potentiation/ depression	Synaptic plasticity
	Neuronal integration	Altered rhythmicity, coherence	HCN channels, K_{2P} channels, extrasynaptic $GABA_A$ receptors, and so on
Central nervous system	Neocortex, hippocampus, amygdala	Sedation, amnesia	θ rhythms, γ rhythms, synchrony
	Diencephalon (thalamus), brainstem (reticular formation)	Unconsciousness	γ-band transfer entropy? Thalamic deafferentation?
	Spinal cord	Immobility	Nocifensive reflex
Cardiovascular system	Heart		
	Myocardium	Negative inotropy	Excitation-contraction coupling
	Conduction system	Dysrhythmias	Cardiac action potential
	Vasculature	Vasodilation	Direct and indirect vasoregulation
Pulmonary system	Vasculature	Vasodilation, reduced	Direct and indirect vasoregulation
	Bronchioles	Bronchodilation	Direct and indirect bronchiolar smooth muscle tone

Ca^{2+}, Calcium ion; *GABA*, gamma aminobutyric acid; *HCN*, hyperpolarization-activated cyclic nucleotide-gated; *K^+*, potassium ion; *K_{2P}* two-pore domain potassium; *Na^+*, sodium ion.
Modified from Perouansky M, Pearce RA, Hemmings Jr HC. Inhaled anesthetic agents: mechanisms of action. In: Miller RD, ed. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone Elsevier; 2010:515–538.

TABLE 11.2 Criteria for Identifying Molecular Targets of Anesthetic Action

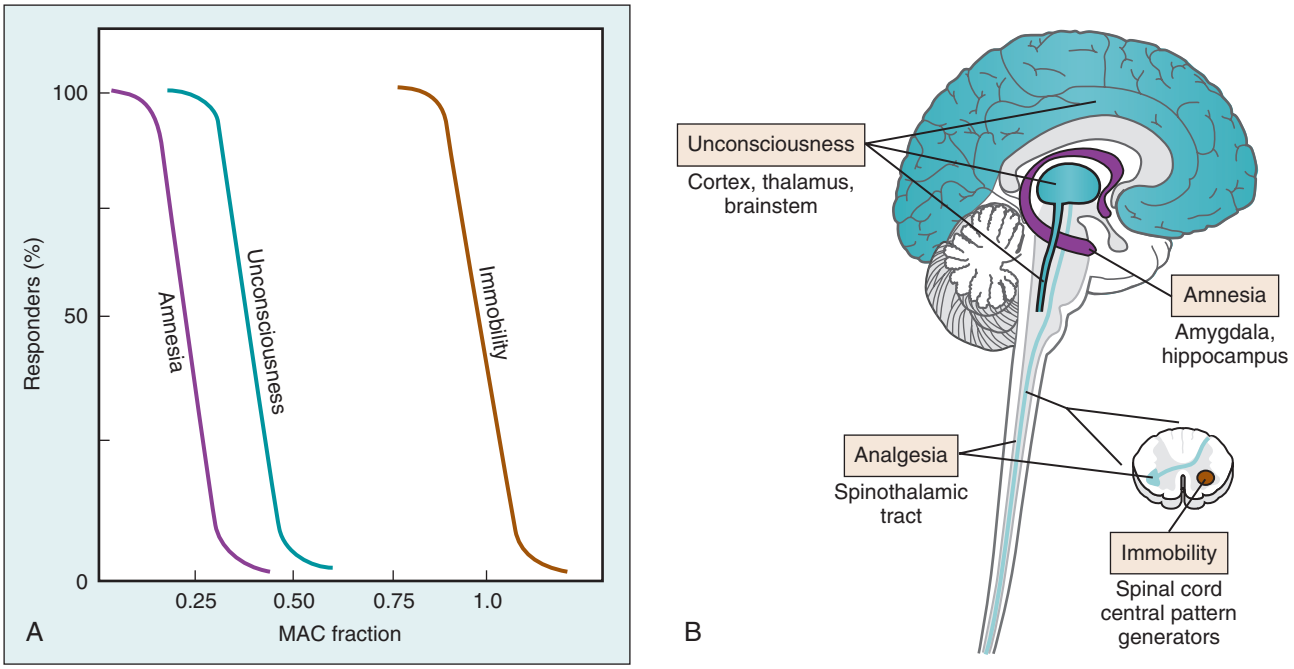
The anesthetic reversibly and directly alters target function at clinically relevant concentrations (sensitivity).
The target is expressed in appropriate anatomic locations to mediate the specific behavioral effects of the anesthetic (plausibility).
Stereoselective effects of the anesthetic or nonimmobilizer in vivo parallel effects on the target in vitro.
Pharmacologic or genetic disruption of the anesthetic sensitivity of the target abolishes the effect of the anesthetic on the relevant endpoint.

amnesia, and immobility; in some cases analgesia and autonomic stability occur, but these endpoints are not universal.[27] These effects are dose-related: amnesia at low doses is followed by sedation, unconsciousness, and eventually immobility (Fig. 11.4A). Current evidence favors the hypothesis that the multiple behavioral endpoints of anesthesia result from multiple distinct molecular targets and distinct anatomic sites of action (see Fig. 11.4B). Unconsciousness is likely due to enhanced inhibition at multiple sites in the cerebral cortex, thalamus, and brainstem involved in arousal. Although the neuronal correlates of consciousness remain unclear, it has been proposed that anything that sufficiently perturbs activity in thalamocortical loops, and hence long-range cortical connectivity, could disorder consciousness.[28] Moreover, individual lesions to brainstem arousal areas and intralaminar thalamus result in transient coma, suggesting that pharmacologic inhibition of these areas is also likely to induce a state of unarousable unresponsiveness.[29]

Amnesia is likely due to altered neurotransmission in the frontal cortex, hippocampus, and amygdala critical to memory acquisition and storage. Immobility is due to effects on spinal cord networks, likely through suppression of central pattern generators critical to coordinated movement.[30,31] Analgesia is likely due to disruption of spinothalamic tract transmission and possible effects on peripheral nociception. A shortcoming of the volatile anesthetics is their poor control of the autonomic nervous system response to painful stimuli. In the modern era, inhalation anesthesia is routinely supplemented with opioids to achieve optimal anesthetic conditions.[32]

Molecular and Cellular Sites of Action

Because of the ability to precisely define and monitor immobilization, this anesthetic endpoint has been investigated more completely



• **Fig. 11.4** Multiple sites of volatile anesthetic action. A, Volatile anesthetics lead to multiple dose-dependent behavioral endpoints. Cardiovascular responses occur at even greater doses (not shown). B, Amnesia, the most sensitive anesthetic endpoint, probably involves the hippocampus, amygdala, medio-temporal lobe, and possibly other cortical structures involved in learning and memory. Unconsciousness likely involves the cerebral cortex, thalamus, and brainstem reticular formation essential to consciousness and arousal. Immobility occurs by anesthetic action on the spinal cord central pattern generators. Anesthetic effects on the spinal cord blunts ascending impulses arising from noxious stimulation, leading to analgesia, and might indirectly contribute to anesthetic-induced unconsciousness.

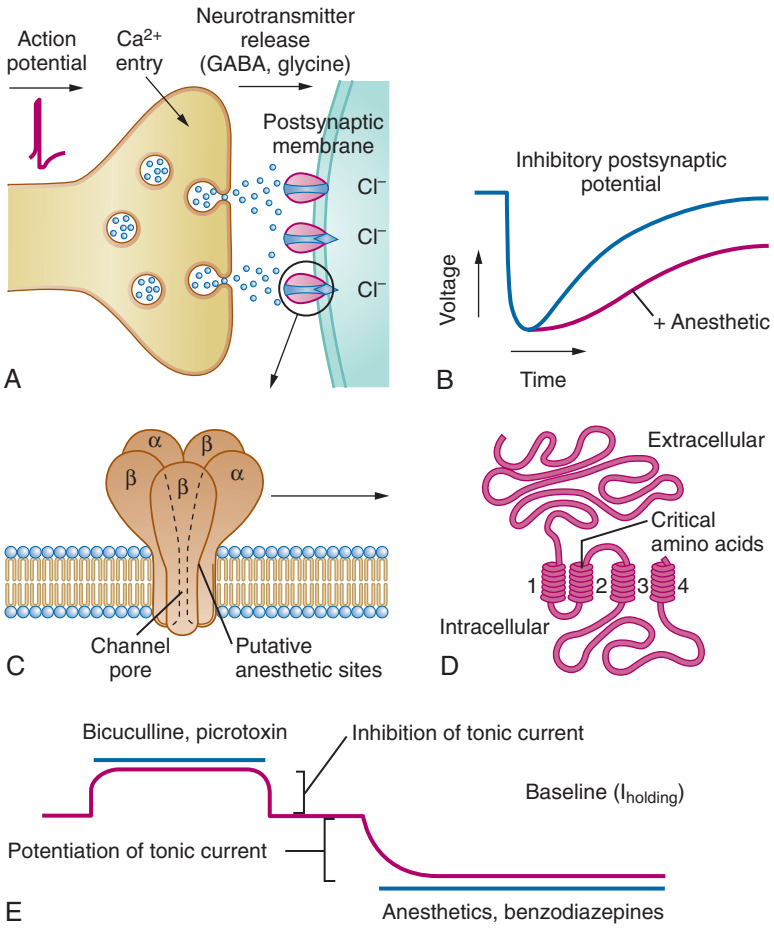
than amnesia and unconsciousness. Inhaled anesthetics produce immobilization at increasing doses primarily via effects on the spinal cord. A series of elegant experiments in vivo showed that the potency of volatile anesthetics for immobilization was determined by effects on the spinal cord.[30,31] Volatile anesthetic immobility does not appear to be mediated by $GABA_A$ receptor effects. Thus the $GABA_A$ receptor antagonist bicuculline does not antagonize the immobility induced by isoflurane.[33] This is in contrast to the intravenous anesthetics propofol and etomidate, whose immobilizing effects are mediated primarily by $GABA_A$ receptors, as evident in their effective antagonism by bicuculline (see Chapter 10). In contrast, mice harboring mutations that reduce sensitivity of $GABA_A$ receptor α_1 or β_3 subunits to volatile anesthetics exhibit only slight resistance to the immobilizing and hypnotic effects of volatile anesthetics, whereas analogous mutations that greatly reduce the effects of propofol or etomidate on the β_3 $GABA_A$ receptor subunit essentially abolish their hypnotic and immobilizing effects.[34,35] This indicates that other targets likely play a more important role in these volatile anesthetic actions.

The amnestic effect of volatile anesthetics, like that of the intravenous anesthetics, probably involves potentiation of specific $GABA_A$ receptor subtypes (Fig. 11.5). For example, amnesia during anesthesia has been attributed to enhanced activation of α_5-subunit–containing $GABA_A$ receptors, which are known to regulate hippocampal-dependent synaptic plasticity and short-term memory.[36] Long-term potentiation (LTP), a cellular model of hippocampal memory, is suppressed by isoflurane, an effect that is reversed by the $GABA_A$ receptor antagonist bicuculline.[37] The finding that both β_3- and α_4-subunit knockout mice are resistant to the amnestic effects of isoflurane indicates a role for $GABA_A$ receptors containing these subunits in the amnestic action of volatile anesthetics.[38,39]

Glycine receptors, members of the ligand-gated ion channel superfamily that are closely related to $GABA_A$ receptors both structurally and functionally, are likewise potentiated by volatile anesthetics (see Fig. 11.5). Their high level of expression in the spinal cord makes glycine receptors putative targets for the immobilizing effects of anesthetics. Partial antagonism of the immobilizing effect of isoflurane by the glycine receptor antagonist strychnine provides pharmacologic evidence supporting a contribution to this anesthetic endpoint.[40]

Neuronal nAChRs are, like $GABA_A$ and glycine receptors, pentameric cys-loop ligand-gated ion channels, but in contrast they are cation-selective excitatory channels (rather than anion-selective inhibitory channels) and are inhibited (rather than potentiated) by volatile anesthetics. Mecamylamine (an antagonist of nAChRs) does not affect MAC for several inhaled anesthetics, suggesting that nAChRs do not contribute to inhaled anesthetic immobility.[41,42] However, they might contribute to the amnestic and hyperalgesic effects of very low doses of volatile anesthetics. This is consistent with the roles of nAChRs in learning and memory in that isoflurane and nonimmobilizers, both of which produce amnesia, block nAChRs.[43,44]

Voltage-gated Na^+ channels are integral to all facets of central nervous system (CNS) function and thus are well positioned to mediate multiple aspects of general anesthesia. Clinical



• **Fig. 11.5** Effects of volatile anesthetics on inhibitory synaptic transmission. A, On binding of released gamma aminobutyric acid *(GABA)* or glycine *(blue dots)* to the pentameric $GABA_A$ or glycine receptor complexes, chloride *(Cl^-)* flows into the postsynaptic neuron, leading to hyperpolarization. B, Volatile anesthetics prolong channel opening and increase postsynaptic inhibition. C, A pentameric $GABA_A$ receptor complex in the lipid bilayer membrane showing the likely binding sites in the transmembrane domains and the chloride conducting ion channel pore. D, Membrane topology of a single receptor subunit showing the extracellular domain that forms the ligand binding site, and the four transmembrane domains, including the critical amino acid residues in transmembrane domain 2 that potentially contribute to the anesthetic binding site. E, Synaptic $GABA_A$ receptors have a low potency and a high efficacy, whereas extrasynaptic $GABA_A$ receptors have a high potency and a low efficacy for GABA and contribute to tonic inhibitory currents in response to low ambient extrasynaptic GABA. Extrasynaptic $GABA_A$ receptors usually contain the δ subunit, have increased sensitivity to anesthetics, and might be important targets for general anesthetics. The role of the tonic current is demonstrated schematically in the depolarization in response to the $GABA_A$ receptor inhibitors bicuculline and picrotoxin, and the hyperpolarization in response to anesthetics and benzodiazepines. *Ca^{2+},* calcium ion.

concentrations of volatile anesthetics inhibit Na^+ channels in isolated rat nerve terminals and neurons. Although not as sensitive to volatile anesthetics as cys-loop ligand-gated ion channels, Na^+ channels are inhibited in vitro in a clinical concentration range.[23,45] Moreover, reductions in neurotransmitter release from presynaptic terminals by volatile anesthetics involve inhibition of presynaptic action potentials through Na^+ channel blockade.[46,47] The presynaptic effects of isoflurane are selective for inhibition of release of the excitatory transmitter glutamate over the inhibitor transmitter GABA, consistent with their neurodepressive actions.[48,49] Intrathecal administration of the specific Na^+ channel blocker tetrodotoxin reduces MAC in rats, whereas the activator veratridine increases MAC, supporting a role for Na^+ channel block in immobility produced by isoflurane.[50,51] Voltage-gated Ca^{2+} channels, which are structurally homologous to Na^+ channels, have also been implicated as targets for volatile anesthetics,[52–54] and for isoflurane-induced immobility in particular.[55] These channels mediate Ca^{2+} entry in excitable tissues and are critical to many anesthetic-sensitive functions such as synaptic transmission and cardiac contractility.

There is also evidence for K^+ channels as targets for inhaled anesthetics. The MAC of chloroform, desflurane, halothane, and sevoflurane is variably increased in a knockout of the TREK-1 K_{2P} K^+ channel.[56] This variable effect on MAC is not paralleled by the effect of these anesthetics to increase channel opening in vitro, which argues against an exclusive causal connection between TREK-1 and

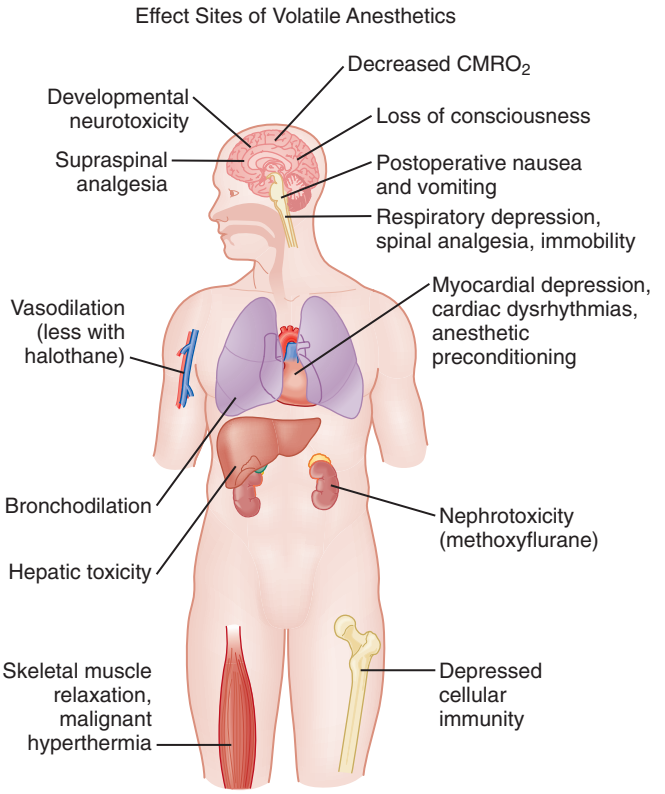
anesthetic effects.[56,57] N_2O, xenon, and cyclopropane also activate TREK-1. The MAC of halothane is increased significantly by knockout of the TASK-3 channel, but the MAC of isoflurane is not.[58] Increased pH opens TASK K^+ channels, but decreases in arterial partial pressure of carbon dioxide ($PaCO_2$) (with associated increases in pH) do not decrease MAC.[59,60] Reduced pH blocks TASK channels, but increases in $PaCO_2$ that decrease pH also decrease MAC.[61] Finally, intravenous and intrathecal infusions of the KCNK-type K^+ channel activator riluzole decrease isoflurane MAC equipotently in rats, which suggests that although activation of K^+ channels might affect anesthetic requirement, the effect is primarily on higher centers rather than the spinal cord.[62] The issue is complicated by the nonspecificity of riluzole, which blocks slowly inactivating Na^+ channels (important for maintaining repetitive firing, and thus likely MAC) even more potently than KCNK channels.[63]

Blockade of receptors for glutamate, the principal excitatory neurotransmitter in the CNS, provides a plausible mechanism for depression of excitatory synaptic transmission and thereby CNS depression by inhaled anesthetics. NMDA-type and α-amino acid-3-hydroxy-5-methyl-4-isoxazole (AMPA)-type receptors are critical for all forms of synaptic function and plasticity, including learning, memory, and nociception among other roles. Blockade of NMDA receptors, as well as hyperpolarization-activated cyclic nucleotide-gated 1 (HCN1) channels, appears important to the anesthetic mechanisms of ketamine (see Chapter 10), and might contribute to inhaled anesthetic effects as well. Isoflurane and xenon inhibit NMDA and AMPA receptors in vitro due to competitive blockade of the glycine coagonist site.[64,65] In addition to K_{2P} channels and nAChRs, NMDA receptors are among the most sensitive targets in vitro to N_2O and xenon and are therefore important to their anesthetic actions, although this conclusion awaits confirmation in vivo.[66] Thus N_2O, xenon, and cyclopropane have a distinct pharmacologic profile with little or no effect on $GABA_A$ receptors but strong inhibition of NMDA and activation of the K_{2P} channel TREK-1.[67]

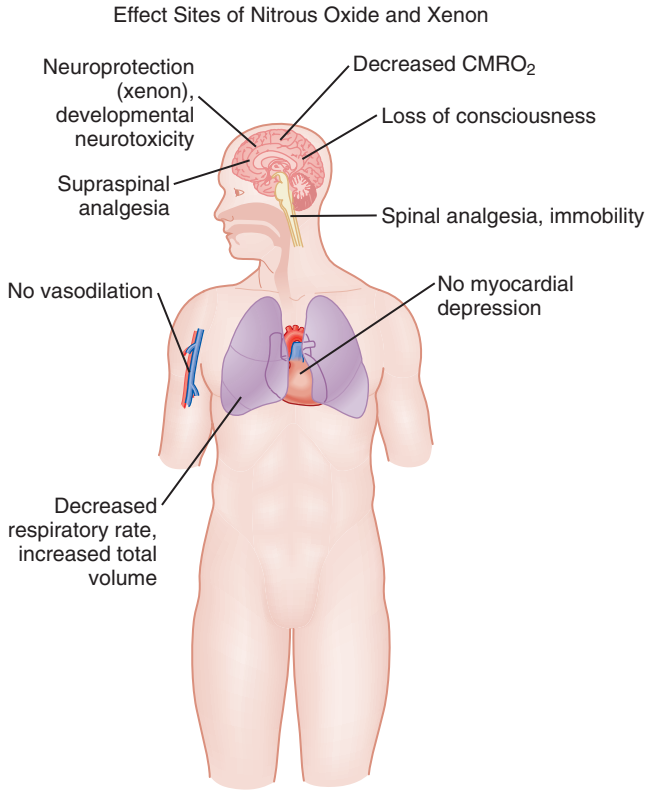
Compared with the intravenous anesthetics (see Chapter 10), inhaled anesthetics are generally more promiscuous in their molecular targets, lacking the receptor-specific, and sometimes receptor subtype–specific, effects of certain intravenous anesthetics. This complicates their pharmacologic characterization, but might also provide considerable redundancy contributing to their marked efficacy across phyla and within species. Such redundancy might also explain the relatively minor effects on anesthetic potency in vivo of mutations that reduce sensitivity of specific molecular targets to inhaled anesthetics in vitro. It is likely that actions on multiple targets rather than a single specific target contribute to the immobilizing effect of volatile anesthetics.[23]

Drug Class Effects

Inhaled anesthetics are characterized by their diverse chemical classes, including the volatile ethers and alkanes, and the gases N_2O and xenon. The molecular effects of inhaled anesthetics are also diverse in that their low potency leads to pleiotropic interactions with multiple molecular targets. This includes a large number of systemic (nonanesthetic) effects. It is instructive to consider the effects of the volatile ethers and alkanes, which exert predominantly GABAergic effects (Fig. 11.6), separately from the gases (Fig. 11.7), which exert predominantly NMDA blocking effects (see Fig. 11.3).



• **Fig. 11.6** Major sites of action of the volatile anesthetics are shown schematically. *$CMRO_2$,* Cerebral metabolic rate of oxygen.



• **Fig. 11.7** Major sites of action of the gaseous anesthetics nitrous oxide and xenon are shown schematically. *$CMRO_2$,* Cerebral metabolic rate of oxygen.

Nonanesthetic Effects

Bronchodilation

Volatile anesthetics relax airway smooth muscle through block of voltage-gated Ca^{2+} channels, depletion of Ca^{2+} stores in the sarcoplasmic reticulum, and possibly through potentiation of GABAergic mechanisms.[68] Because the airways normally have low tone, this effect is evident almost exclusively in the setting of bronchospasm. Baseline pulmonary resistance and dynamic pulmonary compliance are unchanged by 1 or 2 MAC halothane, enflurane, isoflurane, or sevoflurane. However, in subjects challenged with intravenous histamine, volatile anesthetics attenuate the increase in pulmonary resistance.[69] Unlike other volatile anesthetics, this effect is not observed with desflurane.[70] Volatile anesthetics also have antiinflammatory effects on airway epithelial cells mediated by $GABA_A$ receptor potentiation.[71]

Neuromuscular Effects

In contrast to intravenous anesthetics, which can either have excitatory myoclonic effects or produce weak myorelaxation (propofol), volatile anesthetics produce dose-dependent skeletal muscle relaxation and potentiate both depolarizing and nondepolarizing neuromuscular blockers. The mechanisms of skeletal muscle relaxation include decreasing the depolarizing current at the neuromuscular junction in response to acetylcholine owing to direct inhibition of nAChRs and enhancement of spinal cord glycine receptors.[40,72,73] Potentiation of nondepolarizing neuromuscular blocker effects is likely due to potentiation of antagonist affinity at the nAChR.[74] Residual volatile anesthetic can potentiate residual neuromuscular blockade, while elimination facilitates recovery from neuromuscular blockade.

Analgesia and Neuroprotection

Inhibition of NMDA receptors by N_2O, xenon, and cyclopropane probably underlies their unique analgesic properties, and their propensity to produce excitement and euphoria, and therefore abuse as psychotomimetics. In addition, NMDA receptor blockers including xenon and N_2O are both neuroprotective and neurotoxic in animal models (see the "Emerging Developments" section).[66]

Adverse Effects

The promiscuous pharmacologic actions of inhaled anesthetics result in numerous undesirable effects summarized in the following text by system.

Respiratory Depression

All halogenated ethers cause dose-dependent respiratory depression. Even subanesthetic concentrations blunt both the hypoxic and hypercarbic ventilatory responses, though in general hypoxic drive is more sensitive.[75] The acute hypoxic response can remain suppressed for several hours after anesthesia owing to depressant effects of subanesthetic concentrations (0.1 MAC).[76] These effects are multifactorial. The peripheral drive from hypoxia detected by the carotid bodies is blunted. There is a general depression of the central respiratory centers and arousal centers, and motor neuron and respiratory muscle function is suppressed, both leading to reduced respiratory drive and upper airway muscular tone and patency.[77] Minute ventilation is reduced at anesthetic doses mainly through a reduction in tidal volume, while respiratory rate is maintained or increased. These effects are mediated primarily centrally through enhanced postsynaptic inhibitory GABAergic and depressed presynaptic and postsynaptic excitatory glutamatergic transmission.

Hypoxia is sensed by glomus type I cells of the carotid bodies by reduced opening of K^+ channels, although the specific type is difficult to determine and might be species dependent.[78] Volatile anesthetic suppression of peripheral hypoxic respiratory drive might be mediated by reactive oxygen species (ROS), altering the redox state of K^+ channels that detect hypoxia. Halothane, with a relatively large degree of peripheral metabolism and associated production of ROS, dramatically suppresses the carotid body response to hypoxia. Desflurane, with minimal metabolism, minimally suppresses the carotid body reflex.[79] Isoflurane, with an intermediate degree of metabolism, moderately inhibits the carotid bodies. Pretreatment with a mixture of antioxidants prevents suppression of the respiratory response by subanesthetic doses of halothane and isoflurane.[78,80,81]

Cardiovascular Depression

Volatile anesthetics universally produce concentration-dependent myocardial depression, especially halothane. This is due primarily to altered Ca^{2+} entry and sarcoplasmic reticulum Ca^{2+} handling.[82,83] The most significant cardiodepressant effect of halothane is direct myocardial depression. The negative inotropy is compounded by decreases in systemic vascular resistance (SVR) by enflurane, isoflurane, desflurane, and sevoflurane to further reduce blood pressure. In contrast, N_2O and especially xenon have minimal direct cardiovascular effects (Table 11.3). Xenon does not affect the major cation currents in isolated cardiomyocytes, which probably explains the minimal cardiovascular depression. Reduced SVR is most prominent with isoflurane, leading to suggestions that it could promote a steal phenomenon in patients with coronary

TABLE 11.3 Comparison of Cardiovascular Effects of Various Inhalational Anesthetics

	Cardiac Output	System Vascular Resistance	Mean Arterial Pressure	Heart Rate
Halothane	↓	↔	↓	↓↓
Enflurane	↓↓	↓	↓↓	↑
Isoflurane	↓	↓	↓↓	↑
Desflurane	↔	↓	↓	↑
Sevoflurane	↔	↓	↓	↔
Nitrous oxide	↓	↑	↔	↑
Xenon	↔	↔	↔	↓

The arrows indicate an increase, decrease, or no change in the parameter. The number of arrows signifies the approximate magnitude of the effect.
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artery disease. However, there is no convincing clinical evidence that isoflurane is riskier than other inhaled anesthetics in patients with coronary artery disease as long as perfusion pressure is maintained.[84] Rapid increases in inhaled concentrations of isoflurane and especially desflurane can lead to increases in heart rate and blood pressure secondary to sympathetic activation as the result of an irritant effect.[85] Sevoflurane has minimal effects on heart rate.

Cardiac Dysrhythmias

Isoflurane, desflurane, and sevoflurane all prolong the electrocardiographic QT interval, potentially increasing the risk of *torsades de pointes* polymorphic ventricular tachycardia. There is some controversy as to whether halothane presents a similar risk.[86] Prolongation of the QT interval is likely due to inhibition of the delayed rectifier K^+ current through human ether-à-go-go–related gene (hERG) channels that normally contribute to cardiomyocyte repolarization (see Chapter 27).[87] Halothane and cyclopropane are well known for myocardial sensitization to catecholamine-induced arrhythmias. This has been proposed to result from disruption of muscarinic regulation of myocardial adenylyl cyclase.[88,89] These arrhythmias are suppressed by calcium channel blockers and β-adrenergic blockers.[90] The ether anesthetics, xenon, and N_2O have minimal proarrhythmic effects.

Neurophysiologic Effects

Volatile anesthetics decrease the cerebral metabolic rate of oxygen consumption ($CMRO_2$; see Chapter 9). Because of flow-metabolism coupling this should result in reduced cerebral blood flow (CBF) and intracranial pressure. However, these effects are offset by the direct vasodilation effect of volatile anesthetics on cerebral vasculature, particularly at higher doses. N_2O increases CBF with a mild increase in $CMRO_2$. Coadministration of propofol, barbiturates, or opioids counteracts these vasodilatory effects.

Volatile anesthetics lead to characteristic changes in the electroencephalogram (EEG; see Chapter 8). During quiet wakefulness, α and β activity predominate. As anesthetic concentration increases, the EEG shifts to larger-amplitude, lower-frequency activity in the θ and δ range. As concentration increases further, the EEG shows burst suppression, alternating periods of isoelectric activity, and bursts of activity. By the time concentration reaches 1.5 to 2 MAC, the EEG becomes isoelectric. These characteristic shifts in the EEG power spectrum have been exploited to create multiple measures of depth of anesthesia, including the bispectral index (BIS), spectral entropy, and spectral edge. Unfortunately, none has proven to be a compelling monitor for awareness, in that the BIS or Anesthetic Gas to Reduce Explicit Recall (BAG-RECALL) trial failed to demonstrate superiority for awareness prevention when following BIS compared to a protocol to maintain a minimum end-tidal volatile anesthetic concentration.[91] Ketamine and N_2O do not reduce the BIS or suppress midlatency auditory evoked potentials, whereas xenon does. Thus anesthetic depth monitors are inaccurate when ketamine or N_2O is used.

Sevoflurane, isoflurane, and enflurane are notable for producing epileptiform EEG activity at high concentrations.[92,93] This effect is particularly pronounced with hyperventilation and has been detected during pediatric inhalational induction with sevoflurane. This activity is of unclear clinical significance, but it raises concerns of possible neurotoxicity.

Immunomodulatory Effects

Postoperative immunocompromise in surgical patients is primarily related to the neuroendocrine stress response to surgery through activation of the autonomic nervous system and the hypothalamic-pituitary-adrenal axis.[94,95] Monocytes, macrophages, and T cells all have β_2-adrenoreceptors and glucocorticoid receptors through which the perioperative surge in catecholamines, adrenocorticotropic hormone, and cortisol can directly suppress function. This immunomodulatory effect has the potential for significant impact on postoperative outcome, particularly for cancer surgery, because pain and surgery increase tumor metastasis in cancer surgery when comparing groups that received systemic or epidural analgesia in addition to general anesthesia during surgery.[96] This argues that the immune effects of anesthesia are significantly smaller than the effects of surgery, but volatile anesthetics also have immunomodulatory effects.[97]

Data concerning the immunomodulatory effects of volatile anesthetics are somewhat contradictory, but the majority of studies show that they have immunosuppressive properties (see Chapter 38). Volatile anesthetics generally inhibit inflammatory cytokines, either directly or through stimulation of helper T-cell cytokines such as interleukin (IL)-4 and IL-10 that normally function to limit the inflammatory response. Studies have shown decreased lymphocyte proliferation, inhibition of neutrophil function, and suppression of alveolar monocyte responses to cytokines.[98–103] Additionally, volatile anesthetics reversibly inhibit voltage-gated Ca^{2+} channels, decrease intracellular Ca^{2+} concentration, and reduce expression of inducible nitric oxide synthase (iNOS) in lymphocytes, while iNOS expression is increased in alveolar macrophages exposed to isoflurane.[104,105]

Volatile anesthetics inhibit human neutrophil bacterial killing in vitro by reducing production of ROS.[101,106,107] The resulting decrease in ROS suppresses the initial inflammatory response by directly limiting neutrophil-mediated local tissue injury, which itself is responsible for upregulation of endothelial adhesion molecules that recruit more immune cells and launch the systemic immune response. Whereas inhibition of neutrophil ROS production could compromise the immune response, neutrophil ROS release is also a significant contributor to the initial tissue injury that is responsible for reperfusion injury.

Hepatotoxicity

Anesthetic-induced hepatitis was first recognized in the 19th century as a specific risk of chloroform but not ether. Hepatotoxicity has been traced to biotransformation of volatile agents by cytochrome P450 enzymes, producing trifluoroacetylated protein antigens (see Chapter 7).[108] Halothane-induced hepatitis is most common and is classified into two types. Type I occurs commonly (estimates range from 5% to 30% of patients) and results in asymptomatic elevation of serum transaminases 1 to 2 weeks after exposure. No prior exposure is required, and the mechanism of injury is unclear. Leading explanations include a direct toxic effect of halothane itself or an indirect effect as halothane metabolism produces free radicals that interact with cellular components, leading to an autocatalytic peroxidative chain reaction.

Type II halothane hepatitis is much less common (1 in 35,000 halothane anesthetics). An immune-mediated response directed against hepatocytes leads to fulminant hepatitis with high mortality. In most cases there is prior exposure to halothane. Delayed-onset jaundice or postoperative fever is also common. The presentation

can be delayed up to 1 month following anesthesia. Cytochrome P450 2E1 (CYP 2E1) oxidation of halothane produces trifluoroacetyl chloride, which is highly reactive and covalently binds to hepatic proteins, producing trifluoroacetylated protein neoantigens that initiate the immune response responsible for the hepatitis.[109] The trifluoracetylated sites act as haptens to establish an antibody reaction, and serum from patients with type II halothane hepatitis contains antibodies that react with acyl halides bound to liver proteins. Patients also develop autoantibodies against CYP 2E1, but the same autoantibodies have been found in unaffected pediatric anesthesiologists who were routinely exposed to halothane during inhalational inductions, suggesting that these CYP 2E1 antibodies do not have a pathogenic role.[110]

Nephrotoxicity

There are two potential pathways by which volatile anesthetics contribute to nephrotoxicity, either by metabolism leading to inorganic fluoride production or via degradation products, as described earlier for sevoflurane. Fluoride production has a well-documented history of inducing nephrotoxicity, whereas the other degradation product pathways lack reported clinical significance in humans.

Methoxyflurane was withdrawn after reports of severe nephrotoxicity owing to production of inorganic fluoride. A high-output renal failure unresponsive to vasopressin develops in association with serum fluoride concentrations in excess of 50 μM. Sevoflurane is the modern anesthetic with the highest associated serum fluoride concentrations, with some reports of serum levels exceeding 50 μM after as little as 2 MAC hours of exposure, although nephrotoxicity from sevoflurane exposure has not been reported and controlled studies have failed to detect an impact of sevoflurane anesthesia on renal function.[111–113] This is likely secondary to the metabolism of methoxyflurane by cytochrome P450 enzymes 2E1, 2A6, and 3A4 within the kidney, producing fluoride locally within the nephrons themselves. In contrast, there is less renal metabolism of sevoflurane.[114] Sevoflurane metabolism leads to formation of compound A, a nephrotoxic vinyl halide (see Chapters 4 and 7). However, the dose-dependent nephrotoxicity of compound A has been demonstrated only in rats and multiple human studies have not shown evidence of renal impairment.[115]

Malignant Hyperthermia

Malignant hyperthermia is an uncommon inherited genetic disorder of skeletal muscle that can produce a potentially lethal hypermetabolic state after certain triggers (see Chapter 7), which include all the volatile anesthetics, but not N_2O or xenon. A trigger leads to excessive release of Ca^{2+} from intracellular stores, which leads to muscle rigidity and rhabdomyolysis. The associated hypermetabolism increases body temperature, CO_2 production, and O_2 consumption. If left untreated, malignant hyperthermia has an estimated mortality rate of 80%. Mortality is reduced to near 10% by early dantrolene treatment to terminate the hypermetabolic reaction by blocking intracellular Ca^{2+} release and supportive care to manage the sequelae of rhabdomyolysis. A molecular lesion underlying malignant hyperthermia was first traced to a single point mutation in the ryanodine receptor RyR1 in pigs, but it is now known that a variety of mutations, most commonly in RyR1 but also in the α_1 subunit of the dihydropyridine receptor (Cav2.3) and rarely in calsequestrin or sarcoplasmic endoreticular calcium ATPase (SERCA), can lead to this pharmacogenetic reaction (discussed further in Chapter 7).[116]

Postoperative Nausea and Vomiting

All inhaled anesthetics are emetogenic, including the volatile anesthetics, N_2O and xenon; there are no significant differences between the modern volatile ether inhaled agents in their propensity for inducing postoperative nausea and vomiting (PONV). General anesthesia increases the risk of PONV significantly relative to regional anesthesia techniques (see Chapter 34). The incidence of PONV following general inhalational anesthesia involving the use of two triggering agents (opioids and volatile anesthetics) is 25% to 30%. Substituting propofol, which is not emetogenic (but rather is antiemetic) for the volatile anesthetic reduces the relative risk of PONV by 19%, and using nitrogen as a carrier gas rather than N_2O reduces the relative risk by 12%.[117,118]

Metabolic Effects

N_2O can produce megaloblastic bone marrow changes and neurologic complications owing to vitamin B_{12} deficiency (see Chapter 7). The cobalt ion in vitamin B_{12} is oxidized, which inhibits the activity of methionine synthase, which is responsible for conversion of homocysteine to methionine, thymidine, and tetrahydrofolate. Accumulation of plasma homocysteine could in theory increase the risk of perioperative myocardial events, but its clinical significance is unlikely.[119,120]

Unique Features of Individual Agents

Agents With Prominent $GABA_A$ Receptor Activity

Halothane, Enflurane, Methoxyflurane

Halothane, enflurane, and methoxyflurane are no longer used in clinical practice in North America, although halothane is still widely used in the developing world because of its low cost and is on the World Health Association (WHO) Model Lists of Essential Medicines (http://www.who.int/medicines/publications/essentialmedicines/en/) of general anesthetics (along with isoflurane and N_2O). The following information is included for historical interest.

Halothane, a halogenated alkane, is not very pungent and hence is compatible with inhalational induction. Use of halothane is associated with a lower risk of nausea and vomiting than the flourinated methyl ethyl ether agents. Its principal limitations include sensitizing myocardium to catecholamine-induced arrhythmias and occasional, but severe, hepatic necrosis. In pediatric patients, halothane causes bradyarrhythmias. Enflurane, a halogenated methyl ethyl ether, is relatively pungent and high concentrations are associated with seizure-like EEG activity. Enflurane metabolism can release fluoride, which rarely can inhibit renal concentrating ability. Methoxyflurane is a halogenated methyl ethyl ether that provides more analgesia than other volatile agents. However, methoxyflurane produces significant levels of inorganic fluoride because of its high degree of metabolism, and it is associated with high-output renal failure.

Isoflurane

Isoflurane is an isomer of enflurane (see Fig. 11.1), introduced into clinical practice almost simultaneously, with a more favorable

side effect profile. Isoflurane is highly pungent. It is also chemically quite stable.

Sevoflurane

Sevoflurane is a fluorinated methyl isopropyl ether. It is sweet smelling and minimally pungent, and hence well suited to inhalational inductions. Because of its complete fluorination, sevoflurane has a very low blood solubility (among commonly used volatile anesthetics, only desflurane has a lower solubility). It is approximately half as potent as isoflurane. Metabolism of sevoflurane leads to release of inorganic fluoride, similar to enflurane and methoxyflurane. Sevoflurane can form carbon monoxide when exposed to certain dehydrated CO_2 absorbents in an exothermic reaction that can ignite a fire (see Chapter 3). Sevoflurane appears to induce the least cerebral vasodilation of the modern agents, which makes sevoflurane the preferred volatile agent for neurosurgical patients with elevated intracranial pressure.[121]

Desflurane

Desflurane is a fluorinated methyl ethyl ether that is identical to isoflurane save for the substitution of a fluorine atom for the α-ethyl chlorine in isoflurane. The complete fluorination greatly reduces blood solubility and potency, and increases vapor pressure relative to isoflurane, to near atmospheric pressure (672 mm Hg at 20°C). The low boiling point of desflurane requires a specialized pressurized vaporizer (see Chapter 3). Desflurane is the most pungent of the inhaled anesthetics, potentially causing coughing, sialorrhea, breath holding, and laryngospasm. Rapid increases in desflurane concentration cause increased sympathetic activity, with associated tachycardia and hypertension.[85] Desflurane undergoes almost no metabolism, minimizing the risk of hepatitis and nephrotoxicity, but is degraded to carbon monoxide by certain dehydrated CO_2 absorbants (see Chapter 3).

Ether and Chloroform

Diethyl ether (ether) is notable for its high aqueous solubility compared with other anesthetic ethers. Ether is sweet smelling and mildly pungent; although it can be used for inhalational induction, an ether induction is very slow and risks laryngospasm. Ether is still used as an anesthetic in some developing countries because of its low cost and high therapeutic index with minimal cardiac and respiratory depression, but its explosive flammability has eliminated its use in most developed nations. Ether is not a cardiac depressant and maintains the baroreceptor reflex, making it relatively safe in patients with septic shock. Ether has a high incidence of PONV.

Chloroform (trichloromethane) is a sweet-smelling volatile anesthetic that can be used for inhalational induction. Although it was initially developed as an alternative to ether, chloroform was abandoned because of its association with hepatotoxicity and fatal cardiac arrhythmias.

Agents With Prominent NMDA Receptor Activity

Nitrous Oxide

N_2O is a sweet-smelling gas with low solubility, low anesthetic potency (MAC of 104 vol%), and good analgesic properties. Although N_2O is not flammable, it is a powerful oxidizing agent that supports combustion. N_2O is usually used as an anesthetic adjuvant because its low potency prevents it from being used as a sole agent. It does not produce skeletal muscle relaxation. N_2O should be avoided in pregnant patients because of its teratogenic effects. Because of the high delivered concentrations and solubility of N_2O, it has a tendency to rapidly accumulate in closed spaces (see Chapter 3). It is associated with stable hemodynamics in that it does not produce cardiac depression.

Xenon

Xenon is an odorless and nonpungent noble gas with low solubility, leading to rapid induction and emergence, and was first demonstrated to produce human anesthesia in 1951.[122] It is nontoxic and lacks teratogenicity, produces excellent analgesia, and is associated with stable hemodynamics in that it does not produce cardiac depression. Xenon is relatively expensive to obtain and deliver and has low potency (MAC ~ 71 vol%), and hence is not in common use. Systems designed to minimize waste either by recycling or using closed breathing circuits might eventually make its widespread use practical.

Cyclopropane

The cycloalkane cyclopropane is a sweet-smelling and nonpungent gas, and hence is suitable for inhalational induction. Because of the large amount of potential energy attributed to the strain in the carbon-carbon bonds of cyclopropane, it is prone to explosive decomposition when stored in large quantities or when mixed with an oxygen-enriched atmosphere; hence it is no longer in clinical use. Cyclopropane is associated with a high risk for PONV.[123]

Environmental Considerations

All of the inhaled anesthetics except xenon are greenhouse gases with potential global warming effects based on their infrared absorption and atmospheric lifetimes. The impact of the volatile anesthetics is relatively small compared with that of N_2O, which is usually used at higher concentrations and flow rates and is also destructive to the ozone layer.[124,125]

Drug Interactions

Given their multiple mechanisms and pleiotropic effects, it is not surprising that inhaled anesthetics are subject to a number of drug interactions.

Reduction in MAC by Anesthetic Adjuvants

Sedative and hypnotic drugs decrease the MAC of volatile anesthetics (see Chapter 6). GABAergic agents (propofol, benzodiazepines, and barbiturates), opioids, NMDA antagonists (ketamine, N_2O, xenon), and α_2 agonists (dexmedetomidine, clonidine) all reduce the MAC of volatile anesthetics (Table 11.4).[126–129] This fact is exploited in balanced anesthesia to minimize the hemodynamic side effects associated with high-dose volatile agents. The β blocker esmolol appears to potentiate the MAC-reducing effect of opioids.[130]

MAC Additivity

When more than one agent in used, MAC equivalents of anesthetic agents combine additively with no synergism between inhaled anesthetics. For example, the combination of 0.5 MAC desflurane and 0.5 MAC sevoflurane sums to 1 MAC equivalent and thus inhibits movement in response to incision in 50% of subjects. In practice, modern anesthetic vaporizers have a lockout to prohibit

TABLE 11.4 Factors That Alter the Potency of Inhaled Anesthetics (Minimal Alveolar Concentration)

Factors That Decrease MAC	Factors That Increase MAC
Drugs	**Drugs**
α_2 Agonists	Alcohol (chronic)
Barbiturates	
Benzodiazepines	
Opioid analgesia	
Other anesthetics	
Other Factors	**Other Factors**
Increasing age	Young age
Hypothermia	Hyperthermia
Hypoxia	
Hypotension	
Pregnancy	

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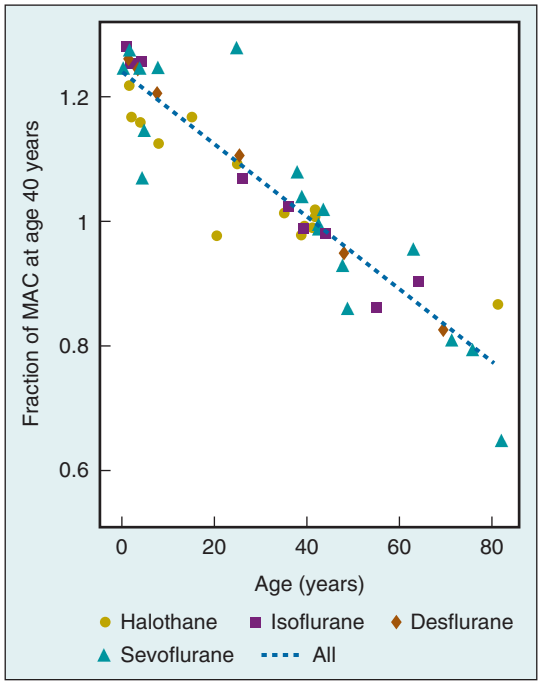


• **Fig. 11.8** Variation of anesthetic potency with age for volatile anesthetics. There is a progressive increase in anesthetic potency with age older than 1 year, with minimum alveolar concentration *(MAC)* decreasing by 6.7% with each increasing decade of life. (Modified from Eger EI. Age, minimum alveolar anesthetic concentration, and minimum alveolar anesthetic concentration-awake. *Anesth Analg*. 2001;93:947–953.)

delivery of multiple volatile agents at the same time to reduce the risk of overdose. Hence the most common application of MAC additivity is the delivery of a volatile anesthetic with N_2O.

Synergy With Opioid-Induced Respiratory Depression

The combination of volatile anesthetic and opioid causes synergistic respiratory depression. For example, the combination of alfentanil and sevoflurane leads to more depression of minute ventilation and heart rate than does the summed effect of each drug administered separately.[131]

Factors Influencing MAC

Despite the surprisingly narrow population range in sensitivity to inhaled anesthetics, certain subject-dependent factors consistently influence individual susceptibility to inhaled anesthetics. MAC is increased by anxiety, thyrotoxicosis, and stimulants (e.g., amphetamines). MAC is decreased by hypothyroidism, hypothermia, hypotension, and pregnancy (see Table 11.4), as well as pharmacogenetic factors.

Age

A major physiologic determinant of MAC is age.[27] In humans, MAC increases in the first few months of life, peaks, and then declines approximately exponentially with age, with a drop of 6% to 7% per decade of life (Fig. 11.8). When quoting MAC for an anesthetic, the standard age of 40 years is the usual default unless otherwise specified. Older patients generally require lower absolute doses to obtain equivalent anesthetic effects, so the MAC fraction should be adjusted for age to avoid overdosing.

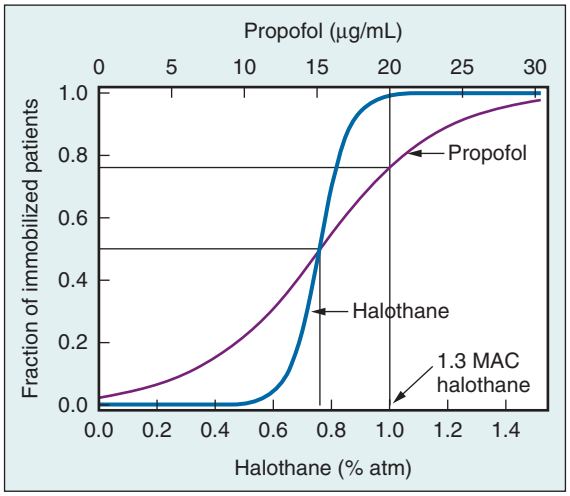
Temperature

The MAC for potent inhaled anesthetics decreases with decreasing body temperature by 4% to 5% per 1°C decrease, with complete elimination of the requirement for anesthesia at 20°C in laboratory mammals. Interestingly, this effect is not observed for N_2O.[27]

Pharmacogenetic Effects on Potency

The population range in anesthetic potency around the median is narrow, with a standard deviation of ~10% of its median value (MAC). This is much narrower than the distribution of effects for most other drugs (Fig. 11.9). Additionally, MAC is roughly the same order of magnitude across multiple species that are widely separated phylogenetically, including *Caenorhabditis elegans* (nematode), *Drosophila* (insect), and vertebrates. This argues that susceptibility to general anesthesia evolved in a very early, likely unicellular, common ancestor and its persistence must contribute to reproductive fitness or is an epiphenomenon of a beneficial trait, although at present it is unclear how.[132]

Given that metabolic factors affect MAC, it should not be surprising that genetic differences can contribute to anesthetic sensitivity. There is a statistically significant difference in MAC among Jews of three different ethnicities (European, Caucasian, and Asian) with the Caucasian population having a 24% higher MAC than the European population.[133] Additional evidence for specific mutations affecting anesthetic requirements originates with the observation that red-haired patients have greater analgesic requirements. Interestingly, 75% of individuals with red hair and pale skin carry at least two inactivating variants of the melanocortin-1 receptor (MC1R).[134] MC1R mediates kappa opioid receptor-induced analgesia, which appears to be more effective in women than men.[134–136] This probably explains the observation that redheads are both more sensitive to thermal pain and relatively resistant to



• **Fig. 11.9** Potency population responses of halothane compared to propofol. The curves are drawn so the minimum alveolar concentration *(MAC)* for halothane *(lower scale)* corresponds to the plasma median effect dose *(EC_{50})* for surgical incision for propofol *(upper scale).* The *vertical lines* indicate the 1.0 MAC and 1.3 MAC (resulting in 99% immobilization) for halothane. At 1.3 times the EC_{50} for propofol, only 75% of subjects are immobilized by propofol *(upper horizontal line).* (Modified with permission from Dilger JP. From individual to population: the minimum alveolar concentration curve. *Curr Opin Anaesthesiol*. 2006;19:390–396.)

subcutaneous lidocaine.[137] A functional consequence of these differences in pain sensation is that redheaded women are more difficult to sedate. Redheaded subjects are less sedated by a plasma-concentration–targeted midazolam infusion than non-redheads.[138] The concentration of desflurane required to suppress movement to a noxious electrical stimulus is significantly higher in redheaded as opposed to dark-haired women; 9 of the 10 redheaded women in the study were either MC1R homozygous or compound heterozygous mutants.[139]

Common Clinical Indications and Considerations

Choices of anesthetic agent for induction and maintenance of anesthesia depend on multiple patient- and procedure-dependent factors. Type and length of surgery, expected disposition, patient comorbidities, and economic factors all figure into the decision-making process for agent selection.

Induction and Maintenance of Anesthesia

Induction of anesthesia with an inhaled anesthetic requires a nonpungent, nonirritating agent, such as halothane, sevoflurane, or N_2O. Because the MAC of N_2O exceeds 1 atm, sevoflurane is frequently used to reliably induce general anesthesia by inhalation owing to its lower solubility—and thus more rapid equilibration—compared with halothane.

Neuroanesthesia and Neuromonitoring

Neuromonitoring can be substantially affected by the potent inhaled anesthetics. Somatosensory evoked potential magnitude is diminished and latency prolonged, such that a balanced anesthetic approach that limits total MAC fraction of inhaled anesthetic is used, depending on the signal quality for the particular patient. Effective communication with the clinical neurophysiology team is important.

Cardiac Anesthesia

Anesthetic preconditioning (see "Emerging Developments: Anesthetic Preconditioning"), which limits the extent of postanesthetic exposure ischemic infarction, represents a potential advantage of using volatile anesthetics in cardiac surgery patients who are predisposed to ischemia. Volatile anesthetics can induce coronary vasodilation. This prompted a theoretical fear of coronary steal, whereby blood flow distal to a fixed, atherosclerotic lesion would decrease when the surrounding, normal vasculature dilated in response to isoflurane, triggering ischemia. Multiple studies have confirmed that this concern is unfounded with isoflurane.[140–142] Interestingly, data from a recent randomized controlled clinical trial suggest patients given sevoflurane anesthesia for surgery requiring cardiopulmonary bypass have better cognitive performance in the immediate postoperative period than patients given propofol.[143] A separate meta-analysis suggested that lower mortality was associated with volatile anesthesia compared with total intravenous anesthesia in cardiac surgery,[144] but no difference was seen in the composite endpoint of prolonged stay in the intensive care unit or death at 1 year in a subsequent multicenter randomized controlled comparison of sevoflurane with propofol anesthesia.[145]

Pediatric Anesthesia

Most pediatric cases are initiated with inhalational induction using sevoflurane, particularly in day surgery cases where the patient arrives without intravenous access. Maintenance of anesthesia can be provided using the agent of choice, adjusting for the higher MAC in children.

Obstetric Anesthesia

The choice of agent for the pregnant patient should take into account safety for the mother and fetus (see Chapter 37). Throughout pregnancy efforts should be maintained to ensure adequate uterine blood flow, so blood pressure should be maintained in a normal range. In the first trimester, teratogenic agents such as N_2O should be avoided. Finally, during delivery, maintenance of uterine tone is essential to achieve adequate postpartum hemostasis. The volatile agents all decrease smooth muscle tone, although this effect might be less with desflurane.[146,147] Hence it has been recommended that volatile agent concentration be minimized, ideally to less than 0.5 MAC with sevoflurane or less than 1 MAC with desflurane, to ensure adequate uterine muscle tone.[147]

Ambulatory Anesthesia

Ambulatory cases represent an increasing fraction of all anesthetic procedures performed. To maximize throughput in busy surgery centers, it is essential to provide a cost-effective anesthetic that minimizes side effects and allows a rapid recovery. Use of the minimally soluble agents desflurane, sevoflurane, and N_2O improves recovery time and drug cost compared with propofol infusion.[148–151] Although the intermediate and late recovery profiles of desflurane, sevoflurane, and propofol are similar for the majority of patients,

desflurane might have the best intermediate recovery profile for obese patients.[152–154] Using a prophylactic antiemetic regimen to minimize PONV when using a volatile anesthetic-based technique can avoid discharge delays.[155,156]

Thoracic Anesthesia

The volatile anesthetics offer several advantages for thoracic surgery, including bronchodilation and decreased airway irritability, as well as the ability to maintain a high fraction of inspired oxygen compared with anesthetics using N_2O. Rapid clearance of volatile anesthetics after the procedure minimizes the need for postoperative ventilation (especially when combined with local anesthetic-based analgesic techniques). Volatile anesthetics cause a dose-dependent attenuation of hypoxic pulmonary vasoconstriction (HPV).[157] This is of particular significance for thoracic surgery given the frequent use of one-lung ventilation, during which HPV diminishes the shunt fraction and hence tends to improve the arterial partial pressure of oxygen (PaO_2). However, the clinical significance of this effect appears low at sub-MAC doses, because anesthetic choice minimally affects the PaO_2 in humans during one-lung ventilation.[158–160] The gaseous anesthetics N_2O and xenon do not affect HPV during one-lung ventilation.

Emerging Developments[161–163]

It has generally been assumed that anesthetics have minimal or no persistent effects after pharmacokinetic elimination. However, general anesthetics act on multiple receptors and second-messenger systems in the CNS with increasing evidence for more durable changes in gene and protein expression, posttranslational modification, and epigenetic effects.[22] On an intermediate timescale, some effects of anesthesia persist after drug clearance even on a cellular level: a single dose of etomidate or a single exposure to isoflurane is capable of increasing the expression of α_5- subunit $GABA_A$ receptors and increasing the tonic-inhibitory current through extrajunctional $GABA_A$ receptors, with resultant impairment of a memory performance task for at least a week after exposure in a murine model.[164] It is therefore not surprising that the assumption that volatile anesthetics have no lasting effects has been called into question. This is particularly true at the extremes of the human life cycle[165] Data are accumulating that neonatal exposure to anesthetics is neurotoxic in animals, although evidence remains uncertain in humans. In older adults, there is concern that anesthesia contributes to postoperative cognitive dysfunction (POCD) and possibly to the progression of neurodegenerative diseases, although again there is a lack of direct evidence in humans.

Developmental Neurotoxicity

Animal data in multiple species indicate that inhaled anesthetics have profound and long-lasting effects when administered during key developmental periods.[166] In the perinatal period, mammals undergo a brain "growth spurt," characterized by a burst of neurogenesis and synaptogenesis. The neural network is then pruned to produce an adult functional architecture through synaptic pruning and programmed cell death, or apoptosis, with ultimate removal of 50% to 70% of neonatal neurons.[167,168] In immature rodents and monkeys at critical developmental periods, exposure to either NMDA antagonist and/or GABAergic agents can lead to increased apoptosis. In rodent and monkey models, anesthetic exposure can lead to long-term cognitive deficits, but translating these findings to humans is difficult because of differences in neurodevelopment and difficulty in comparing duration of exposure.

Although data for some drugs are conflicting, early exposure to most anesthetic agents produces increased apoptosis.[169] NMDA receptor blockade by ketamine in the developing rodent brain causes excessive apoptosis.[170,171] A compelling study of more commonly used drugs exposed postnatal day 7 (P7) rat pups to a cocktail of isoflurane, midazolam, and N_2O at levels sufficient to maintain a surgical plane of anesthesia for 6 hours. The rat pups developed excessive and widespread neuronal apoptosis immediately following exposure. This had persistent behavioral consequences with impairment of hippocampal long-term potentiation and of spatial reference memory as juveniles that lasted into adulthood. Even though isoflurane exposure in isolation led to significant apoptosis, the addition of other agents to the cocktail substantially increased the degree of apoptosis, suggesting that drug combinations might be more detrimental.[172]

The increased neuronal death with additional agents from other drug classes suggests that the significant event might be the pharmacologically induced coma itself rather than the particular agent used to achieve the anesthetic state. Consistent with this hypothesis, equipotent exposure of neonatal mice to desflurane, isoflurane, and sevoflurane produced similar increases in apoptotic cell death.[173] Disruption of neurotrophic factor secretion in the developing nervous system by anesthetic suppression of spontaneous activity might underlie anesthetic neurotoxicity.[174] At sensitive ages (P0-14 rats), the chloride gradient is reversed compared to adults owing to developmental changes in expression of the potassium-chloride cotransporter. Hence, in the immature brain the increase in chloride permeability associated with $GABA_A$ receptor activation leads to depolarization of neurons, with resultant excitation and possibly excitotoxicity (however, this does not explain the neurotoxic effect of perinatal ketamine). A significant number of P7 rats have seizures with sevoflurane anesthesia, and postanesthetic apoptosis that could be mitigated by bumetanide, a N^+-K^+-$2Cl^-$ cotransporter 1 inhibitor, which suggests that apoptosis after anesthesia involves excitotoxicity rather than withdrawal of trophic factors.[175] Subsequent investigations have found other interventions to mitigate long-term cognitive deficits after neonatal anesthesia, including cotreatment with nitric oxide synthase inhibitors,[176] synthetic ROS scavengers,[177] and even post-exposure environmental enrichment.[178]

Despite robust laboratory evidence of increased apoptosis after anesthesia in neonatal animal models, the clinical significance of these observations remains controversial. It remains unclear what the minimum required exposure is for a significant effect on neurodevelopment. Cognitive deficits have been demonstrated in rhesus monkeys after exposure to 24 hours of ketamine anesthesia at P5-6,[179] yet a smaller exposure of 3 hours at P5 demonstrated no neurodegeneration.[180] Significant apoptotic and necrotic cell death occurred in neonatal monkeys exposed to ketamine for 9 hours or isoflurane for 5 hours.[180,181] Anesthetic exposure must occur during the critical period of neurogenesis and synaptogenesis to have significant apoptotic sequelae and it is unclear when this period is in humans. The rat peak critical period for anesthesia exposure approximates the 20th week of gestation in humans, whereas the rhesus critical period approximates the 26th week of gestation in humans.[182] Translation to humans suggests that anesthetic neurotoxicity is likely most significant for the premature human fetus rather than term neonates or infants.

A number of retrospective analyses have examined the possible association between exposure to general anesthesia (and by necessity

with surgery) at an early age with delayed neurocognitive deficits in children. In one series, children exposed to multiple anesthetics before the age of 4 years had twice the incidence of learning disability diagnoses later in life.[183] Another retrospective cohort study found that children who underwent hernia repair before 3 years of age were more than twice as likely as controls to have a developmental or behavioral disorder diagnosis.[184] Because of the retrospective nature of these studies, the relative contributions of surgery, anesthesia, and comorbid conditions and other potentially confounding factors remain undefined.

Recently investigations are beginning to move beyond just retrospective data in humans. Thus far, prospectively collected data appear reassuring regarding single, limited exposures to anesthesia. The PANDA (Pediatric Anesthesia and Neurodevelopment Assessment) study was a multisite, sibling-matched cohort study that compared retrospectively identified siblings exposed to general anesthesia before 36 months of age to unexposed control siblings who were then followed prospectively for neurocognitive deficits. Intelligence quotient assessed at approximately 10.5 years of age did not differ significantly between exposed and unexposed siblings.[185] The GAS (General Anaesthesia compared to Spinal anaesthesia) study is a multisite randomized clinical trial that assigned infants younger than 60 weeks postgestational age to receive either awake-regional anesthesia via spinal or sevoflurane general anesthesia to compare cognitive function at 5 years of age. Only the secondary outcome of 2-year cognitive assessment with the Bayley Scales of Infant and Toddler Development III has been reported, with no evidence of adverse neurodevelopmental outcomes with an average of about 1 hour of sevoflurane exposure.[186] Further delineation of possible early anesthetic exposure phenotypes in humans is expected to come from the ongoing MASK (Mayo Anesthesia Safety in Kids) study, which is following a cohort of all children born in Olmsted County, Minnesota, between 1994 and 2007 to compare neuropsychological testing in children with no, single, or multiple anesthetic exposures.[187]

Anesthesia and Neurodegenerative Disease

The existence and prevalence of postoperative cognitive dysfunction (POCD) in older adults were established in the International Study of Post-Operative Cognitive Dysfunction,[188] although the definition has continued to evolve, making interpretation of the literature difficult. Although short-term cognitive dysfunction was associated with multiple comorbid medical conditions, the predominant risk factor for prolonged cognitive decline (at 6–12 months) was advanced age. Some groups have responded with doubts that POCD is even an actual entity,[189] given that a recent retrospective cohort study found that long-term cognitive decline could be independently attributed to illness or surgery with neither apparently speeding progression to dementia. However, patients who had initial dementia declined more rapidly over the course of the study than those who did not.[190] Research to determine what role, if any, anesthesia plays in POCD is ongoing, with suggestive laboratory models finding parallels between neurodegenerative disorders and effects of anesthesia exposure on neuropathologic mechanisms.

POCD could reflect altered drug responses, loss of functional reserve, or cumulative effects of chronic disease over time. With aging, neurogenesis and synaptogenesis slow, the total number of neurons decreases, and potentially toxic by-products accumulate. These processes gradually deplete physiologic reserves, potentially increasing brain vulnerability to insults, including exposure to perioperative stressors. Current hypotheses of POCD posit roles for direct toxic effects via alterations in Ca^{2+} homeostasis, systemic inflammatory effects secondary to surgical insults leading to neuroinflammation, age-sensitive suppression of neuronal stem cell function, and/or acceleration of ongoing endogenous neurodegenerative processes such as production of aggregated amyloid beta (Aβ) peptide oligomers and tau hyperphosphorylation, thereby unmasking preexisting pathophysiology.[191–196]

Alzheimer disease (AD) is a neurodegenerative process resulting in diffuse atrophy of the cerebral cortex characterized neuropathologically by plaques composed of Aβ and accumulation of neurofibrillary tangles made up of hyperphosphorylated tau protein.[197] Research has focused on the toxic effects that result from selective proteolysis of amyloid precursor protein (APP) into Aβ peptide oligomers.[198] Aβ formation and apoptosis are increased in rodent brains exposed to isoflurane, isoflurane with N_2O, sevoflurane, and desflurane with hypoxia.[196,199–202] However, not all data implicate a postanesthetic Aβ mechanism for POCD. In a transgenic mouse model of AD, increased production of amyloid plaque had no associated cognitive deficits after daily exposure to halothane or isoflurane, whereas wild-type mice developed cognitive impairment after repeated isoflurane exposure.[203] Aβ might not be the only neurodegenerative component increased by anesthetic exposure, in that multiple anesthetic agents appear to promote hyperphosphorylation of the microtubule-associated protein tau, either with hypothermia or normothermia.[204,205] Interpreting these data is further complicated in that the choice of anesthetic exposure duration and total dose vary, with several studies suggesting a potential neuroprotective preconditioning effect with lower exposures.[206–208]

Neuroinflammation and Cognitive Dysfunction

Systemic inflammation resulting from a surgical insult could lead to neuroinflammation and resultant postoperative delirium, which could possibly progress to POCD. Adult rats undergoing splenectomy with neuroleptanesthesia had impaired cognitive function on postoperative days 1 and 3 compared with rats anesthetized without surgery (which were indistinguishable from nonanesthetized controls). Increased IL-1β expression in hippocampus suggests that systemically triggered neuroinflammation contributes to cognitive impairment.[192] In a similar model, memory dysfunction after surgery was mitigated both by nonspecific immunosuppression with minocycline or by pretreatment with an IL-1 receptor antagonist, and was less prominent in IL-1 receptor knockout mice.[209] This IL-1 response appears to be mediated by tumor necrosis factor α (TNFα) as peripheral TNF-α blockade attenuates both the neuroinflammatory response mediated by IL-1 and its associated POCD, suggesting that pretreatment with an anti-TNF antibody might prevent POCD. This neuroinflammatory response appears to be more prominent in older mice, consistent with POCD in humans.[210,211] However, anesthesia might also contribute to the neuroinflammatory response, as increased levels of TNF-α, IL-6, and IL-1β have been observed following isoflurane anesthesia alone. This increase was more marked in transgenic AD model mice, suggesting that neuroinflammation might contribute to the increase in neurodegenerative markers after anesthesia.[212] Finally, intervening to prevent high-mobility group box 1 protein from activating and trafficking circulating bone marrow–derived macrophages to the brain prevented postoperative neuroinflammation and memory decline in a mouse model.[213]

Despite animal data linking AD pathophysiology to anesthesia exposure, data in humans are contradictory. There was no significant

difference in mean cumulative duration of general anesthesia between control and AD patients and no association between the number of surgical operations and the risk of AD, or between anesthesia exposures over a 1- to 5-year window preceding the onset of AD.[195,214] However, an association between cumulative anesthesia exposure before age 50 years and earlier onset of AD suggests that the time horizon for accumulating effects might be quite long.[195]

Although clinical and animal model data suggest an association between anesthesia, surgery, and detrimental cognitive changes in the aged brain, the data do not yet support a claim of causation.[215] Some investigators have found an association of postoperative delirium, which is associated with POCD, with very low BIS values (<20), but POCD incidence was not reported.[216] Perhaps the strongest evidence to date that anesthetic technique could be causally linked to POCD comes from a prospective cohort study with a nested, randomized controlled intervention trial that used intraoperative BIS and cerebral oxygen saturation monitoring in the intervention arm and showed a reduction in mild and moderate POCD incidence in the intervention arm.[217] This will need to be confirmed in multicenter prospective clinical trials to determine the contributions of anesthesia, surgery, and illness to cognitive dysfunction if we are to resolve the association between anesthesia and POCD and progression of neurodegenerative disease.

Inhaled Anesthetic Sensitivity: Triple Low

One of the major questions with adverse cognitive outcomes after anesthesia is whether the stress of the perioperative period is revealing patients with particular vulnerability to anesthetics who might benefit from depth of anesthesia monitoring. A substudy of the B-Unaware trial (see Chapter 3) found no evidence of harm associated with cumulative duration of BIS values less than 45 in noncardiac surgery,[218] though there was association with mortality in cardiac surgery.[219] Perhaps most concerning in this regard, a retrospective analysis of the Cleveland Clinic database found that the conjunction of low bispectral index (BIS < 46), low blood pressure (defined, rather liberally, as mean arterial pressure < 87), and low administered anesthetic dose (MAC fraction < 0.56), which the investigators labeled "triple low," was associated with a threefold increased in 30-day mortality.[220] Analysis of an independent database found that accounting for patient disease severity eliminated any association of mortality with duration of the triple low condition.[221] At present it does not appear that the triple low is a consistent predictor of high mortality after surgery, but further exploration is warranted.

Anesthetic Preconditioning

Volatile anesthetic exposure before induction of myocardial ischemia decreases severity of the ensuing ischemia-reperfusion injury, a property known as *anesthetic preconditioning*. Isoflurane concentrations as low as 0.25 MAC confer protection, although higher concentrations might have greater efficacy.[222] Preconditioning appears to involve production of ROS during the anesthetic exposure, as bracketing the anesthetic exposure with ROS scavengers attenuates the anesthetic preconditioning effect.[223] A similar phenomenon known as *ischemic preconditioning* has been observed whereby brief episodes of ischemia minimize the ischemia-reperfusion injury sustained from a subsequent, more profound episode of ischemia. (Indeed, a criticism of numerous early reports is the failure to report avoidance of hypotension induced by the anesthetics.) Although exposure to isoflurane and to brief episodes of ischemia upregulates several common cell defense signaling pathways and genes, ischemic and anesthetic preconditioning appear to have distinct phenotypes.[224] The magnitude of the anesthetic preconditioning effect diminishes with age in animal models.[225] Exposure to anesthetic agents after the ischemic event also diminishes ischemia-reperfusion injury, an effect known as *anesthetic postconditioning*. It appears that anesthetic preconditioning and postconditioning have similar effects and are not additive.[226] In addition to cardiac protection, anesthetic preconditioning by volatile anesthetics has been demonstrated in other organs as well, including brain, kidney, and lung.[227]

Immunomodulation and Cancer

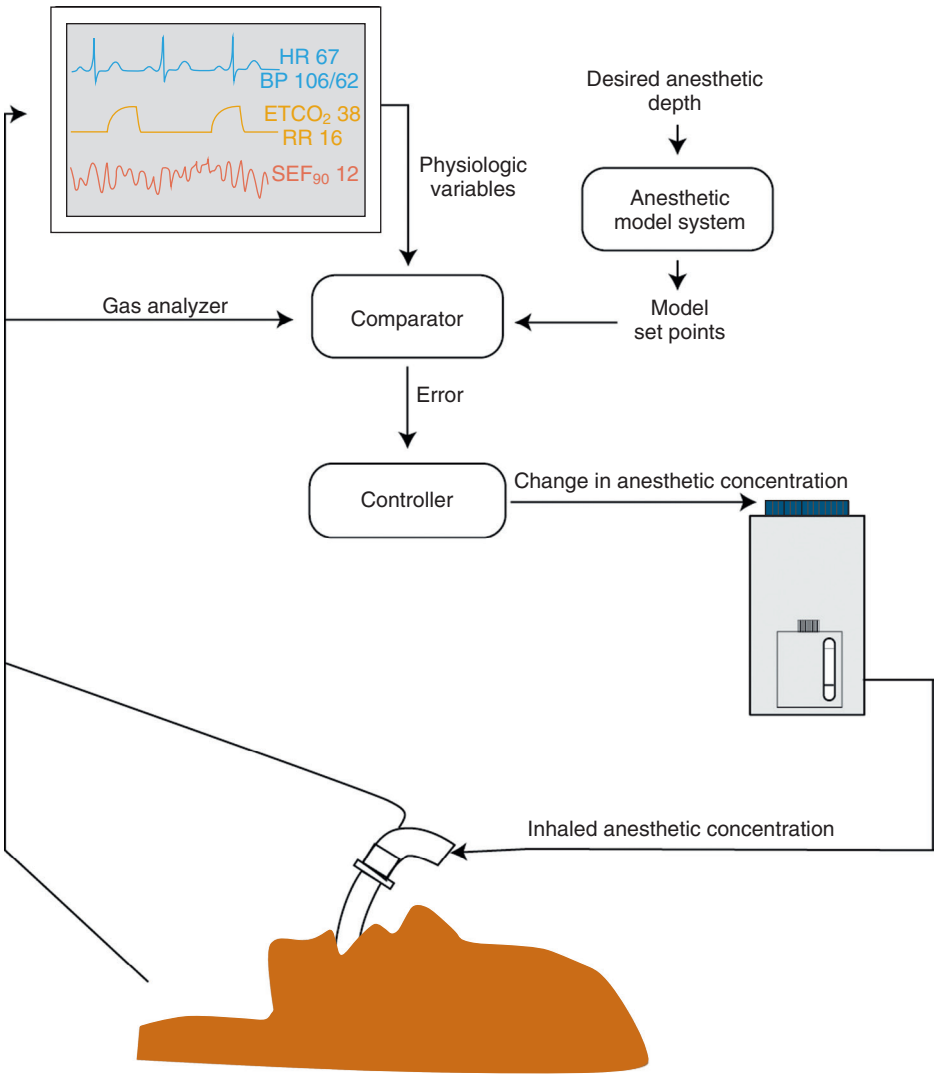
Volatile anesthetics suppress the activity of natural killer (NK) cells.[228] Significant suppression of NK cell function in the perioperative period has been associated with increased cancer patient mortality.[228–231] This argues that volatile anesthetics might increase the risk of retained tumor metastasis owing to reduced immune surveillance by NK cells, but on balance the effect is significantly smaller than the immune suppression triggered by the stress response to surgery without general anesthesia.[96] There is currently insufficient evidence to avoid volatile anesthetics for cancer patients. Yet anesthesiologists should remain aware of their possible contributions to postoperative immune function, particularly in patients who are immunosuppressed at baseline.

Closed-Loop Anesthetic Delivery

Anesthetic delivery systems continue to evolve beyond those based on population pharmacokinetic models. Substantial investigator interest has focused on developing "closed-loop" anesthetic delivery, where anesthetic delivery is titrated automatically via an algorithm based on real-time physiologic information (Fig. 11.10). (This titration to individual patient responsiveness contrasts with target-controlled drug delivery that attempts to replicate a target serum concentration using a population model of pharmacokinetics.) Principal challenges in the development of meaningful closed-loop technology focus on patient safety, user interface, and regulatory concerns.

Key safety concerns in automated anesthetic delivery include graceful degradation without harming patients, with a transparent and predictable approach that offers a meaningful advantage to the anesthesiologist in reducing cognitive workload. Although automated closed-loop systems, like a thermostat, may be more reliable than a human in maintaining measured variables within a target range,[232] they will not reduce the need for vigilance within an operative environment.[233]

The development of closed-loop technology has been aided on the regulatory front by the introduction in 2007 of an international standard for physiologic closed-loop control[234] and subsequent U.S. Food and Drug Administration engagement to develop a consistent regulatory perspective focused on the risk-benefit ratio of the technology.[233] Closed-loop control of inhalational anesthetics based on maintaining an end-tidal concentration has been in clinical use for more than a decade outside the United States.[235] Within the United States, computer-assisted personalized sedation using propofol was approved in 2013 in the form of the Sedasys system, developed and marketed by Johnson and Johnson. Although strictly speaking the system was not closed loop, the propofol delivery was kinetic model based and semiautomated using feedback signals from the monitoring package. Although the system performed as



• **Fig. 11.10** A closed-loop anesthesia system. A closed-loop system depends on a feedback controller that automatically changes anesthetic delivery based on real-time feedback about a targeted anesthetic state. In this theoretical system, an anesthesiologist interacts with the system by choosing a desired anesthetic depth. This value is used to generate desired model set points for physiologic variables that are compared to the currently measured vital signs from the patient (such as heart rate *[HR],* blood pressure *[BP],* respiratory rate [RR], electroencephalographic [EEG] waveforms, and values derived from the EEG, such as spectral edge frequency [SEF90]). A comparator computes the difference between the current and targeted vital sign values and incorporates information about the current delivered drug value (from the gas analyzer) to derive an integrated error signal. This error signal is then fed to a controller that changes the vaporizer (and potentially fresh gas flow) to change the delivered anesthetic concentration to move the vital signs and delivered anesthetic toward desired targets. Subsequent measurements refine the anesthetic delivery rate to converge on the target physiologic state. *$ETCO_2$,* End-tidal carbon dioxide.

designed,[236] the device was eventually withdrawn because of poor market uptake.

Accelerated Emergence

Recent work has begun to focus on whether unconsciousness caused by volatile anesthetics can be pharmacologically antagonized, offering a pharmacologic reversal agent to speed emergence, also termed active emergence or "reanimation." The most promising work to date has focused on the norepinephrine-dopamine reuptake inhibitor methylphenidate. Motivated by the well-established observation that stimulants increase MAC requirement, Solt and colleagues have demonstrated that emergence can be actively induced in a rat model at a steady state of isoflurane anesthesia,[237] with demonstration of cognitive recovery in addition to recovery of a righting reflex. (Note that, because the emergence from anesthesia happens at a lower end-tidal anesthetic concentration than induction,[238] this is not a foregone conclusion.) This effect appears to result from the dopaminergic effect of methylphenidate as droperidol blocks the effect[237] and optogenetic stimulation of the dopaminergic population in the ventral tegmental area can produce the same behavioral effect.[161] Early results suggest that the parabrachial nucleus may also offer a target for reanimation from isoflurane anesthesia.[239]

Key Points

- Inhaled anesthetics as single agents provide all of the essential features of general anesthesia, including amnesia, unconsciousness, and immobility. Each of these components results from agent-specific actions on distinct neuronal pathways in the central nervous system.
- The characteristic immobilizing effect of volatile anesthetics involves a site in the spinal cord. Amnesia and unconsciousness involve incompletely understood supraspinal mechanisms.
- The principal effects of inhaled anesthetics on the nervous system involve alterations in synaptic transmission, the mechanism for chemical transmission between neurons.
- The precise mechanisms by which inhaled anesthetics produce each of their principal actions have not been fully elucidated despite a number of promising candidate molecular targets.
- The physicochemical nature of the typical anesthetic binding site is hydrophobic and amphipathic.
- In contrast to intravenous anesthetics, inhaled anesthetics can act at a number of membrane-bound ion channels and receptors at clinically relevant effect site concentrations. Volatile anesthetics have potentiating effects on inhibitory $GABA_A$ and glycine receptors and K^+ channels, and inhibitory effects on excitatory Na^+ and Ca^{2+} channels. The gaseous anesthetics nitrous oxide and xenon have predominant NMDA-type glutamate receptor blocking effects.
- Inhaled anesthetics have a diverse range of clinically significant effects on multiple organ systems, both beneficial and potentially adverse. Potentially beneficial effects include organ protection, while adverse effects include respiratory and cardiovascular depression.
- Inhaled anesthetics have agent-specific pharmacologic, pharmacokinetic, and side effect profiles that determine their optimal clinical applications based on patient and procedure specific applications.
- Anesthetic-induced neurotoxicity occurs in animal models at critical periods in early brain development with unclear clinical significance.

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12

Drugs for Neuropsychiatric Disorders

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Historical Perspective

In 2016, 395 million prescriptions for drugs used in the treatment of mental health were dispensed in the United States. A further 387 million prescriptions were dispensed for other neurologic disorders. Combining these two therapeutic classes, neuropharmacologic agents represent the most prescribed family of drugs, exceeding antihypertensives (721 million), antinociceptives (460 million), antibacterials (270 million), lipid regulators (264 million), and diabetes treatments (224 million).[1] Antidepressants are the most frequently used drugs in adults aged 18 to 44 years and are taken by 13% of persons aged 20 years and older.[2,3] Neuropharmacology also includes a heterogeneous and expanding collection of antipsychotics, mood stabilizer agents, psychostimulants, and drugs used in the treatment of epilepsy, Parkinson disease, and addiction. Considered together, drugs used to treat mental health and neurologic disorders are encountered by anesthesiologists as a matter of routine daily practice. They have diverse effects on neuronal systems, including those that are the principal targets of anesthetic agents, and many are associated with significant unwanted actions on central and peripheral signaling across broad transmitter classes. Many alter hepatic cytochrome P450 isoenzyme (CyP)

activity and thus can have significant drug interactions by affecting metabolism of other agents. The potential impact of psychopharmacologic drugs on perioperative physiology is enormous. In addition to altering the central nervous system (CNS) response to sedative and hypnotic agents, they can alter autonomic responsiveness, cardiac conduction, bleeding, seizure potential, the endocrine response to stress, and multiple other physiologic variables that fall under the purview of anesthesiology. Similar considerations apply to the anticonvulsant and anti-parkinsonian therapeutic classes. Finally, drugs of abuse, with wide-ranging short- and long-term effects on the CNS, have critically important implications for the safe delivery of anesthesia in both the acutely intoxicated and addicted patient.

Because the core aspects of clinical practice in both psychiatry and neurology are distinct from those of anesthesiology, and because many psychopharmacologic agents have emerged only very recently, anesthesiologists might have an incomplete baseline awareness of the actions and adverse effects associated with these drugs and be less likely to encounter timely updates. This chapter presents a focused introduction to most of the neuropsychiatric drugs encountered in perioperative patients. An exhaustive description can be found in dedicated reference texts.[4]

Antidepressant Drugs

Tricyclic Antidepressants

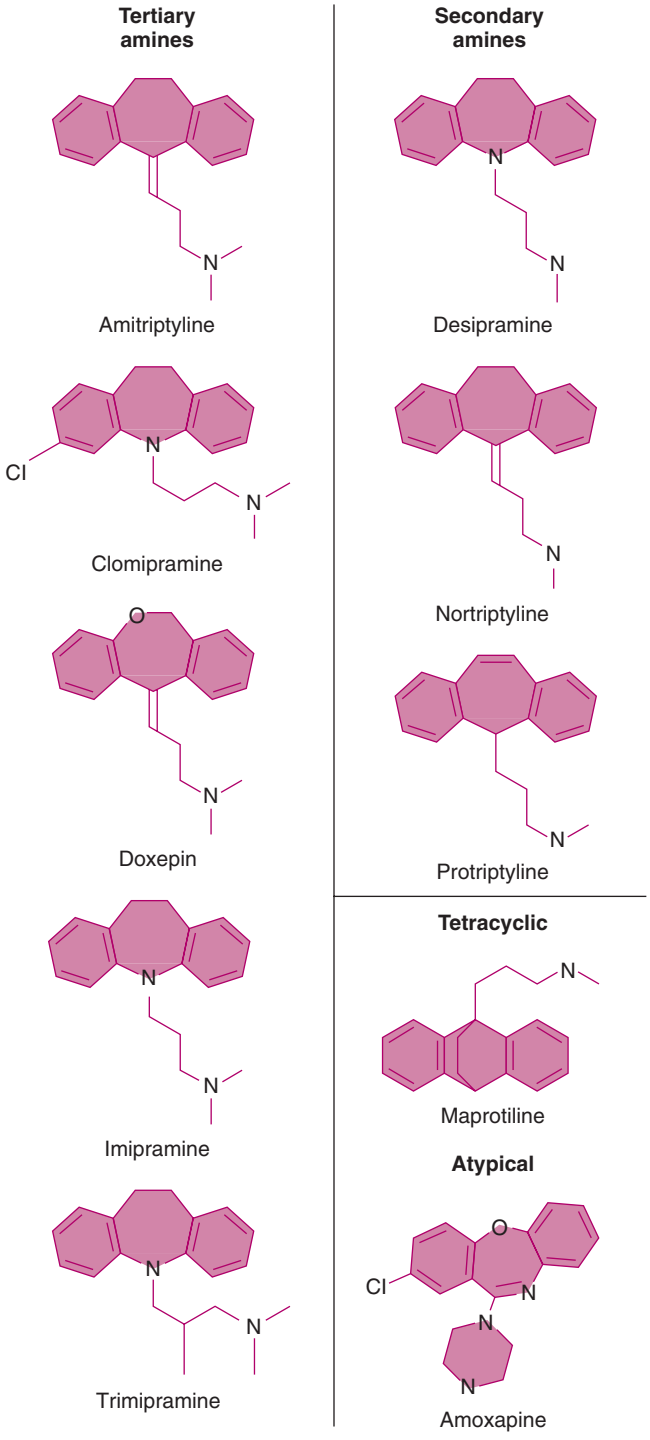
History

The iminodibenzyl derivatives were initially investigated in humans in the 1950s for their sedative and antihistaminic properties. The sedative properties of the archetypal drug imipramine proved to be of little benefit in the treatment of agitated patients, but serendipitously it was noted to relieve the symptoms of depression.[5] Subsequently, several other tricyclic compounds were developed, and the class remained the first-line treatment for depression until the rapid expansion in use of selective serotonin reuptake inhibitors (SSRIs) in the 1990s. Early advances in the neuropsychopharmacology of depression—including the importance of the serotonin and noradrenergic pathways—owed much to the study of this class of compounds.

Basic Pharmacology

Structure-Activity

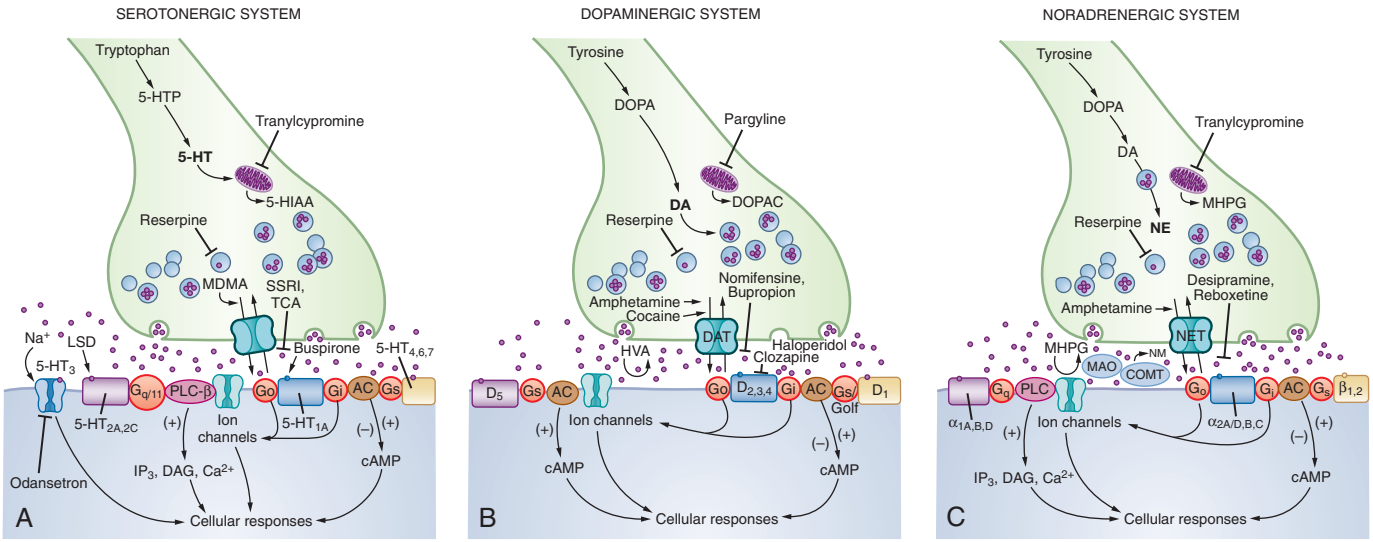
The tricyclic antidepressants are named because of their central three-ring complex with a single side chain. The class is then further divided into two subgroups on the basis of the side chain: the *tertiary amines* have two methyl groups at the end of the side chain, whereas the *secondary amines* possess a single methyl group (Fig. 12.1). Although these compounds block both the serotonin transporter and the norepinephrine transporter, the relative potency for each is largely determined by the nature of the side chains. The tertiary amines have dominant effects on serotonin reuptake, whereas the secondary amines have greater potency on norepinephrine reuptake.[6] Amoxapine is a structurally unique tricyclic antidepressant derived from the antipsychotic loxapine; it is characterized by potent inhibition of norepinephrine reuptake and dopamine receptor block by the metabolite 7-hydroxy-amoxapine.[7] Maprotiline is unique in possessing a four-ring central structure and is referred to as a tetracyclic or heterocyclic. It possesses the secondary amine side chain and predictably has dominant effects on norepinephrine transport.



• **Fig. 12.1** Chemical structure of the tricyclic and tetracyclic antidepressants.

Mechanism

The antidepressant effects of the tricyclic drugs are mediated by effects on two monoaminergic systems—serotonin and norepinephrine—although it is not clear to what extent this implicates specific abnormalities of serotonin and norepinephrine signaling and pharmacology in the biochemical pathogenesis of depression (Fig. 12.2). Although modulation of reuptake occurs rapidly, clinical benefit is not seen until several weeks of treatment,



• **Fig. 12.2** The serotonergic, dopaminergic, and noradrenergic systems in psychopharmacology. A, In the serotonergic system, L-tryptophan is converted to 5-hydroxytryptophan *(5-HTP)* and then to serotonin *(5-HT).* Presynaptic regulation occurs through somatodendritic 5-HT_{1A} and 5-$HT_{1B,1D}$ autoreceptors (not shown). Binding to G-protein–coupled receptors (G_o, G_i, etc.) that are coupled to adenylyl cyclase *(AC)* and phospholipase C-β *(PLC-β)* results in a cascade of second-messenger and cellular effects. Reuptake occurs via the 5-HT transporter (5-HTT), after which 5-HT is either repackaged into vesicles or metabolized to 5-hydroxyindolacetic acid *(5-HIAA)* by mitochondrial monoamine oxidase (MAO). The SSRIs and TCAs block reuptake at the 5-HTT. Tranylcypromine inhibits mitochondrial MAO. Reserpine, an antipsychotic, causes depletion of storage vesicles. Buspirone is a presynaptic and postsynaptic partial 5-HT_{1A} agonist. Lysergic acid diethylamide *(LSD)* likely interacts with numerous 5-HT receptors, while MDMA ("ecstasy") alters 5-HTT function. B, In the dopaminergic system, L-tyrosine is converted to L-dihydroxyphenylalanine (L-DOPA), and then to dopamine *(DA).* Presynaptic regulation occurs through somatodendritic and nerve terminal D_2 receptors (not shown). Reuptake is via the dopamine transporter *(DAT),* after which DA is either sequestered into vesicles or metabolized to dihydroxyphenylalanine *(DOPAC)* by mitochondrial MAO. DA can also be degraded to homovanillic acid *(HVA)* through synaptic MAO and catechol-*O*-methyltransferase *(COMT).* Reserpine causes depletion of storage vesicles. Pargyline inhibits MAO selectively in DA neurons. Haloperidol is a D_2 antagonist, and clozapine is a nonspecific D_2/D_4 antagonist. Bupropion interacts with the DA system, but its exact action is unclear. Cocaine and amphetamine alter DAT function. C, In the noradrenergic system, L-tyrosine is metabolized through L-DOPA and DA to norepinephrine *(NE).* Presynaptic regulation occurs through somatodendritic and nerve terminal α_2-adrenoreceptors (not shown). Reuptake occurs via the NE transporter *(NET),* after which NE is either sequestered into vesicles or metabolized to 3-methoxy-4-hydroxyphenylglycol *(MHPG)* by mitochondrial MAO and aldehyde reductase. Metabolism also occurs synaptically to MHPG via MAO or to normetanephrine (NM) via COMT. Reserpine causes depletion of NE in storage vesicles. Tranylcypromine inhibits mitochondrial MAO. The selective NE reuptake inhibitor and antidepressant reboxetine and TCA desipramine interfere with the reuptake of NE. Amphetamine facilitates NE release by altering NET function. *cAMP,* Cyclic adenosine monophosphate; *DAG,* Diacylglycerol; *IP3,* inositol-1,4,5-triphosphate; *NMDA,* N-methyl-d-aspartate; *SSRI,* selective serotonin reuptake inhibitor; *TCA,* tricyclic antidepressant. (Modified from Schatzberg AF, Nemeroff CB. *The American Psychiatric Publishing Textbook of Psychopharmacology*. 4th ed. Arlington, VA: American Psychiatric Publishing; 2009.)

suggesting that downstream changes in gene expression and neuroplasticity are critically involved. The decreased uptake initially causes feedback inhibition via presynaptic 5-HT_{1A} autoreceptors, but this is followed by desensitization and a return to normal firing rate after 2 weeks.[8] Postsynaptic 5-HT_{1A} receptors become sensitized, while antagonism of postsynaptic 5-HT_2 receptors further increases the effects of serotonin.[9] In contrast, presynaptic α_2-receptors do not desensitize, and the firing rate of noradrenergic neurons remains inhibited throughout treatment.[10] The noradrenergic mechanism likely includes complex modulatory effects on the expression of postsynaptic α_1-, α_2-, and β-adrenergic receptors and on their second-messenger systems. Tricyclic antidepressants also have variable antagonist activity at 5-HT_6, 5-HT_7, N-methyl-D-aspartate (NMDA)-type glutamate, H_1- and H_2-histaminergic, and muscarinic acetylcholine receptors. They also have variable agonist activity at μ_1-opioid receptors.[11] Accumulating evidence also suggests that the antidepressant effects of the tricyclics, and other classes of antidepressants, may involve transduction by the neurotrophin brain-derived neurotrophic factor (BDNF) and the tropomysin-related kinase B (TrkB) receptor.[12,13]

Metabolism

Metabolism is almost exclusively hepatic and dominantly involves either hydroxylation of the ring structure or demethylation of

the side chain. The tertiary amines are demethylated to active secondary amines (e.g., imipramine to desipramine), which incurs an increase in noradrenergic activity. Many of the hydroxylated metabolites are also active. The principal CYP) isoenzymes involved are 2D6, 1A2, 3A4, and 2C19. Variability in metabolism and plasma levels can be dramatic, owing to both exogenous modulation of the CYP system and to genetic polymorphisms that occur in up to 20% of Asian and 10% of Caucasian and African black populations.[14,15]

Clinical Pharmacology

Pharmacokinetics

The tricyclic antidepressants are rapidly absorbed from the small intestine and mostly attain peak plasma levels in 2 to 8 hours. They are highly protein bound (>90%) and lipophilic, with large volumes of distribution up to 60 L/kg. Bioavailability is variable, with on average about 50% to hepatic first-pass metabolism. Plasma half-life is longer than 24 hours for most drugs (the exception being amoxapine), allowing for once-a-day dosing. However, variation is significant and determined largely by genetic and phenotypic variability. The daily dose is thus not a reliable determinant of steady-state plasma levels. Further, a relationship between plasma concentration and therapeutic response, while demonstrated for some drugs, has not been established across the entire class.[16] Monitoring of plasma levels, though often suggested, remains controversial because of the lack of validated interpretation studies. The level of recommendation for plasma monitoring is highest for amitriptyline, nortriptyline, clomipramine, and imipramine.[17] Dosing is often started low and increased gradually based on therapeutic response, with monitoring of plasma levels reserved for patients suspected to be at the extremes of rapid and slow metabolizers.

Pharmacodynamics

Therapeutic Effects. Tricyclic antidepressants have demonstrated efficacy in the treatment of major depression. Response rates for patients completing treatment with imipramine, the most studied drug, exceed 65%. However, substantial caution must be implied in the interpretation of efficacy studies, as the response to placebo is ~40%; a recent Cochrane review suggests that compared with placebo, the median number needed to treat was 9.[18] They are also effective for maintenance therapy, with up to 80% of patients successfully maintained for 3 years.[19] Relative to other classes of antidepressants, the tricyclics might have an efficacy advantage in patients with severe or endogenous depression, or in those who are hospitalized, although this is not clearly established. Low doses (75–100 mg) of tricyclics are as effective as higher doses.[20] They have no particular advantage over other agents in the treatment of anxious, atypical, psychotic, bipolar, or late-life depression. Because of its high serotonergic activity, clomipramine is effective and is used for the treatment of obsessive-compulsive disorder.[21] The tricyclics are also used in panic disorder. Desipramine is effective in the treatment of attention deficit/hyperactivity disorder,[22] but its use is contraindicated in children because of reports of sudden cardiac death. Tricyclics are also widely used in the treatment of chronic and neuropathic pain syndromes (see Chapter 19), and are more effective than the SSRIs in this regard. A recent Cochrane review showed a number-needed-to-treat of 3.6 and a relative risk of 2.1 for at least moderate relief of neuropathic pain with tricyclic antidepressants.[23] The effects appear independent of those on depression, and generally occur at lower doses, consistent with a distinct underlying mechanism, with antinociceptive actions mediated by effects on descending serotonin and norepinephrine spinal pathways.[24]

Adverse Effects. The most common side effects associated with tricyclic antidepressants result from their antimuscarinic and antihistaminic actions. Amitriptyline and clomipramine have the greatest antimuscarinic potency and desipramine the lowest. Dry mouth, urinary hesitancy, decreased gastric motility, and blurred vision are relatively common. Ocular crisis can be precipitated in patients with narrow-angle glaucoma. H_1-histaminic blockade results in sedation. Confusion and delirium are dose-dependent and result from the combination of anticholinergic and antimuscarinic activity. Patients with preexisting dementia or psychotic depression are especially at risk, and the incidence is highest with amitriptyline. There is also a dose-dependent risk of seizure, although the incidence is poorly defined. It is less than 1% across the drug class if plasma level monitoring is appropriately used.[25] A recent study of more than 150,000 patients found the incidence of seizure to be no greater than in nonusers of antidepressants.[26] Nonetheless, use of these drugs in patients with elevated seizure risk is not advisable. The overall incidence of CNS toxicity is approximately 6%.[27] Tricyclic antidepressants cause orthostatic hypotension, especially in patients receiving antihypertensive therapy, and also cause a persistent increase in heart rate. They inhibit sodium-potassium adenosine triphosphatase (Na^+,K^+-ATPase) and act like class Ia (quinidine-like) antiarrhythmics by stabilizing excitable membranes and delaying His bundle conduction, and so must be used cautiously in patients with a prolonged QTc interval. In overdose, sudden death can occur from cardiac arrhythmia at doses of only 10 times the therapeutic dose.[28] Largely because of this arrhythmia risk, the mortality associated with tricyclic overdose is approximately 15 times that associated with SSRI overdose[29] a significant factor in the rapid acceptance of SSRIs as first-line therapy for treatment of depression.

Drug Interactions

The complex effect of tricyclic antidepressants on presynaptic and postsynaptic noradrenergic signaling can alter the response of patients to sympathomimetic drugs used in the perioperative period (see Chapter 25). During initial treatment, patients can have an exaggerated response to indirect-acting sympathomimetics such as ephedrine owing to increased presynaptic availability of norepinephrine. In contrast, adrenergic desensitization and catecholamine depletion can result in a relatively refractory response to sympathomimetics in patients treated long term; such patients might respond best to the potent direct-acting sympathomimetic norepinephrine.[30] Tricyclic antidepressants can exaggerate rebound hypertension following discontinuation of antihypertensives, likely owing to changes in norepinephrine uptake.[31] Tricyclic antidepressants can increase arrhythmogenicity in the presence of volatile anesthetics, although these observations are dominantly with halothane and have not been seen with newer volatile anesthetics.[32,33] The anticholinergic effects of tricyclic antidepressants are expected to be additive to those of other drugs used in the perioperative period, and special caution should be used in administering centrally acting anticholinergics in those patients taking tricyclics who are at increased risk of delirium and dementia. Chronically administered barbiturates are potent inducers of CYP3A4 and can increase metabolism of tricyclic antidepressants, but significant effects are unlikely after a single anesthetic administration. Tricyclics are not known to have any effects on CYP isoenzyme induction or inhibition that are of significance to common anesthetic management.

Selective Serotonin Reuptake Inhibitors

History

The SSRIs were developed in the early 1970s when series of compounds derived from 3-phenoxy-3-phenylpropylamine—which is structurally similar to diphenhydramine—were tested for selective inhibition of serotonin (5-HT) reuptake.[34] The most potent and selective of the compounds was identified and named fluoxetine, and was eventually approved by the U.S. Food and Drug Administration (FDA) for the treatment of major depression in 1987 (Prozac). This was followed by sertraline (Zoloft) in 1991, paroxetine (Paxil), citalopram (Celexa) in 1998, and escitalopram (Lexapro) in 2002. Fluvoxamine (Luvox) was approved in 1993, and is distinctive because its FDA approval is restricted to the treatment of obsessive-compulsive disorder; it is, however, approved for the treatment of depression in other countries. A highly favorable safety profile compared with the tricyclic antidepressants rapidly propelled fluoxetine and later SSRIs to become the dominant antidepressant agents, although in recent years their commercial success relative to their clinical efficacy has been questioned.[35,36]

Basic Pharmacology

Structure-Activity

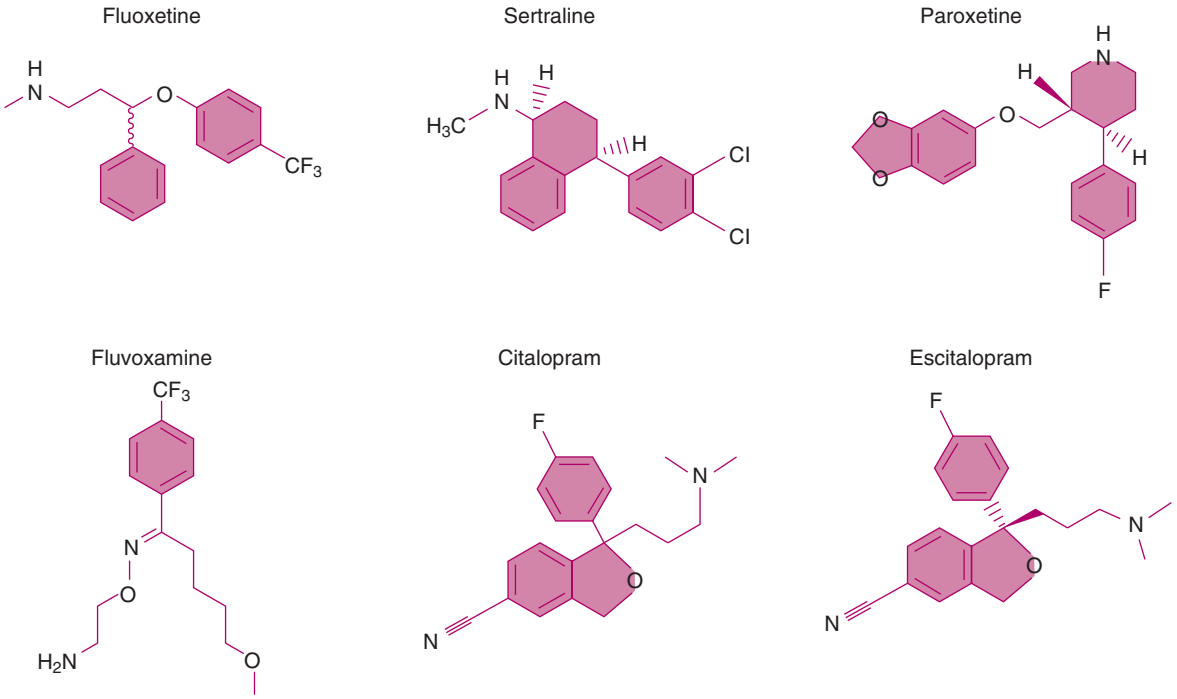
There is considerable diversity in the chemical structure-activity relations among the SSRIs (Fig. 12.3). Fluoxetine exists as a racemate, with both the *(S)*- and *(R)*-enantiomers pharmacologically active. Citalopram was initially introduced as a racemate, with the more potent *(S)*-enantiomer (escitalopram) subsequently isolated. All SSRIs possess relatively high affinity for serotonin uptake sites, low affinity for norepinephrine uptake sites, and very low affinity for neurotransmitter receptors, although there is considerable variability. Fluoxetine is the least selective of the class, with citalopram and escitalopram the most selective.[37] Sertraline is unique as a more potent inhibitor of dopamine uptake than any of the SSRIs or tricyclic antidepressants. Activity at H_1-histaminergic, α_1-adrenergic, and muscarinic receptors is minimal and unlikely to be of clinical significance, which is responsible for the absence of many of the side effects associated with tricyclic antidepressants.

Mechanism

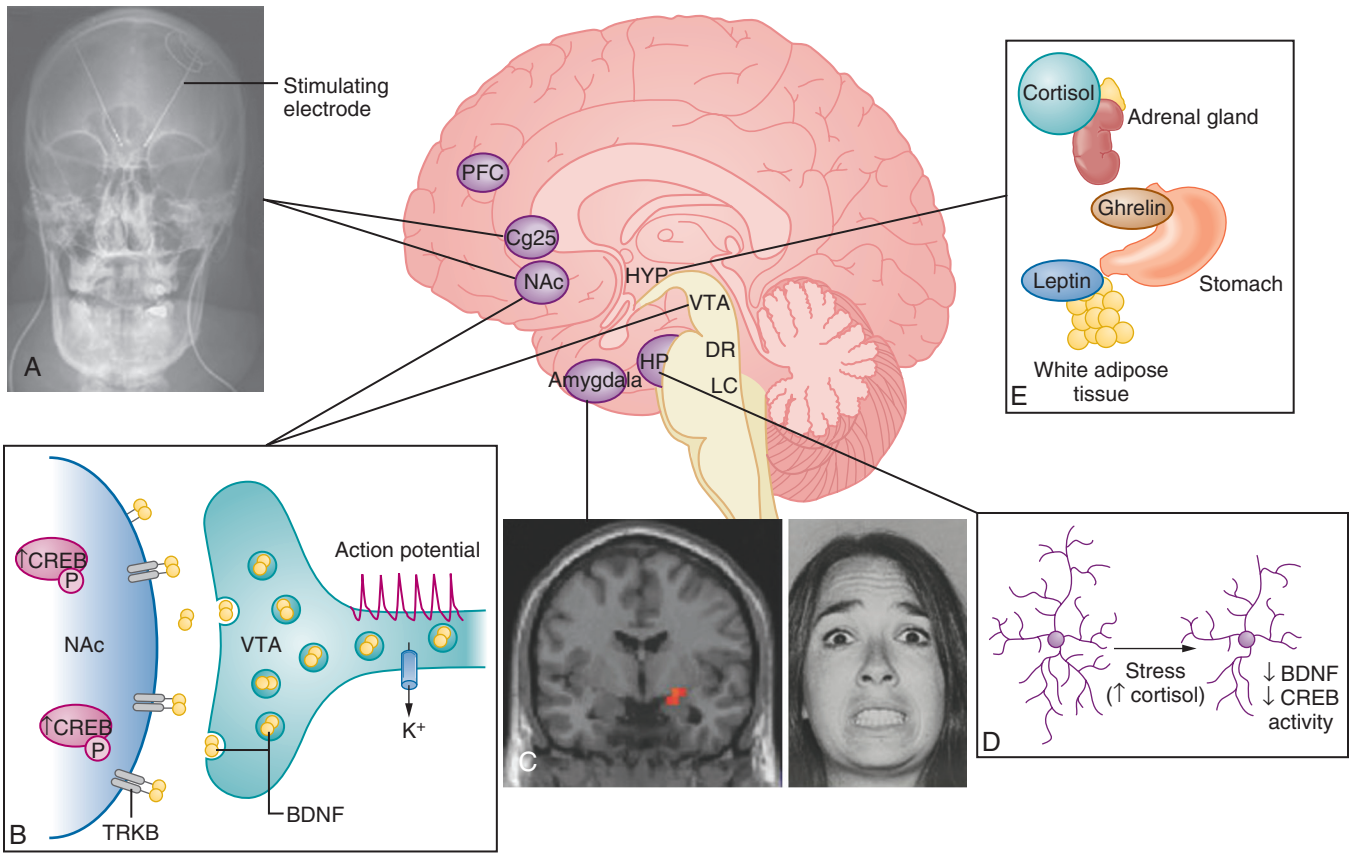
The mechanisms for the therapeutic effects of the SSRIs are not clearly established, but were initially believed to derive from blockade of 5-HT reuptake into serotonergic neurons, prolonging the duration of exposure to 5-HT at postsynaptic binding sites (see Fig. 12.2).[38] In contrast to direct 5-HT receptor agonists, the action of SSRIs depends on presynaptic 5-HT release, and they are ineffective if release of 5-HT is compromised. Because therapeutic effects are not fully realized within 2 to 8 weeks, it is unlikely that reuptake inhibition, which occurs far sooner, is mechanistically sufficient. Several downstream effects have been mechanistically postulated. Initially, inhibitory autoreceptors in the soma ($5\text{-}HT_{1A}$) and terminals ($5\text{-}HT_{1B}$) are stimulated, and neuronal firing rates decrease. Normalization of firing rates occurs with downregulation of these autoreceptors and decreased production of $5\text{-}HT_{1B}$ messenger ribonucleic acid (mRNA), and coincides temporally with the onset of therapeutic efficacy.[39] In the same temporal window there is increased production of neuroprotective proteins, including BDNF (Fig. 12.4).[40] SSRIs also possess significant antiinflammatory properties, which may target proinflammatory signaling associated with the onset of depression.[41]

Metabolism

SSRIs are oxidatively metabolized in the liver. Several CYP isoenzymes are involved, including 2D6, 2C9, 2C19, 1A2, and 3A4, with significant differences among the drugs in relative importance. While all SSRIs except fluvoxamine have pharmacologically active



• **Fig. 12.3** Chemical structure of selective serotonin reuptake inhibitors.



• **Fig. 12.4** The neural circuitry of depression beyond monoamines. Several brain regions are implicated in the pathophysiology of depression. A, Deep brain stimulation of the subgenual cingulate cortex *(Cg25)* or the nucleus accumbens *(NAc)* has an antidepressant effect on individuals with treatment-resistant depression thought to be mediated through inhibition of these regions either by depolarization blockade or by stimulation of passing axonal fibers. B, Increased activity-dependent release of brain-derived neurotrophic factor *(BDNF)* within the mesolimbic dopamine circuit (dopamine-producing ventral tegmental area *[VTA]* to dopamine-sensitive NAc) mediates susceptibility to social stress, occurring in part through activation of the transcription factor *CREB* (cyclic adenosine monophosphate response element-binding protein) by phosphorylation *(P).* C, Neuroimaging studies implicate the amygdala (*red pixels* show activated areas) as an important limbic node for processing emotionally salient stimuli, such as fearful faces. D, Stress decreases the concentrations of neurotrophins (such as BDNF), the extent of neurogenesis, and the complexity of neuronal processes in the hippocampus *(HP).* These effects are mediated in part through increased cortisol concentrations and decreased CREB activity. E, Peripherally released metabolic hormones in addition to cortisol, such as ghrelin and leptin, produce mood-related changes through their effects on the hypothalamus *(HYP)* and several limbic regions. *DR,* Dorsal raphe; *LC,* locus coeruleus; *PFC,* prefrontal cortex; *TRKB,* tropomyosin-related kinase B. (Reproduced from Krishnan V, Nestler EJ. The molecular neurobiology of depression. *Nature*. 2008;455:894–902.)

major metabolites, only that of fluoxetine (norfluoxetine) is likely of therapeutic significance.

Clinical Pharmacology

Pharmacokinetics[42]

The SSRIs are well absorbed from the small intestine and most attain peak plasma levels in 2 to 8 hours. Protein binding is high (>80%), except with escitalopram, with volumes of distribution mostly in the range of 10 to 20 L/kg, somewhat less than seen with the tricyclic antidepressants. Plasma half-life is mostly around 20 to 30 hours, with fluoxetine somewhat longer (24–72 hours) and fluvoxamine shorter (15 hours). Norfluoxetine, the active metabolite of fluoxetine, has a half-life of 1 to 3 days. Once-a-day dosing is commonly used for all drugs except fluvoxamine, for which twice-daily dosing is preferred. There are known age and sex effects on plasma concentrations: sertraline concentrations are approximately 40% lower in young males than in older males or females, while fluvoxamine concentrations are 40% to 50% lower in males across all ages. Because no clear relationship between therapeutic efficacy and steady-state plasma concentrations has been established and because the therapeutic index is wide, plasma level monitoring is not used.[43]

Pharmacodynamics

Therapeutic Effects. SSRIs are efficacious in the initial treatment of major depression. There is little evidence to support that SSRIs as a class are more efficacious than other classes of antidepressants, including the tricyclic antidepressants, although one 2009

meta-analysis suggests that sertraline and escitalopram could have therapeutic advantages over other drugs, including other SSRIs.[44] There is little evidence to support efficacy in children and adolescents, with a 2016 meta-analysis identifying that only drug in the class with possible benefit over placebo is fluoxetine.[45] Although frequently prescribed for less severe depression, recent meta-analyses—some including trial data submitted to the FDA—question whether SSRIs have any significant therapeutic benefit.[35,36,46] The onset of clinical improvement takes 2 to 3 weeks and might not be maximal for up to 8 weeks, suggesting that downstream effects, rather than 5-HT reuptake inhibition per se, are responsible.

SSRIs are also prescribed and are probably efficacious in several other psychiatric disorders believed to involve abnormalities of 5-HT systems. Meta-analysis has demonstrated SSRIs, and especially sertraline, to be effective in the initial treatment of obsessive-compulsive disorder, although it is unclear how serotonergic selectivity confers therapeutic benefit.[47] SSRIs are also used for the prevention of panic attacks in panic disorder, and, because of postulated involvement of 5-HT in feeding behaviors, have been used in bulimia nervosa, anorexia nervosa, and obesity.[48] They reduce symptoms of premenstrual dysphoric disorder and post-traumatic stress disorder, and are effective in the treatment of premature ejaculation.[49–51]

Adverse Effects. The SSRIs have a highly favorable side effect profile compared with other classes of antidepressants. The most common side effects include sexual dysfunction, weight changes, dizziness, and insomnia. Although the effects of SSRIs on suicidality in adults are unclear,[52] they increase suicidality in patients younger than 24 and carry an FDA black box warning for use in this age group.[53] SSRIs have effects on cardiac Na^+, K^+, and Ca^{2+} channels and can theoretically cause QTc prolongation, but there is no observable increase in the risk of dysrhythmia.[54] SSRIs decrease platelet 5-HT content and inhibit platelet aggregation, and can increase bleeding, especially when combined with other anticoagulants.[55,56] One retrospective study of orthopedic patients demonstrated a significantly increased risk of transfusion in patients taking serotonergic antidepressants, but not with those taking nonserotonergic agents,[57] while another demonstrated a significant, though not clinically important, increase in bleeding in patients undergoing hip arthroplasty.[58] However, there is insufficient consensus to support perioperative changes in SSRI therapy on the basis of bleeding risk. SSRIs have effects on bone metabolism and are associated with increased risk of fracture.[59] Overdose with a single SSRI is very rarely fatal and is usually associated with minimal sequelae. Citalopram is the most likely to cause QTc prolongation, but even with extremely high doses, arrhythmias are exceedingly rare.[60]

Serotonin syndrome is a potentially fatal adverse reaction to serotonergic drugs resulting in mental status changes, autonomic hyperactivity, and neuromuscular hyperactivity. Initially this can be very difficult to distinguish from malignant hyperthermia.[61] Although theoretically possible, induction of serotonin syndrome by a single SSRI is rare, and they are usually only implicated in combination with other drugs. Several drugs used in the perioperative period—notably cocaine, ondansetron, and fentanyl—have the potential to directly or indirectly augment serotonergic activity, and this should be considered when assessing patients exhibiting hypermetabolic activity.

Drug Interactions

Significant drug interactions are less likely with SSRIs than with earlier classes of antidepressants. Perhaps the most likely source of interaction results from SSRI-induced inhibition of specific CYP isoenzymes, notably 2D6 and 2C19. However, this effect is of little relevance to the vast majority of drugs handled by anesthesiologists. Anesthesiologists should be aware of the potential for SSRIs to potentiate the QTc prolongation and antiplatelet effect of other drugs used in the perioperative period, and the serotonergic effect of methylene blue.

Monoamine Oxidase Inhibitors

The antidepressant actions of monoamine oxidase inhibitors (MAOIs) were identified in the 1950s. One member of this class—iproniazid—historically represents one of the earliest attempts to treat depression pharmacologically. MAOIs continue to have clinical utility in the treatment of resistant depression, and can be particularly effective in treating atypical depression. However, because of their severe and dangerous food and drug interactions, the classic MAOIs remain a treatment of last resort and are encountered relatively rarely. However, it is critical for anesthesiologists to recognize and be aware of these drugs, in that the potential for adverse interactions with agents used in the perioperative period exceeds that of any other psychopharmacologic class.

Basic Pharmacology

Monoamine oxidase (MAO) exists as two isoenzymes, MAO-A and MAO-B. MAO-A preferentially deaminates serotonin, epinephrine, norepinephrine, and melatonin, whereas MAO-B preferentially deaminates phenylethylamine, phenylethanolamine, tyramine, and benzylamine. Dopamine and tryptamine are deaminated by both isoenzymes. In the CNS, MAO-A is concentrated in dopaminergic and noradrenergic neurons, whereas MAO-B is concentrated in serotonergic neurons.[62] Both are also found in glial cells. Outside the CNS, MAO-A is found in the gastrointestinal tract, liver, and placenta, and MAO-B in platelets. The reason for the apparent discrepancy between the dominant substrates and localization is unknown.

MAOIs act by inhibiting MAO, thereby increasing the availability of monoaminergic transmitters (see Fig. 12.2). All MAOIs currently available in the United States bind irreversibly, inhibiting enzyme activity for up to 2 weeks. Changes in α_1-, α_2-, 5-HT_1, and 5-HT_2 receptors emerge after several weeks. Phenelzine is a hydrazine derivative and nonselective, while tranylcypromine is nonselective and chemically related to amphetamine. Selegiline is selective for MAO-B at lower doses but becomes nonselective at higher doses; metabolites of selegiline include L-amphetamine and L-methamphetamine. In 2006, selegiline became available as a transdermal patch. This system avoids inhibition of intestinal and hepatic MAO-A, thereby reducing food-drug interactions and obviating the need for dietary restriction.

Clinical Pharmacology

MAOIs are used to treat a variety of psychiatric conditions but have received greatest acceptance for atypical depression, which is characterized by early age of onset, dysthymia, alcohol abuse, and sociopathy. They are more effective than the tricyclic antidepressants in treating this disorder.[63] MAOIs are also therapeutic in typical major depression, panic disorder, bulimia nervosa, atypical facial pain, and treatment-resistant depression.[64] The transdermal patch form of selegiline is approved for use in major depression, although its efficacy relative to other drugs is not well studied.[65]

Adverse Effects, Dietary Interactions, and Drug Interactions

Common adverse effects of MAOIs include dizziness, headache, dry mouth, nausea, weight gain, peripheral edema, urinary hesitancy, and myoclonic movements. Orthostatic hypotension is common in older patients and can necessitate mineralocorticoid treatment. MAOIs can augment the response to insulin and other hypoglycemic agents increasing the risk of hypoglycemia. Phenelzine has anticholinergic action.

Dietary Interactions

Orally ingested MAOIs inhibit the catabolism of dietary amines. The consumption of foods containing tyramine can lead to severe hypertensive crisis within an hour of eating. Decreased first-pass breakdown of tyramine leads to elevated systemic levels. Tyramine is transported via vesicular monoamine transporter (VMAT) into synaptic vessels, where it displaces norepinephrine, and the release of norepinephrine precipitates the hypertensive crisis.[66] Patients using oral MAOIs must adhere to dietary restrictions to avoid precipitation of a crisis. Key foods that must be avoided include cheese, sausage meats, red wine, overripe fruits, fermented products, and some yeasts. Transdermal selegiline does not require dietary restrictions.

Drug Interactions

Irreversible inhibition of MAO by MAOIs leads to several potentially dangerous drug interactions when therapy is combined with sympathomimetic agents. In the outpatient setting, significant caution is required when crossing over to or from other psychopharmacologic agents that alter monoaminergic activity, such as SSRIs, tricyclic antidepressants, or stimulants. Several over-the-counter medications contain indirect-acting sympathomimetics and are able to precipitate a hypertensive crisis. In the perioperative setting, several drugs have the potential for dangerous interactions. The most notable of these is meperidine, which can precipitate a type I excitatory response with hypertension, clonus, agitation, and hyperthermia, or a type II depressive response with hypotension, hypoventilation, and coma.[67] This effect is believed to result from meperidine's serotonin reuptake inhibition properties. Members of the phenylpiperidine opioids, which include tramadol, fentanyl, alfentanil, sufentanil, and remifentanil, are also serotonin reuptake inhibitors and have been associated with perioperative serotonergic toxicity, as has methadone. Morphine does not appear to precipitate serotonergic crisis and is perhaps the drug of choice when opioids must be used in patients taking MAOIs. Indirect sympathomimetics, such as ephedrine, can precipitate an exaggerated pressor response owing to increased release of norepinephrine and so should be avoided. Direct-acting drugs such as phenylephrine are preferable, although the response can be exaggerated owing to receptor hypersensitivity.[68] Ketamine should similarly be avoided, although its safe use has been described.[69]

Atypical Antidepressants

Several drugs currently used in the treatment of depression and related disorders have structures and mechanisms that cannot be placed in any of the broad classes described and are commonly referred to as atypical, second-generation antidepressants. The most important of these are summarized in Table 12.1. Like the tricyclic antidepressants and SSRIs, the therapeutic mechanism of these agents is poorly understood. All drugs share effects on signaling or transmitter availability in at least one monoaminergic (serotonergic, noradrenergic, or dopaminergic) pathway.

Anxiolytic Drugs

Benzodiazepines

History

The first benzodiazepine, chlordiazepoxide (Librium), was introduced in 1960. This was followed in 1963 by diazepam (Valium), the archetypal compound from which many derivatives were synthesized. The benzodiazepines were rapidly embraced as treatments for anxiety because they were considerably safer than the barbiturate alternatives and were extensively prescribed until the 1980s. In the past 25 years, benzodiazepine use has declined, partly because of awareness and concerns regarding addiction, withdrawal, and recreational abuse, and also because of the evolution of the SSRIs as a safe and effective first-line therapy for anxiety and panic disorder. Nonetheless, alprazolam (Xanax), a triazolobenzodiazepine introduced in 1981 for the treatment of panic disorder, remains the single most prescribed psychiatric medication, with 48 million prescriptions in 2016.[1]

Basic Pharmacology

Structure-Activity

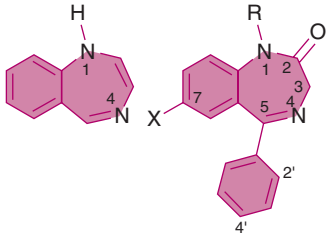
The core structure of the benzodiazepines is the fusion of benzene and diazepine ring systems. All therapeutically active drugs are substituted 1,4-benzodiazepines, with many containing a 5-phenyl-1 *H*-benzo[*e*][1,4]diazepin-2(3*H*)-one substructure (Fig. 12.5).

Mechanism

Benzodiazepines act by binding at the interface of the α and γ subunits of the $GABA_A$ receptor. This binding site is distinct from that of endogenous agonist GABA (which binds between the α and β subunits), and also from other GABAergic drugs, such as barbiturates (Fig. 12.6). Benzodiazepines allosterically modulate the receptor such that it has greater affinity for GABA. This increases the opening time of the associated chloride channel, which leads to hyperpolarization or stabilization of the resting membrane potential near the chloride equilibrium potential. Because binding requires a specific histidine residue in the α subunit, benzodiazepines act only at receptors containing α_1, α_2, α_3, or α_5 subunits, and have no action on receptors containing α_4 or α_6 subunits. Benzodiazepines are heterogeneous in their affinities for various $GABA_A$ receptor subtypes, which underlies the differences in their pharmacologic effects. For example, anxiolysis is associated with greater relative affinity for the α_2 subunit.[70]

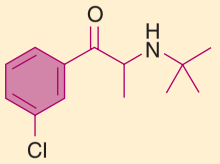
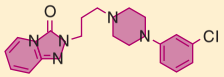
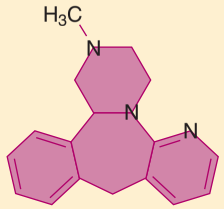
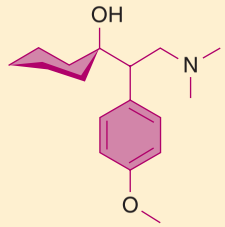
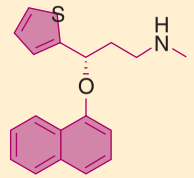
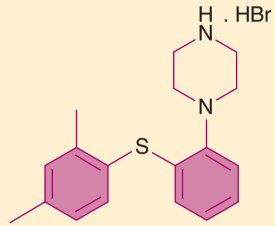
Metabolism

Most benzodiazepines are highly protein bound and undergo microsomal oxidation in the liver via CYP enzymes, especially

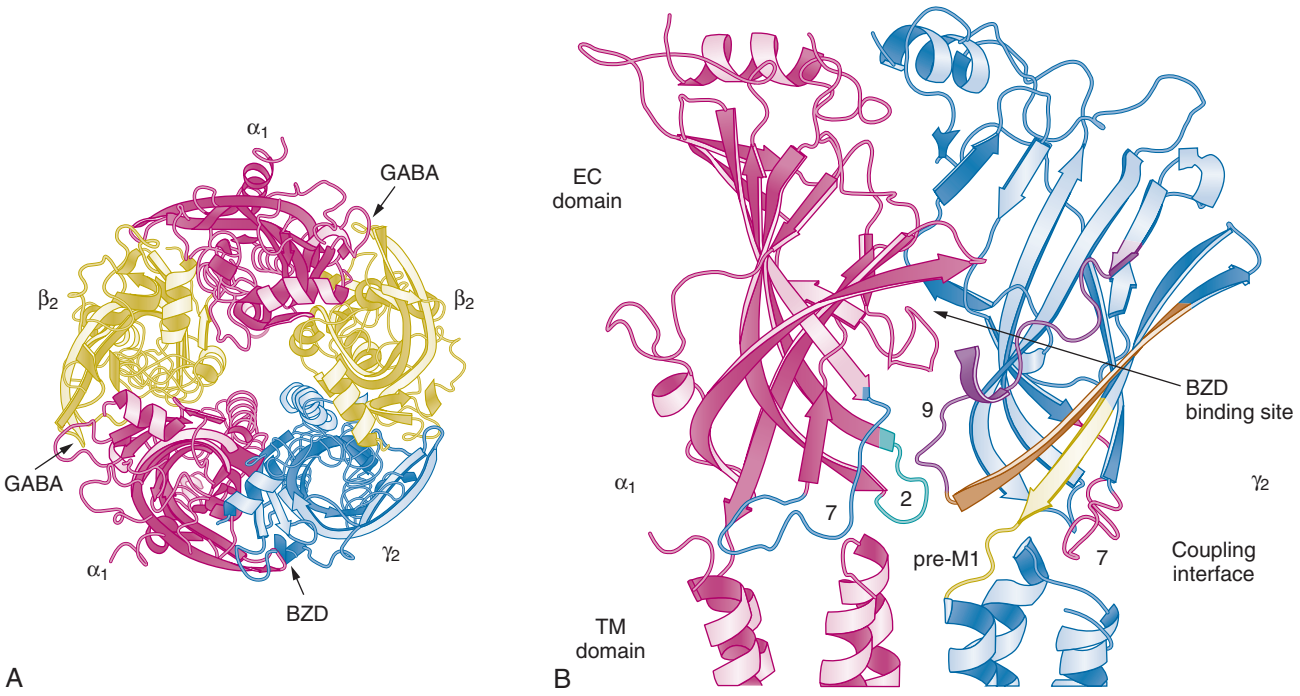


• **Fig. 12.5** Benzodiazepine structure. The 1,4-benzodiazepine ring system is shown on the left side of the figure. The right side shows the most common skeleton, which contains a 5-phenyl-1 *H*-benzo[*e*][1,4]diazepin-2(3*H*)-one substructure.

TABLE 12.1 Atypical Antidepressants

	Bupropion	Trazodone	Mirtazapine	Venlafaxine	Duloxetine	Vortioxetine
Structure						
Common trade name	Wellbutrin	Oleptro	Remeron	Effexor	Cymbalta	Brintellix
Class	Dopamine and norepinephrine reuptake inhibitor	Serotonin antagonist and reuptake inhibitor (SARI)	Noradrenergic and specific serotonergic antidepressant	Serotonin-norepinephrine reuptake inhibitor (SNRI)	SNRI	Serotonin modulator and stimulator
Metabolism	CYP2B6 to hydroxybupropion (active)	CYP3A4 to *m*-chlorophenylpiperazine (active)	CYP 1A2, 2C9, 2D6, 3A4	CYP 2D6 to *O*-desmethylvenlafaxine (active) and others	CYP 1A2, 2D6	CYP 2D6 to inactive metabolite
Half-life	21 hours	7-10 hours	20-40 hours	5 hours	12 hours	66 hours
Approved therapeutic indications	Major depression Seasonal depression Smoking cessation	Major depression	Major depression	Major depression Generalized anxiety Social anxiety Panic disorder	Major depression Generalized anxiety Diabetic neuropathy Fibromyalgia Musculoskeletal pain	Major depression
Adverse effects	Common: nausea, dry mouth Dose-related increase in seizures May cause increased blood pressure and tachycardia.	Common: sedation, headache, dizziness May cause orthostatic hypotension, priapism, and QT prolongation. Arrhythmias have been reported. May impair platelet aggregation and increase bleeding risk.	Common: sedation, weight gain, hypercholesterolemia May cause decreased gastric motility, urinary retention, hyponatremia, and akathisia. Agranulocytosis is rare.	Common: nausea, dry mouth, dizziness, sexual dysfunction May cause increased blood pressure, tachycardia, and hypercholesterolemia. May impair platelet aggregation and increase bleeding risk.	Common: nausea, sexual dysfunction May impair platelet aggregation and increase bleeding risk. May increase serum glucose in diabetic patients. May cause hepatotoxicity in at-risk patients.	Common: nausea, sexual dysfunction, dizziness May cause abnormal bleeding May cause hyponatremia.
Drug interactions	May reduce the effectiveness of codeine and tramadol due to CYP 2D6 inhibition. Caution should be used when combining with other drugs that lower the seizure threshold.	May potentiate action of antiplatelet drugs, drugs that prolong QTc, antihypertensives, and sedatives, including anesthetic drugs, and drugs that can trigger serotonin syndrome. Should not be combined with MAOIs.	May potentiate action of sedatives, including anesthetic drugs, anticholinergic drugs, drugs that lower the seizure threshold, and drugs that can trigger serotonin syndrome. May potentiate the effect of warfarin. Should not be combined with MAOIs.	May potentiate action of antiplatelet drugs, drugs that lower seizure threshold, and drugs that can trigger serotonin syndrome. Should not be combined with MAOIs. No known significant anesthetic interactions.	Ciprofloxacin may significantly increase serum concentration and toxicity. May potentiate action of antiplatelet drugs, drugs that lower seizure threshold, and drugs that can trigger serotonin syndrome. Should not be combined with MAOIs. No known significant anesthetic interactions	May potentiate action of antiplatelet drugs, drugs that lower seizure threshold, and drugs that can trigger serotonin syndrome. Should not be combined with MAOIs. No known significant anesthetic interactions

MAOIs, Monoamine oxidase inhibitors.



• **Fig. 12.6** $GABA_A$ receptor structure and benzodiazepine binding site. A, Homology model of the $\alpha_1\beta_2\gamma_2$ $GABA_A$ receptor as seen from the extracellular membrane surface. The α_1, β_2, and γ_2 subunits are highlighted in *red, yellow,* and *blue,* respectively. *Arrows* indicate that GABA binds at the β_2/α_1 interfaces, whereas benzodiazepines *(BZDs)* bind at the α_1/γ_2 interface of the receptor. B, Side view of the α_1 and γ_2 extracellular domains; the location of the BZD binding site is indicated by an *arrow*. Relevant loops at the coupling interface are highlighted as follows: γ_2 loop 9, purple; γ_2 pre-M1, yellow; γ_2 loop 7, red; α_1 loop 2, green; α_1 loop 7, blue. *GABA,* gamma aminobutyric acid. (Reproduced from Hanson SM, Morlock EV, Satyshur KA, et al. Structural requirements for eszopiclone and zolpidem binding to the gamma-aminobutyric acid type-A ($GABA_A$) receptor are different. *J Med Chem*. 2008;51:7243–7252.)

CYP 3A4. Their metabolism is therefore altered by the presence of drugs that either inhibit or induce CYP activity, as well as by age and disease. Several benzodiazepines have active metabolites, including a number with half-lives considerably longer than the parent compound; the half-life of the partial agonist N-desmethyldiazepam, the principal metabolite of diazepam, can exceed 100 hours. Three benzodiazepines—oxazepam, lorazepam, and temazepam—are metabolized by glucuronidation and have no significantly active metabolites; these are therefore preferred in older adults and in patients with hepatic disease.

Clinical Pharmacology

Pharmacokinetics

Benzodiazepines vary substantially in their absorption and rate of elimination (Table 12.2). Although differences in affinities for specific $GABA_A$ receptor subtypes lead to greater or lesser propensity to alter a particular cognitive function, heterogeneity in pharmacokinetic properties largely determines the clinical application of individual drugs. Duration of action is principally a function of α phase (distribution-redistribution) dynamics rather than rate of elimination in most applications.

Pharmacodynamics

Therapeutic Effects. Benzodiazepines have a wide spectrum of uses in psychopharmacology owing to their sedative, hypnotic, amnesic, anxiolytic, anticonvulsant, and muscle-relaxant properties. They are efficacious in the short-term treatment of panic disorder, but have largely been replaced by SSRIs as the first-line pharmacotherapy and are generally not regarded as appropriate for long-term monotherapy or combination therapy.[71,72] Similarly, they are effective in the initial management of generalized anxiety disorder, but do not modify the course when used long term.[73] Benzodiazepines remain a common therapy for short-term treatment of insomnia, although their use has declined with greater awareness of dependence and cognitive side effects in older adults. The time to onset and duration of sleep are prolonged, but there is a characteristic reduction in rapid-eye movement (REM) sleep, increase in non-REM sleep, and reduction in delta electroencephalographic activity.[74] They are also used as second-line treatment in the nonacute management of seizure disorders and as first-line treatment in alcohol withdrawal syndrome.[75] Benzodiazepines are also used for their muscle relaxant properties. Despite clear evidence that long-term benzodiazepine use is rarely helpful and can be harmful, long-term use remains common.

Adverse Effects. Benzodiazepines can cause prolonged sedation, impaired cognition, and psychomotor performance, and unwanted amnesia. In older patients, they can precipitate delirium states and increase the risk of accidents and falls. Drugs with long-acting metabolites pose the greatest risk. However, the most significant risks associated with benzodiazepine use occur owing to dependence and withdrawal effects. Abrupt withdrawal can precipitate delirium, anxiety, panic, seizures, insomnia, and muscle spasm.[76]

TABLE 12.2 Benzodiazepine Pharmacokinetics

Class	Drug	Common Trade Name	Onset (min)	Duration (hr)	Vd (L/kg)	Protein Binding (%)	$t_{1/2}$ (hr)
Desmethyldiazepam	Diazepam	Valium	30	2–3	0.8–1.0	98	20–50
	Chlordiazepoxide	Librium	60–120	≤24	3.3	90–98	6.6–25
Desalkylflurazepam	Flurazepam	Dalmane	15–20	7–8	3.4	97	74–90
	Clonazepam	Klonopin	20–60	≤12	1.5–4.4	85	19–50
Triazolobenzodiazepine	Triazolam	Halcion	15–20	6–7	0.8–1.8	89	1.5–5.5
	Alprazolam	Xanax	60	3.5–7	0.9–1.2	80	11.2
Thienodiazepine	Nitrazepam	Mogadon	20–50	6–10	2.4	87	30
	Flunitrazepam	Rohypnol	15–30	7–8	4.6	78	22
Oxazolobenzodiazepine	Oxazepam	Serax	45–90	6–12	1.0–1.3	86–99	2.8–5.7
	Lorazepam	Ativan	5–20	6–8	1.3	85	12.9
	Temazepam	Restoril	20–40	6–8	1.4	96	9.5–12.4

$t_{1/2}$, Half-life; *Vd*, volume of distribution.

Drug Interactions

Although widely believed, it is not clear that patients on chronic benzodiazepine therapy have significant cross-tolerance to non-benzodiazepine GABAergic anesthetic agents, or that the risk of intraoperative recall is elevated with long-term use.[77] Acutely, benzodiazepines augment the CNS depressant effects of sedative-hypnotic anesthetic drugs and opioids, such that dosage reduction is appropriate. Although many benzodiazepines are metabolized by CYP 3A4, they are generally not strong inducers or inhibitors, and effects on the metabolism of other drugs used in the perioperative period are generally not significant.[77]

Antipsychotic Drugs

First-Generation (Typical) Antipsychotics

The introduction of chlorpromazine (Thorazine) in 1952 arguably represents the most significant single development in psychopharmacology. Before that, treatment for psychosis was largely supportive and ineffective, with only electroconvulsive therapy and psychosurgery standing as controversial therapeutic options. The ability to treat psychosis effectively with drugs heralded massive deinstitutionalization as patients were discharged from psychiatric long-term care facilities and integrated into the community.

Pharmacology

The first-generation, or *typical,* antipsychotics include drugs from several classes: phenothiazines, butyrophenones, thioxanthenes, dihydroindolones, dibenzepines, diphenylbutylpiperidines, benzamides, and iminodibenzyls (Table 12.3). The butyrophenone class includes haloperidol (Haldol) and droperidol, two of the only psychopharmacologic agents commonly administered by anesthesiologists, although the latter is usually used for its antiemetic rather than its antipsychotic actions (see Chapter 34).

The principal mechanism for treatment of schizophrenia and other psychoses is blockade of D_2 dopamine receptors in the mesolimbic dopamine system. Dopamine receptors are G-protein–coupled receptors that exist in multiple subtypes (Table 12.4). They can be grouped as D_1-like (activate adenylyl cyclase) or D_2-like (inhibit adenylyl cyclase) based on their signaling mechanisms. However, first-generation antipsychotic (FGAs) are not selective and have variable effects on D_1, D_3, and D_4 receptors; M_1 muscarinic cholinergic receptors; H_1-histamine receptors; α_1- and α_2-adrenergic receptors; and both 5-HT_1 and 5-HT_2 serotonergic receptors. The effects on these other receptors appear to have little influence on the therapeutic efficacy, but they are of considerable importance to the side effect profile of individual drugs. Most FGAs are highly protein bound and lipophilic, and have large volumes of distribution (10–40 L/kg) with very significant variation in steady-state plasma concentrations. Oral preparations undergo extensive hepatic first-pass metabolism through hydroxylation, demethylation, and glucuronidation via CYP enzymes, and metabolites are dominantly eliminated in urine and bile. Elimination half-lives vary from 18 to 40 hours, allowing for once-a-day dosing. In the United States, depot preparations of haloperidol and fluphenazine are available as the decanoate ester suspended in sesame oil. After intramuscular injection, the esterified drug is slowly excreted from the oil and hydrolyzed, permitting dosing at intervals of 2 to 4 weeks.

Side Effects

Extrapyramidal Side Effects

First-generation antipsychotics are associated with a spectrum of potentially severe side effects involving multiple organ systems. The most characteristic are a cluster of movement disorders termed extrapyramidal symptoms (EPS) with an overall incidence exceeding 50%.[78] The precise mechanism of EPS is unclear, but is in part related to D_2 receptor effects in the nigrostriatal pathway.[79] *Dystonia* is the earliest of the acute-onset EPS and is characterized by involuntary and frequently painful sustained muscle contractions, most often involving head and neck muscles. Although dystonic torticollis appears to have no significant effect on anesthetic airway management, sudden death resulting from laryngeal dystonia has been described.[80,81] Dystonic reactions are most likely following treatment with high-affinity D_2 receptor antagonists, which include haloperidol and droperidol. Acute dystonic reactions are usually responsive to the anticholinergic benztropine (2 mg every 30 minutes

TABLE 12.3 First-Generation Antipsychotic Drugs

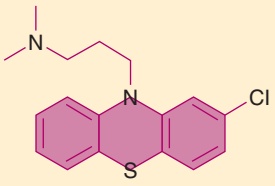
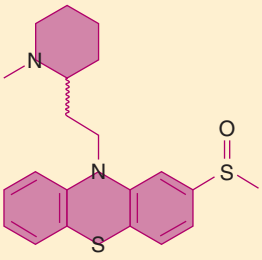
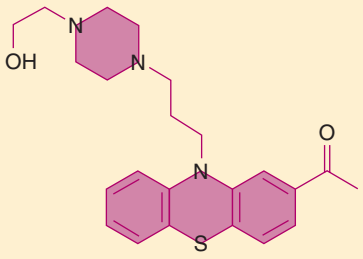
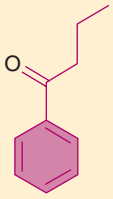
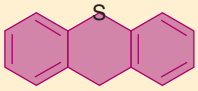
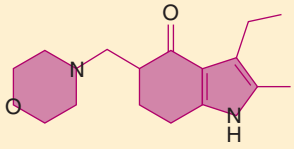
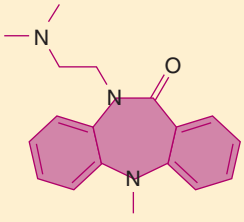
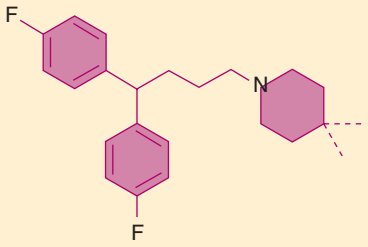
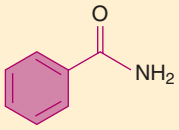
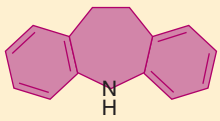
Class	Structure	Potency	Drugs
Phenothiazines			
Aliphatic		Low/medium	Chlorproethazine, chlorpromazine, cyamemazine, levomepromazine, promazine, triflupromazine
Piperidine		Low/medium	Mesoridazine, pericyazine, piperacetazine, pipotiazine, peopericiazine, sulforidazine, thioridazine
Piperazine		Medium/high	Acetophenazine, butaperazine, dixyrazine, fluphenazine, perazine, perphenazine, prochlorperazine, thiopropazate, thioproperazine, trifluoperazine
Butyrophenones		High	Benperidol, bromperidol, droperidol, fluanisone, haloperidol, melperone, moperone, pipamperone, timiperone, trifluperidol
Thioxanthenes		Low/medium	Chlorprothixene, clopenthixol, flupenthixol, thiothixene, zuclopenthixol
Dihydroindolones		Low/medium	Molindone, oxypertine
Dibenzepines		Low/medium	Clotiapene, loxapine

TABLE 12.3 First-Generation Antipsychotic Drugs—cont'd

Class	Structure	Potency	Drugs
Diphenylbutylpiperidines		High	Fluspirilene, penfluridol, pimozide
Benzamides		Low	Nemonapride, sulpiride, sultopride, tiapride
Iminodibenzyl		Medium	Clocapramine, mosapramine

Modified from Nasrallah HA, Tandon R. Classic antipsychotic medications. In: *American Psychiatric Publishing Textbook of Psychopharmacology*. 4th ed. Washington, DC: American Psychiatric Publishing; 2009:534.

TABLE 12.4 Dopamine Receptor Subtypes

Dopamine Receptor Subtype	D_1	D_{2s}	D_{2l}	D_3	D_4	D_5
Gene symbol	*DRD1*	*DRD2*	*DRD2*	*DRD3*	*DRD4*	*DRD5*
Molecular weight	49,300	47,347	50,619	44,225	41,487	52,951
Amino acids	446	414	443	400	387	477
Family classification	D_1	D_2	D_2	D_2	D_2	D_1
Adenylyl cyclase action	Stimulate	Inhibit	Inhibit	Inhibit	Inhibit	Stimulate
G-protein coupling	$G\alpha_s$, $G\alpha_{olf}$	$G\alpha_i$, $G\alpha_o$	$G\alpha_i$, $G\alpha_o$	$G\alpha_i$, $G\alpha_o$	$G\alpha_i$, $G\alpha_o$	$G\alpha_s$, $G\alpha_q$
Principal brain expression sites	Striatum, NA, SN, olfactory bulb, amygdala	Striatum, NA, olfactory tubercle	Striatum, NA, olfactory tubercle	NA, olfactory tubercle, islands of Calleja	Frontal cortex, amygdala, hippocampus	PFC, PMC, entorhinal cortex, SN, hypothalamus, hippocampus, dentate gyrus
Clinical selective agonists	Fenoldopam	Bromocriptine, pergolide, cabergoline, ropinirole	Bromocriptine, pergolide, cabergoline, ropinirole	Pramipexole, rotigotine	None	None
Clinical selective antagonists	None	Haloperidol, spiperone, raclopride, sulpiride, risperidone	Haloperidol, spiperone, raclopride, sulpiride, risperidone	Nafadotride	None	None

NA, Nucleus accumbens; *SN*, substantia nigra; *PFC*, prefrontal cortex; *PMC*, premotor cortex.
Modified from Beaulieu JM, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol Rev*. 2011;63:182–217.

until symptom abatement) or the antihistamine diphenhydramine (25–50 mg). *Akathisia* is an unpleasant sensation of motor restlessness with an irresistible urge to move, leading patients to continuously perform patterns of complex motor activity. Symptomatically, akathisia resembles restless legs (Wittmaack-Ekbom) syndrome. Propranolol (20–120 mg/day) is the most consistently effective treatment, although antihistamines, anticholinergics, benzodiazepines, and serotonin antagonists are also used.[82]

Neuroleptic-induced pseudoparkinsonism mimics classical Parkinson disease and must further be distinguished from depression or the negative symptoms of schizophrenia. Symptoms usually develop after several weeks of treatment, and acute events are rare. Approaches to treatment resemble those for akathisia, with the addition of dopaminergic agents such as amantadine. *Tardive dyskinesia* is a late development following chronic use of FGAs and is characterized by persistent and often stereotyped choreoathetoid movements that can involve any part of the body, but most commonly involve conspicuous oral and facial dyskinesias. Tetrabenazine is considered first-line treatment but is associated with significant side effects; other agents include amantadine, benzodiazepines, β-blockers, vitamin E, and botulinum toxin for focal dystonias.[83] The overall effectiveness of treatment is poor, and the development of symptoms can be irreversible. Patients in whom tardive dyskinesia develops while taking FGAs can change medications to clozapine or another second-generation antipsychotic (SGA, see later text), as these agents decrease the incidence and severity of symptoms. In contrast to their efficacy in other forms of EPS, anticholinergics worsen tardive dyskinesia and should be avoided. Furthermore, anesthesiologists must be aware that the D_2-receptor antagonist metoclopramide, used perioperatively for its antiemetic and gastroprokinetic properties, can also trigger or exacerbate tardive dyskinesia and is contraindicated in patients receiving FGAs.[84]

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a life-threatening emergency that closely resembles malignant hyperthermia (MH). It is characterized by hyperthermia, muscle rigidity, severe hypermetabolic dysautonomia, and mental status changes. It can be triggered by a single dose of any antipsychotic, but is most commonly associated with the high-potency FGAs, including haloperidol and droperidol. Rhabdomyolysis with elevated creatine kinase and renal failure are common secondary features. Overall mortality has been reported as in excess of 50%, but is probably closer to 10% to 20%.[85]

As with MH, first-line management is dantrolene (0.5–2.5 mg/kg every 6–12 hours), aggressive hydration, and supportive management. The dopamine agonist bromocriptine is also used. Although NMS is sometimes described as a neurogenic form of MH, the genetic and mechanistic relationship between the two is unclear.[86] Evidence relating MH susceptibility on muscle contraction testing with a history of NMS is inconsistent but is sufficient to manage such patients with full MH precautions.[87]

Other Side Effects

Several of the FGAs—notably thioridazine, haloperidol, droperidol, and pimozide—are associated with QTc prolongation and sudden cardiac death caused by *torsades de pointes,* likely via blocking the rapidly activating component of the delayed rectifier K^+ current.[88] In December 2001, the FDA issued a black box warning for droperidol, and a safety alert was issued for haloperidol in September 2007. The warning for droperidol refers to doses greater than 2.5 mg, which is greater than the common antiemetic dose of 0.625 to 1.25 mg.[89] Nonetheless, its use in anesthesia has virtually disappeared in the United States. The risk with haloperidol is greatest with intravenous administration, which although off-label, is commonly used in the treatment of delirium in the intensive care setting. The QTc should be assessed in all patients before the administration of droperidol or intravenous haloperidol with the electrocardiogram monitored following administration.

The M_1 anticholinergic activity of FGAs contributes to cognitive impairment, such as sedation, decreased memory function, and delirium, as well as to gastrointestinal effects, such as nausea, vomiting, ileus, dry mouth, and urinary retention. Weight gain, dyslipidemia, hypertension, and the induction of diabetes mellitus secondary to H_1 histaminic, M_1 cholinergic, and 5-HT_{2C} serotonergic blockade are most pronounced with the SGAs, but can occur with the FGAs. Antagonism of tuberoinfundibular dopaminergic tracts causes hyperprolactinemia, with several secondary endocrine effects. The α_1-adrenergic blockade can cause orthostatic hypertension and dizziness, especially early in the treatment course.

Second-Generation (Atypical) Antipsychotics

The description of an antipsychotic medication as *atypical* is pharmacologically imprecise, but is historically based only on a lower incidence of EPS. The group is, in fact, pharmacologically heterogeneous. When clozapine was introduced in 1961, there was little interest in conducting human trials because primate studies had demonstrated minimal EPS, and the prevailing theory was that EPS were a necessary (albeit unwanted) feature of antipsychotic efficacy. Clozapine was introduced in Europe in the early 1970s, but withdrawn in 1975 following reports of fatal agranulocytosis. However, a large trial demonstrated that it was effective in otherwise treatment-resistant schizophrenia, and clozapine received cautionary approval from the FDA in 1990.[90] The search for agents with a similarly low incidence of EPS but lower risk of agranulocytosis led to several other SGA drugs during the 1990s and 2000s. The newer SGAs—largely under patent protection and considerably more expensive—have replaced FGAs as the dominant pharmacotherapy for schizophrenia and other psychotic disorders. However, the Clinical Antipsychotic Trials of Intervention Effectiveness CATIE) and Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study (CUtLASS) trials suggest that, perhaps with the exception of clozapine, SGAs have no better therapeutic efficacy than FGAs and offer no consistent advantage in long-term quality of life indicators,[91–93] although meta-analyses have suggested that other agents may have efficacy and have a lower withdrawal rate owing to side effects.[94]

Individual Agents

Clozapine (Clozaril)

Clozapine is a dibenzodiazepine that is structurally related to loxapine. The mechanism of its low incidence of EPS and unique efficacy in treatment-refractory patients remains unclear. It is a weak antagonist at D_1, D_2, D_3, and D_5 dopamine receptors, but a strong antagonist at D_4 receptors. Positron emission tomography ligand studies demonstrate that clozapine is therapeutically effective when it occupies 20% to 67% of D_2 receptors, in contrast to FGAs, which become therapeutic only at 80% D_2 occupancy.[95] This reduced affinity for D_2 receptors might underlie the lower incidence of EPS and further suggests that the therapeutic efficacy is related to activity other than D_2-receptor antagonism. Clozapine

also has high affinity for adrenergic, cholinergic, and 5-HT_{2C} and 5-HT_{2A} serotonergic receptors. Like most SGAs, it has a pK_i (5-HT_{2A})/pK_i (D_2) ratio higher than is observed with FGAs, an observation central to the *serotonin–dopamine hypothesis* of SGA action. This hypothesis suggests that interactions between the serotonin and dopamine systems play an important role in the mechanism of action of SGAs because relatively potent blockade of 5-HT_{2A} receptors coupled with weaker antagonism of dopamine D_2 receptors has been found as the only pharmacologic feature shared by most atypical antipsychotic drugs.[96–98] Clozapine is highly protein bound and is extensively metabolized in the liver via CYP 1A2; monitoring of plasma levels and adjustments in dosage must be considered when agents that induce or inhibit CYP activity are added or removed.

Clozapine carries five FDA black box warnings. Agranulocytosis is most likely in the first 3 months of treatment. The incidence in the absence of monitoring is as high as 1% to 2%; however, strict adherence to monitoring reduces the incidence to less than 0.5%.[99] Treatment should not be initiated if the white blood cell count is less than 3500 cells/μL or the absolute neutrophil count is less than 2000 cells/μL, and cell counts should be monitored. A number of cardiovascular side effects are reported, and a boxed warning exists for myocarditis. Myocarditis and cardiomyopathy are most common in the first 2 months of therapy and might involve an immunoglobulin E–mediated hypersensitivity reaction.[100] Boxed warnings also exist for orthostatic hypotension, seizures, and an increased risk of death in older patients receiving clozapine for dementia-related psychosis. Hyperglycemia and other diabetogenic effects, including ketoacidosis, are also seen. Because of the severity and incidence of these and other adverse effects, although clozapine is clearly the most effective antipsychotic in the treatment of schizophrenia, its use is usually restricted to patients in whom therapy with at least two other pharmacologic agents has failed.

Olanzapine (Zyprexa)

Olanzapine is a thienobenzodiazepine structurally similar to clozapine that received FDA approval in 1997 and in 2004 was approved for the long-term treatment of bipolar disorder. Olanzapine is also available in a combined preparation with fluoxetine. Like other SGAs, selectivity for D_2-dopamine receptors is significantly less than for FGAs, although it does have relatively greater selectivity for D_2 than does clozapine. Antagonist affinity for the 5-HT_{2A} receptor is greater than for dopamine receptors, while affinity for the 5-HT_{2C} receptor is similar to that for D_2. There is also antagonism of α_1-adrenergic, H_1-histaminergic, and $M_{1\text{-}5}$ muscarinic receptors. Olanzapine also has weak activity at $GABA_A$ receptors. Although interaction with GABAergic anesthetics is not defined, olanzapine is considered to potentiate the effects of benzodiazepines, and fatalities from cardiorespiratory depression have been reported when intramuscular olanzapine has been combined with benzodiazepines.[101] Olanzapine is highly protein bound and predominantly metabolized by CYP 1A2.

Olanzapine is associated with weight gain, diabetogenesis, and dyslipidemia, with an incidence and magnitude greater than other SGAs or FGAs.[102,103] Boxed warnings exist for increased risk of death in older patients receiving olanzapine for dementia-related psychosis, and for excessive sedation and delirium following intramuscular injection. The incidence of EPS is less than that of the FGAs, but greater than that with clozapine. Although a small number of cases of olanzapine-induced leukopenia and agranulocytosis have been reported, scheduled monitoring is not required. Similarly, while cardiac conduction abnormalities have been reported, myocarditis and cardiomyopathy are not features, and the overall cardiac risk is significantly less than that associated with clozapine.

Quetiapine (Seroquel)

Quetiapine is a dibenzothiazepine approved by the FDA for the treatment of schizophrenia in 1997 and for the treatment of bipolar disorder in 2004. At 12 hours after the last dose, positron emission tomography ligand studies demonstrate that quetiapine occupies only 30% of D_2 receptors, which is significantly less than that considered necessary for therapeutic efficacy.[104] However, occupancy is higher when measured at shorter intervals; this has led to the theory that transient occupancy of D_2 receptors provides clinical potency, but also permits dynamics of dopamine release in nigrostriatal and tuberoinfundibular pathways, accounting for the low incidence of EPS and hyperprolactinemia.[105] Quetiapine has high affinity for 5-HT_{2A} receptors but relatively weak affinity for 5-HT_{2C} or 5-HT_1 receptors. It has very strong affinity for H_1-histamine receptors, which likely accounts for it being the most sedating of the SGAs, and also for α_1-adrenergic receptors, accounting for postural hypotension. Protein binding is 83%, and it is metabolized by CYP 3A4. Its active metabolite, norquetiapine, has similar or even greater potency than the parent compound at many receptors. The most characteristic side effect of quetiapine is sedation. It is associated with weight gain, diabetogenesis, and dyslipidemia, although the effect is not as great as that seen with clozapine or olanzapine. It can also cause orthostatic hypotension, but unlike clozapine it does not carry a boxed warning for this effect. Boxed warnings exist for an increased risk of death in older patients receiving quetiapine for dementia-related psychosis and for suicidality in children, adolescents, and young adults. The incidence of EPS and hyperprolactinemia is especially low compared with other FGAs and SGAs.[106] Dysrhythmias have been reported, but earlier concerns that quetiapine causes prolongation of QTc are probably unfounded.[88]

Aripiprazole (Abilify)

Aripiprazole is a dihydroquinolinone antipsychotic that is chemically and pharmacologically distinct from other first- and second generation antipsychotic drugs. It received FDA approval for the treatment of schizophrenia in 2002, for acute manic and mixed episodes associated with bipolar disorder in 2004, as an adjunctive therapy for major depression in 2007, and for irritability in autistic children in 2009. In contrast to other antipsychotics, which are D_2- and 5-HT_{1A} receptor antagonists, aripiprazole is a *partial agonist* at these receptors and at 5-HT_{2C} receptors.[107,108] It is a strong antagonist at 5-HT_{2A}, 5-HT_7, and D_3 receptors, and has moderate effects at D_4, H_1-histamine, and α_1-adrenergic receptors. It has virtually no affinity for muscarinic cholinergic receptors. Protein binding is at least 99%, and it is metabolized by CYP 2D6 and CYP 3A4. Its active metabolite, dehydro-aripiprazole, has similar affinity for D_2 receptors. Because of its partial agonist activity on nigrostriatal and tuberoinfundibular pathways, aripiprazole causes minimal EPS or hyperprolactinemia despite D_2-receptor occupancy of 70% to 95%. It also appears to be largely free of the adverse weight gain, diabetogenesis, and dyslipidemia associated with other SGAs. Aripiprazole does not cause prolongation of the QTc.[109] It is generally well tolerated. As with all the SGAs, aripiprazole carries a boxed warning for increased risk of death in older patients receiving antipsychotics for dementia-related psychosis and for suicidality in children, adolescents, and young adults.

Risperidone (Risperdal)

Risperidone is a benzisoxazole derivative approved by the FDA for treatment of schizophrenia in 1994, for short-term treatment of the mixed and manic states of bipolar disorder in 2003, and for treatment of irritability in children with autism in 2006. In 2007 it was approved as a treatment for schizophrenia and bipolar disorder in children. Its pharmacology is characterized by binding affinity for 5-HT_{2A} receptors that is 20 times that for D_2-dopamine receptors. D_2-receptor affinity is approximately 50 times, and 5-HT_{2A} receptor affinity approximately 20 times that of clozapine. Risperidone also has strong affinity for α_1-/α_2-adrenergic and H_1-histamine receptors. Affinity for D_1 receptors is low, and it has no affinity at muscarinic receptors. Protein binding is 90%, and it is metabolized by CYP 2D6. D_2-receptor occupancy at therapeutic doses is 63% to 89%, which would be expected to be associated with a significant incidence of EPS.[110] The addition of strong serotonergic antagonism, with a 5-HT_2 receptor occupancy of 95%, is thought to confer protection against D_2 antagonist effects on the nigrostriatal pathway, and the incidence of EPS is low. Nonetheless, unlike other SGAs with relatively lower affinities for D_2 receptors that permit dynamic responses to surges in dopamine, risperidone is tightly bound and does cause significant hyperprolactinemia.[111,112] It can also cause orthostatic hypotension during early treatment. Risperidone does not cause prolongation of the QTc and is less arrhythmogenic than other antipsychotics. It carries a boxed warning for increased risk of death in older patients receiving antipsychotics for dementia-related psychosis.

Mood Stabilizer Drugs

Lithium

History

Lithium was first used medicinally in the late 19th century as a treatment for gout and other disorders, and was used as a substitute for table salt in the first half of the 20th century until several deaths from toxicity were reported. Just as cocaine was initially added to Coca-Cola for medicinal purposes, lithium was part of the original recipe for the beverage 7 Up. It was first identified as a treatment for mania in 1949, but at least partly because of concerns about toxicity, did not receive FDA approval for the treatment of acute mania until 1970 and for prophylaxis in bipolar disorder in 1974.

Basic Pharmacology

Structure-Activity. Lithium is the third element of the periodic table and exists as a monovalent cation. It shares some properties with sodium and potassium, and substitution or competition with other cations can contribute to its effects.[113]

Mechanism

The therapeutic mechanism of lithium remains fundamentally unknown, although several proposals have been developed. Lithium depletes free intracellular inositol through noncompetitive inhibition of inositol monophosphate. This depletion can lead to changes in G-protein–coupled second-messenger systems and protein kinase C actions linked to inositol phosphate signaling, which are important in adrenergic, serotonergic, and cholinergic signaling.[114,115] Lithium also inhibits glycogen synthase kinase-3 (GSK-3), mimicking the Wnt protein signaling pathway to stimulate protein kinase C activity.[116,117] Effects on glutamate, Na^+-K^+-ATPase, cyclic adenosine monophosphate response element-binding protein, and gene expression have also been described.[118] Lithium has effects on serotonin and norepinephrine signaling and is an antagonist at 5-HT_{1A} and 5-HT_{1B} autoreceptors, increasing serotonin availability.[119,120] Lithium also causes a resetting of hypothalamic circadian oscillators, which are dysfunctional in bipolar disorder and depression.

Metabolism

As a monovalent cation, lithium undergoes no metabolism, but is excreted renally.

Clinical Pharmacology

Pharmacokinetics[121]

Lithium is rapidly and completely absorbed from the gastrointestinal tract and attains peak plasma concentration in 1 to 2 hours with rapid-release preparations and 4 to 12 hours in extended-release preparations. It is not protein bound and is evenly distributed in the total body water. The initial volume of distribution is 0.3 to 0.4 L/kg and in steady state is 0.7 to 1 L/kg. Bioavailability is nearly 100% for the rapid-release preparations and 60% to 90% with the extended-release preparations. It is excreted unchanged in the urine with an elimination half-time of 18 to 24 hours or longer in older adults and those with renal impairment. Time to steady-state is 5 to 7 days. Filtered lithium ion (Li^+) (80%) is reabsorbed in the proximal convoluted tubule, which is competitive with Na^+ reabsorption. As a consequence, changes in renal functional dynamics such as diuretic therapy, sodium intake, and hydration status can alter plasma concentration, so monitoring of serum Li^+ concentrations is required. The target concentration is 0.8 to 1.2 mM. Although there is no clear recommendation for therapeutic monitoring in surgical patients, there are numerous pharmacologic and physiologic events in the perioperative period that can affect Li^+ plasma concentrations.

Pharmacodynamics

Therapeutic Effects

Lithium remains a first-line therapy for the treatment of acute mania, with a response rate in excess of 70%, and it is at least as effective as other first-line agents.[122–125] It is also first-line treatment for bipolar depression and significantly reduces suicide attempts and successful suicide.[126–128] It is effective as prophylaxis and maintenance therapy in bipolar disorder, which is usually a lifelong disease characterized by recurrent acute mood episodes.[129,130] Lithium can also be effective as adjunctive therapy in treatment-resistant unipolar depression.[131] Although it is less well tolerated in older adults, lithium appears to have neuroprotective effects, and in animal models it is protective against Alzheimer disease. Some data suggest that it might modify the course of Alzheimer disease in humans.[132,133] Lithium enhances remyelination of peripheral nerves.[134]

Adverse Effects. Lithium is associated with a number of significant adverse effects and has a narrow therapeutic index. The most common side effects at therapeutic concentrations are weight gain and disturbed cognition and coordination. Lithium impairs renal concentrating ability, and a significant number of patients experience diabetes insipidus with polyuria and polydipsia, which is usually responsive to amiloride.[135] Renal tubular damage and even acute renal failure are reported. Neurotoxic reactions such as encephalopathy, delirium, memory changes, and movement disorders are possible and can be irreversible. Hypothyroidism is common and is more prevalent in females. Abnormal thyroid function occurs in excess of 35% of patients using long-term lithium therapy.[136]

Clinically significant cardiac conduction abnormalities are unusual in patients without preexisting cardiac disease, but sinus node dysfunction, atrioventricular block, and T-wave flattening can occur.[137] Caution and monitoring is essential in patients with elevated cardiac risk. Tremor may occur in up to 65% of patients.[138]

Drug Interactions

A number of drugs used in the perioperative period can alter plasma lithium concentrations. Thiazide diuretics increase concentrations by a compensatory increase in proximal tubule reabsorption, whereas loop diuretics such as furosemide generally have minimal effect, as do the potassium-sparing diuretics. Osmotic diuretics lower lithium concentrations and so are useful in the treatment of toxicity. Angiotensin-converting enzyme inhibitors increase lithium levels, as do angiotensin II receptor blockers, many nonsteroidal antiinflammatory agents, and several antibiotics.[139,140] Caution should be observed in using neuroleptic medications such as droperidol and haloperidol, in that the risk of extrapyramidal side effects and neuroleptic malignant syndrome is increased. Lithium prolongs the action of both depolarizing and nondepolarizing neuromuscular blocking drugs.[141,142]

Anticonvulsant Mood Stabilizers

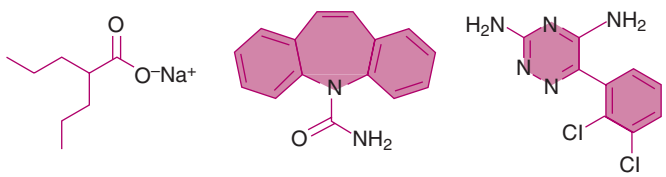
Several heterogeneous compounds used initially as anticonvulsants possess or have been investigated for therapeutic benefit in bipolar disorder (Fig. 12.7). The anticonvulsant properties of valproate were serendipitously established in 1963 when its incidental mood-enhancing effects stimulated interest in its use as a mood stabilizer. It received FDA approval for the treatment of mania in 1995. Lamotrigine was approved for maintenance therapy of bipolar disorder in 2003, and carbamazepine for the treatment of mania and mixed episodes in 2004. Valproate and carbamazepine are considered alternative first-line agents to lithium for the treatment of mania, although they are frequently used in combination therapy.[143,144] Valproate might be superior to lithium in the treatment of patients with mixed states.[145] Several other anticonvulsant drugs, including gabapentin, pregabalin, and topiramate have been investigated but do not have clearly established efficacy.

Individual Agents

Valproate (Depakote)

Valproate is an eight-carbon, branched-chain carboxylic acid that suppresses seizures without affecting focal activity. The therapeutic mechanism for suppression of mania is unclear. Valproate facilitates GABAergic transmission through increased expression of mRNA for glutamate decarboxylase (the GABA synthetic enzyme), reduces protein kinase C activity in manic patients, and inhibits inositol cycling and GSK-3, although via different pathways than lithium.[114,146–148] It is 80% to 90% protein bound and attains peak plasma concentration in approximately 4 hours. It is hepatically metabolized via glucuronide conjugation and mitochondrial β oxidation. Elimination half-life is 9 to 16 hours.

Valproate carries FDA black box warnings for hepatic failure, acute pancreatitis, and use in pregnancy. Hepatotoxicity is greatest in children younger than 2 years of age, but fatalities have been reported in adults. Fatal acute pancreatitis has been reported in both adults and children, including in those who have been on stable, long-term therapy. Hyperammonemia with encephalopathy is reported. Of special significance to surgical patients, valproate can cause thrombocytopenia, inhibition of platelet aggregation, and increased bleeding, but modification of therapy during the perioperative period is not recommended.[149] No drug interactions specific to anesthetic care are known.



• **Fig. 12.7** Anticonvulsant mood stabilizers.

Carbamazepine (Tegretol)

Carbamazepine is an iminostilbene derivative with a dibenzazepine nucleus, and thus has a tricyclic structure similar to imipramine. Like lithium and valproate, carbamazepine increases limbic $GABA_B$ receptors and has effects on inositol cycling. It has unique effects at peripheral-type benzodiazepine receptors, increases stimulatory G-protein alpha subunits ($G_s\alpha$), and decreases inhibitory G-protein subunits ($G_i\alpha$). It appears to lack the effects on GSK-3 and protein kinase C possessed by lithium and valproate. It has anticholinergic, antidiuretic, and muscle relaxant properties. Carbamazepine is 75% to 90% protein bound, with a volume of distribution of 0.6 to 2 L/kg in adults. It is hepatically metabolized via CYP 3A4 to an active epoxide metabolite and is a strong CYP inducer. Elimination half-life is highly variable and is initially 25 to 65 hours but decreases to 12 to 17 hours after several weeks of therapy owing to autoinduction. Plasma level monitoring is not required.

Carbamazepine carries two FDA black box warnings for blood dyscrasias and dermatologic reactions. A spectrum of hematologic abnormalities, including agranulocytosis, aplastic anemia, neutropenia, leukopenia, and thrombocytopenia, have been reported and monitoring standards similar to those for clozapine are recommended.[150] Severe dermatologic reactions include fatal toxic epidermal necrolysis and Stevens-Johnson syndrome. The risk of dermatologic reactions is strongly linked to the HLA-B*1502 allele, which is prevalent in Asian populations. Patients of Asian descent should be screened for HLA-B*1502 and carbamazepine should be voided if the test result is positive.[151] A syndrome resembling that of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is occasionally observed in older patients. Cardiac conduction abnormalities, including atrioventricular nodal block, have also been reported. Carbamazepine has strong induction effects on CYP 1A2, 2B6, 2C8, 2C9, 2C19, 3A4, and P-glycoprotein and thus has the potential for significant drug interactions. The metabolism of midazolam, alfentanil, fentanyl, methadone, tramadol, and most nondepolarizing muscle relaxants is increased, but the effect of reduced plasma concentration is countered by generalized enhancement of the CNS depressant effects of anesthetic drugs.[152]

Lamotrigine (Lamictal)

Lamotrigine is a phenyltriazine that is structurally unrelated to the other anticonvulsant mood stabilizers. It reduces folate activity via inhibition of dihydrofolate reductase. It suppresses paroxysmal bursts from Na^+ channels, and inhibits glutamate release in response to ischemia and to the Na^+ channel activator veratrine.[153] It has no demonstrated effects on reuptake of dopamine, norepinephrine, or serotonin, and has minimal affinity for α_1, α_2, β, D_1, D_2, GABA,

H_1, M_1, M_2, or κ and σ opioid receptors. It is a weak inhibitor of 5-HT_3.[154] Lamotrigine is 55% protein bound, with a volume of distribution of 0.9 to 1.3 L/kg. It undergoes hepatic and renal metabolism, primarily via glucuronic acid conjugation to inactive metabolites. Elimination half-life is 25 to 33 hours. Plasma level monitoring has been suggested[155] but is not required.

Lamotrigine carries an FDA black box warning for dermatologic reactions, including potentially fatal Stevens-Johnson syndrome and toxic epidermal necrolysis. Other significant concerns include an increased risk of aseptic meningitis and the development of blood dyscrasias, including neutropenia, leukopenia, thrombocytopenia, and pancytopenia.[156,157] Most of the common adverse effects are relatively mild. No characteristic cardiac conduction defect is described, although rare events of arrhythmias in patients taking lamotrigine have been reported. When used as monotherapy, induction and inhibition of CYP isoenzymes does not occur, and changes in the metabolism of other drugs are not of significance. In general, lamotrigine augments the CNS depressant effects of drugs used in the perioperative period, but no interaction with any specific anesthetic drug is known.

Psychostimulants

Amphetamine, first synthesized in 1887, was available without prescription as a decongestant inhalant under the trade name Benzedrine from the 1930s to 1960s. Its utility as a stimulant was recognized during World War II, when it was used to combat fatigue in soldiers. Methylphenidate, identified as a stimulant in the 1950s, was used to treat children with the conditions that would subsequently be named attention deficit disorder (ADD) or attention deficit/hyperactivity disorder (ADHD), marketed under the name Ritalin. Diagnosis and treatment of ADD/ADHD has exploded over the past 25 years and has expanded to include a greater number of adult patients. Modafinil was approved for use in the United States in 1998 and has significantly improved the pharmacologic treatment of narcolepsy and other disorders of wakefulness.[158] The psychostimulant drugs are briefly summarized in Table 12.5.

Long-term use of amphetamine and methylphenidate leads to catecholamine depletion, which can blunt the sympathetic response to hemodynamic stress. Significant perioperative events, including cardiac arrest during induction of anesthesia, have been rarely reported.[159] However, there is no basis to recommend discontinuation of therapy before surgery.[160] Direct-acting sympathomimetics such as phenylephrine are preferred, and pretreatment with atropine can be used in selected pediatric patients.

Pharmacologic Treatment of Parkinson Disease

Levodopa

History

The discovery in the 1950s that the loss of dopaminergic neurons in the substantia nigra leads to Parkinson disease (PD) was swiftly followed by the introduction of the dopamine precursor levodopa for the treatment of motor symptoms.[161] Levodopa has remained the gold standard treatment for the past 50 years, but concerns about the development of long-term motor complications led to the preferential use of dopamine agonists and MAO-B inhibitors as initial therapy in patients with milder motor symptoms. More recent studies have supported the use of levodopa for all stages of the disease.

Basic Pharmacology

Structure-Activity

Levodopa is the levorotatory isomer of 3,4-dihydroxyphenylalanine. The dextrorotatory isomer has no biologic activity. Levodopa is an intermediate in the biosynthesis of dopamine. It is formed endogenously in humans by the action of tyrosine hydroxylase on the amino acid L-tyrosine.[162]

Mechanism

Unlike exogenous dopamine that cannot cross the blood-brain barrier, levodopa is actively transported into the CNS and is rapidly converted to dopamine by the enzyme aromatic L-amino acid decarboxylase (AAAD). The converted dopamine is available throughout the CNS and binds to presynaptic and postsynaptic dopamine receptors. In the corpus striatum, increased levels of dopamine normalize the levels of this neurotransmitter caused by dopaminergic neuronal loss.

Metabolism

Only a fraction of levodopa reaches the CNS, while the majority is converted to dopamine peripherally by AAAD. For this reason, levodopa is always coadministered with an AAAD inhibitor (carbidopa or benserazide). These agents increase cerebral bioavailability and reduce adverse effects associated with peripheral excesses of dopamine, including nausea and hypotension.

Decarboxylation of levodopa by endogenous catechol-*O*-methyltransferase (COMT) reduces bioavailability and shortens half-life. This leads to phasic stimulation of dopamine receptors in the basal ganglia, which can contribute to the development of motor fluctuations and dyskinesias. To ameliorate this, COMT inhibitors (entacapone or tolcapone) are often given concurrently. Tolcapone is rarely associated with severe liver injury and frequent monitoring of liver function is now recommended on initiation of therapy.

Clinical Pharmacology

Pharmacokinetics

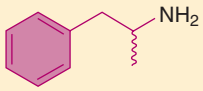
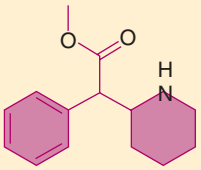
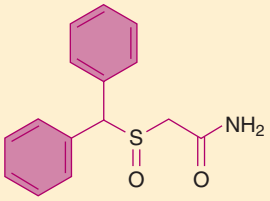
The absorption of levodopa approaches 100% in the presence of an AAAD inhibitor. The duration of action of the immediate-release formulation is 2 to 4 hours and of the sustained-release formulation is 3 to 6 hours.[162] It is not appreciably bound to plasma proteins. Elimination of levodopa and metabolites is primarily renal.

Because of the short half-life and the absence of a parenteral formulation, levodopa should be continued perioperatively including shortly before induction of anesthesia.[163] Interruption of administration can lead to exacerbation of motor symptoms and interfere with ventilation. During longer procedures, consideration should be given to administration of levodopa via a gastric tube. Intrajejunal therapy with levodopa (Duodopa) is now registered for treatment of motor fluctuations and dyskinesia. Because of the expense and technical challenges associated with maintenance of this therapy in an outpatient population, it is usually reserved for those with advanced PD that cannot be controlled with oral pharmacotherapy.[164]

Pharmacodynamics

Therapeutic Effects. Levodopa is effective in treatment of bradykinesias, gait disturbances, and tremor at all stages of PD.

TABLE 12.5 Psychostimulants

	Amphetamine	Methylphenidate	Modafinil
Structure			
Common trade names	Adderall (amphetamine, dextroamphetamine mixed salts) Dexedrine (dextroamphetamine) Desoxyn (methamphetamine)	Ritalin Metadate Concerta Focalin (dexmethylphenidate)	Provigil Nuvigil (armodafinil)
Class and mechanism	Noncatecholamine sympathomimetic amine. Enhances dopaminergic, serotonergic, and noradrenergic release in neural network specific regions via complex transporter effects	Norepinephrine and dopamine (dominant) reuptake inhibitor. Blocks the dopamine transporter (DAT). Has regionally specific effects similar to amphetamine	Mechanism is unclear. Does not appear to involve dopamine or noradrenergic pathways. May involve glutamatergic and GABAergic effects.
Metabolism	CYP 2D6 with no significantly active metabolites	Hepatic via carboxylesterase CES1A1 to inactive metabolites	CYP 3A4
Half-life (hours)	10–15	1–4	15
Approved therapeutic indications	ADHD Narcolepsy Obesity (methamphetamine)	ADHD Narcolepsy	Narcolepsy Shift work sleep disorder Obstructive sleep apnea/ hypopnea syndrome (OSAHS)
Adverse effects	Common: insomnia, headache, anxiety, weight loss, tachycardia, hypertension May cause cardiac arrhythmia, seizure, and hyperpyrexia in susceptible patients. High potential for abuse Abrupt discontinuation may precipitate withdrawal.	Common: insomnia, headache, anxiety, weight loss, tachycardia, hypertension May cause cardiac arrhythmia, seizure, and hyperpyrexia in susceptible patients. High potential for abuse Discontinuation symptoms generally less pronounced than for amphetamine.	Common: headache, nausea Generally less arrhythmogenic than amphetamine and methylphenidate, but events are described. May cause severe rashes, including Stevens-Johnson syndrome.
Drug interactions	May reduce the sedative effect of drugs used in anesthesia, and potentiate the analgesic effect of opiates. May unpredictably alter the response of the sympathomimetic drugs. May potentiate the action of arrhythmogenic drugs and drugs that lower the seizure threshold.	May reduce the sedative effect of drugs used in anesthesia, and potentiate the analgesic effect of opiates. May unpredictably alter the response of the sympathomimetic drugs. May potentiate the action of arrhythmogenic drugs and drugs that lower the seizure threshold.	May unpredictably alter the response to sympathomimetic drugs. No known significant anesthetic interactions.

ADHA, Attention deficit/hyperactivity disorder; *GABA*, gamma aminobutyric acid.

It does not have any appreciable effect on non-dopaminergic aspects of the disease such as dementia or autonomic dysfunction.

Adverse Effects. Adverse effects not already mentioned include somnolence, psychosis, cardiac irritability, and orthostatic hypotension. Neuroleptic malignant syndrome has been reported on sudden discontinuation and responds to reinstatement of levodopa.[165] Earlier concerns that levodopa hastens progress of PD have not been borne out by recent clinical studies.

Dopamine Agonists

History

Motor complications arising from PD treatment with levodopa led to the search for other agents. The ergot derivative and dopamine agonist, bromocriptine, was first used for the treatment of PD in the mid-1970s. Since that time a number of other ergot (cabergoline, lisuride) and non-ergot derivatives (pramipexole and ropinirole)

have been approved for PD therapy. The association of the oral ergot derivatives with pulmonary, valvular, and retroperitoneal fibrosis has severely curtailed their use for the management of PD.[166] One of the oldest known non-ergot derivatives, apomorphine, was approved for PD management in 2004 but the technical challenges of delivery due to high first pass metabolism have prevented wider use.

Basic Pharmacology

Structure-Activity

Agents from this class have chemically distinct structures. Pramipexole is a synthetic aminothiazole while ropinirole is an indole derivate. Apomorphine is a derivative of the quinolone alkaloid aporphine. The name refers to its historical derivation as a morphine decomposition product but there are no structural elements of morphine present in apomorphine. Apomorphine has two stereoisomers with only the R-enantiomer having dopaminergic activity. All three of these agents are chemically unrelated to the ergoline dopamine agonists.

Mechanism

The dopamine agonists activate presynaptic and postsynaptic dopamine receptors directly. The enteral non-ergot derivatives preferentially bind D_2 and D_3 receptors. The affinity for D_3 receptors is up to 10 times higher than for D_2 receptors. Apomorphine has affinities for the D_1, D_2, D_3, and D_4 receptors similar to those of dopamine.[167] Enteral ergot derivatives not only bind D_1 and D_2 but also some serotonin and adrenergic receptors.

Metabolism

Ropinirole is inactivated in the liver by CYP 1A2 with none of the major metabolites having pharmacologic activity. Pramipexole has negligible metabolism and more than 90% is excreted unchanged in the urine. Apomorphine undergoes extensive first-pass inactivation in the liver and is largely metabolized by systemic oxidation.

Clinical Pharmacology

Pharmacokinetics

The two most commonly used enteral agents, pramipexole and ropinirole, have distinct pharmacokinetic profiles. Bioavailability for pramipexole is greater than 90%, whereas that of ropinirole is around 50%. These agents remain in the body longer than levodopa; the immediate-release formulations of pramipexole and ropinirole have elimination half-lives of 8 hours and 6 hours, respectively. Pramipexole is largely renally cleared, whereas ropinirole is predominantly cleared by the liver. Because apomorphine has extensive first-pass metabolism, it is not effective as an oral agent. Instead it is most commonly administered subcutaneously or intranasally. The drug has a clinical effect within 20 minutes of subcutaneous administration and has an elimination half-life of 30 to 60 minutes.

Pharmacodynamics

Therapeutic Effects. The oral dopamine agonists in clinical use are effective in the treatment of the major motor symptoms of PD, in particular bradykinesias and tremor. They are used as sole agents in PD patients with mild-moderate motor symptoms and as an adjunct to levodopa in more severe disease. Ropinirole and pramipexole are also approved for the treatment of restless legs syndrome. Apomorphine can be used as a rescue therapy to improve mobility in patients experiencing "off" periods. It is as effective as levodopa in the management of motor symptoms but technical difficulties associated with long-term subcutaneous delivery have limited its clinical utility. Apomorphine can be used as an alternative to gastric administration of levodopa during longer anesthetics.[163]

Adverse Effects. As a class the dopamine agonists are generally well tolerated and have a side effect profile similar to levodopa. The prevalence of dyskinesias and motor fluctuations is reduced, which is postulated to result from longer elimination half-lives of the enteral agents. Unlike levodopa, the enteral agents can cause headaches and psychiatric symptoms, including confusion, compulsive gambling, and hypersexuality.[167] Some caution is required in the advanced stages of PD owing to the likelihood of cognitive impairment since these agents have the potential to induce or enhance hallucinations. Apomorphine is associated with nausea and vomiting, necessitating the concurrent administration of domperidone. There are no significant interactions between the dopamine agonists and anesthetic agents. Because of the longer half-life of the enteral agents, concerns regarding interruption of administration are not as pertinent as for levodopa.

MAO-B Inhibitors

MAO-B inhibitors act by reducing synaptic and glial metabolism of dopamine, leading to enhanced activity and reuptake. They are effective as monotherapy in early PD and are used as adjuncts to either dopamine agonists or levodopa in more severe disease. Selegiline and rasagiline are approved for PD treatment. Unlike selegiline, rasagiline has no amphetamine metabolites, which may account for the lower incidence of cognitive side effects.[168] Details of the pharmacology of these agents have been presented earlier in this chapter.

Pharmacologic Treatment of Myasthenia Gravis

Myasthenia gravis (MG) is an antibody-mediated disorder of neuromuscular transmission. Modern therapy is based on increasing the availability of acetylcholine (ACh) at the neuromuscular junction with anticholinesterases and modulating the immune response. Agents used to moderate autoimmune injury include corticosteroids, cyclosporine, azathioprine, tacrolimus, and rituximab (see Chapter 38 and Gilhus[169]).

Anticholinesterases

History

In 1934, the anticholinesterase physostigmine was demonstrated to markedly improve muscle strength in a patient with myasthenia. This finding strongly implicated the neuromuscular junction in the etiology of MG. Physostigmine was the mainstay of treatment for three decades before the introduction of the longer-acting oral agent pyridostigmine. Substantial improvements in the life expectancy of patients with MG during the middle of last century owed much to the introduction of the anticholinesterases and improved therapies for respiratory failure. Pyridostigmine remains the most frequently used anticholinesterase for MG treatment, with neostigmine only rarely used because of its shorter duration of action and higher rate of gastrointestinal side effects. The short-acting edrophonium is used as an aid in the diagnosis of MG and cholinesterase inhibitor overdose.

Basic Pharmacology

Structure-Activity

Pyridostigmine, neostigmine, and edrophonium all contain a quaternary ammonium group, limiting lipid solubility and preventing passage through the blood-brain barrier. Physostigmine lacks the quaternary ammonium group enabling it to pass freely into the CNS.[170] The longer-acting agents, pyridostigmine, neostigmine, and physostigmine, contain a carbamate group that forms a reversible covalent bond with acetylcholinesterase. Edrophonium, lacking a carbamate group, forms short-lived electrostatic and hydrogen bonds with acetylcholinesterase, accounting for its shorter activity.

Mechanism

Binding of acetylcholinesterase inhibits the breakdown of ACh, increasing the amount of neurotransmitter available to stimulate the reduced number of ACh receptors in the synaptic cleft of the neuromuscular junction.

Metabolism

The carbamate-containing anticholinesterases undergo hydrolysis by cholinesterases and are also metabolized by microsomal enzymes in the liver. Although physostigmine is extensively metabolized, the majority of neostigmine and pyridostigmine is excreted unchanged by the kidneys.

Clinical Pharmacology

Pharmacokinetics

Agents containing a quaternary ammonium group are poorly absorbed and have oral bioavailabilities of only 2% for neostigmine and between 7% and 25% for pyridostigmine.[171] The duration of action is between 3 to 6 hours and elimination half-life varies from 2 to 4 hours. Slow-release formulations can help patients who become symptomatic during the night but owing to variable absorption are not used for awake patients. Around 90% of pyridostigmine is renally cleared unchanged, and dose reductions are recommended for MG patients with reduced renal function and in older adults.[172] Edrophonium acts within 2 minutes of administration. It has an elimination half-life of 30 to 110 minutes but a duration of action much shorter owing to transient binding to acetylcholinesterase. It is predominantly renally cleared.

Pharmacodynamics

Therapeutic Effects. Pyridostigmine is the most commonly used initial treatment for MG. It is particularly effective at reversing muscle weakness and fatigability early in the course of the disease. Over time tolerance can develop, necessitating higher doses. Beyond single doses of 120 mg, little clinical benefit is seen and the rate of adverse effects increases significantly. Infants of myasthenic mothers can have muscle weakness lasting for up to 4 weeks that responds to pyridostigmine but occasionally requires mechanical ventilation.

Adverse Effects. Pyridostigmine is well tolerated in most patients, but at standard doses the muscarinic side effects of nausea and abdominal cramps are frequent. For some, intractable diarrhea prevents continued usage. Uncommonly bradycardia can lead to orthostatic hypotension and require dose reduction. An increase in airway secretions can worsen reactive airway disease and can be confused with respiratory muscle involvement with MG.[169] The development of respiratory failure requiring intubation during a myasthenic crisis often leads to discontinuation of the cholinesterase inhibitors owing to excessive airway secretions. Increased nicotinic activity can lead to muscle cramps and fasciculation that rarely leads to dose adjustment. Excessive administration of an anticholinesterase can lead to increased muscle weakness and muscarinic side effects ("cholinergic crisis"). Increased weakness in response to edrophonium can be used to help differentiate this from a myasthenic crisis.

Drug Interactions

The decision to continue anticholinesterase treatment perioperatively should be individualized. These agents interfere with neuromuscular blockers, if used, during general anesthesia. The cholinesterase inhibitors also act on plasma cholinesterase and can slow the metabolism of ester-type local anesthetics and succinylcholine.

Antiepileptic Drugs

The chronic neurologic disorder of epilepsy, which affects more than 50 million people worldwide, is characterized by seizures and hypersynchronous firing of neuronal networks. The antiepileptic drugs (AEDs) constitute a chemically diverse class. Some of these agents (carbamazepine, valproate, and lamotrigine) are also approved for use as mood stabilizers and details of their pharmacology are reviewed earlier in this chapter.

History

In the latter half of the 19th century, bromides were introduced as the first AEDs. While effective, they had numerous toxicities and were supplanted by phenobarbital on its introduction after World War I. The low cost of phenobarbital has helped it remain a popular first-line antiepileptic in developing countries to this day. In 1938 the antiseizure properties of phenytoin were discovered. With an efficacy similar to phenobarbital but without excessive sedation, it continues to be widely used.[173] Through the 1990s the discovery of new AEDs was infrequent but saw the introduction of the benzodiazepines, valproate, and carbamazepine to the armamentarium. Since then, a continuing stream of drugs has been released, including lamotrigine, topiramate, gabapentin, pregabalin, levetiracetam, and the carbamazepine-derivative oxcarbazepine.[174] In the past 5 years, a prodrug similar to oxycarbazepine (eslicarbazepine) and three drugs with novel action (ezogabine, perampanel, and brivaracetam) have seen FDA approval. It remains unclear where these newest agents fit within established epilepsy treatment protocols and comparative efficacy trials are lacking.

Basic Pharmacology

Structure-Activity

All of the AEDs are synthetic compounds. Individual structural details are listed in Table 12.6. Phenytoin is related to the barbiturates but contains a five-member carbon ring instead of the four-carbon basic structure. Gabapentin and pregabalin are both cyclic analogs of GABA, although pregabalin is around three times more potent. Oxcarbazepine is a keto-analog of carbamazepine.

Mechanism

Agents in this class act through a variety of mechanisms. Molecular targets of action include voltage-gated Na^+, K^+, and Ca^{2+} channels; $GABA_A$ receptors; glutamate receptors; some enzymes; and synaptic proteins. Table 12.7 summarizes the targets of each member of the AEDs. They all act by tilting the balance in favor of synaptic inhibition,[175] thereby preventing abnormal neuronal excitation

TABLE 12.6 Pharmacokinetics of the Antiepileptic Drugs

Drug	Structure	Elimination	Bioavailability (%)	Half-Life (hours)	Protein Binding (%)
Phenytoin	Related to barbiturates	Hepatic	Oral and IV: 70–100	Highly variable avg. 20–30	90
Oxcarbazepine	Carbamazepine derivative	Renal	>95	1–2.5 active metabolite (MHD): 9	40
Topiramate	Aminosulfonic derivative of monosaccharide	Renal	>90	19–23	9–17
Gabapentin	Cyclic analog of GABA	Renal	55–65	6–8	<5
Pregabalin	Cyclic analog of GABA	Renal	>90	5–7	<5
Levetiracetam	Pyrollidine derivative	Renal	>95	7	10
Ezogabine	Carbamic acid ethyl ester	Renal	60	8	60–80
Perampanel	Bipyridine	Hepatic	100	45	95
Brivaracetam	Pyrollidine derivative; analog of levetiracetam	Hepatic	>95	7–8	20
Eslicarbazepine	Carbamazepine derivative	Renal	95	10–12	30

GABA, Gamma aminobutyric acid; *IV,* intravenous; *MHD,* monohydroxy derivative

TABLE 12.7 Mechanism of Action of the Antiepileptic Drugs

Drug	Increased GABA Levels	$GABA_A$ Receptor Affinity	Sodium Channel Blockade	Calcium Channel Blockade	Glutamate Inhibition	Potassium Channel Activation	Synaptic Vesicle Protein 2A Ligand
Phenytoin			+				
Oxcarbazepine			+	+ (N, P-type)			
Topiramate	+	+	+	+ (L-type)	+		
Gabapentin				+ (N, P/Q-type)			
Pregabalin				+ (N, P/Q-type)			
Levetiracetam		+		+ (N-type)			Weak
Ezogabine	+	+				+Kv7.2–7.5	
Perampanel					+ (AMPA antagonist)		
Brivaracetam			+				+
Eslicarbazepine			+	+ (N, P-type)			

AMPA, 2-Amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid.
Adapted from Lasoń W, Dudra-Jastrzębska M, Rejdak K, et al. Basic mechanisms of antiepileptic drugs and their pharmacokinetic/pharmacodynamics interactions: an update. *Pharmacol Rep.* 2011;63:271–292.

and suppressing the spread of ongoing pathologic activity. The AEDs also affect neuroplastic processes and have genetic and epigenetic effects with longer-term changes on the evolution of the disease.

Metabolism

Phenytoin is extensively metabolized in the liver to an inactive metabolite by CYP 2C9. This process is capacity-limited and at higher doses demonstrates zero-order kinetics. Around 20% of topiramate is also metabolized by CYP 3A4 but most is renally cleared unchanged.[175] Oxcarbazepine and eslicarbazepine are rapidly metabolized by reduction to pharmacologically active metabolites, which are subsequently glucuronidated and renally excreted. Ezogabine is metabolized in the liver by glucuronidation and acetylation by enzymes independent of the CYP system. It has an active metabolite with some antiepileptic activity but lower potency than the parent drug. The agents levetiracetam, gabapentin, and pregabalin are not appreciably metabolized and are excreted unchanged in the urine. Perampanel and brivaracetam are extensively metabolized to pharmacologically inactive metabolites.

Clinical Pharmacology

Pharmacokinetics

Pharmacokinetic parameters of the AEDs are summarized in Table 12.7. At therapeutic doses, the metabolism of phenytoin is nonlinear (first-order kinetics) but becomes linear at toxic doses. Plasma level monitoring is required owing to its unpredictable pharmacokinetics and narrow therapeutic index.

Pharmacodynamics

Therapeutic Effects. There are no placebo-controlled trials of the AEDs as monotherapy for seizure control but there is widespread consensus that these drugs are effective.[175] The addition of newer AEDs as second-line agents in epilepsy refractory to standard monotherapy is supported by clinical data, but is associated with a higher rate of adverse effects. With optimal pharmacotherapy, around 50% of patients achieve total seizure control and a further 25% have significant improvement. AEDs are often used prophylactically in patients with brain tumors, severe traumatic head injuries, and intracerebral hemorrhages.[176] Definitive data demonstrating efficacy for brain tumors and hemorrhages are lacking and there is a paucity of information on the use of the newer AEDs for prophylaxis.

Adverse Effects. Unlike older AEDs, some of which carry FDA black box warnings (see earlier), with the exception of perampanel, the newer AEDs are generally well tolerated. Adverse effects that are common to most agents in the group include dizziness, somnolence, headaches, and memory impairment.

Phenytoin is more frequently associated with adverse effects than other members of this class. Specific problems include gingival hyperplasia, nystagmus, Stevens-Johnson syndrome, and osteomalacia. Phenytoin is also linked with an increased risk of congenital birth defects. Rapid intravenous administration of phenytoin can lead to hypotension and arrhythmias, hence the recommendation to limit delivery rate to 50 mg/min in adults. Gabapentin and pregabalin are associated with an increased risk of depression and suicide. Sudden withdrawal of these agents can precipitate seizures, even in patients who have not had seizures previously. Rarely, hepatotoxicity is linked to gabapentin use. Oxcarbazepine causes SIADH in around 3% of patients. It has been associated with photosensitivity and, given its similarity to carbamazepine, is considered to be a potential teratogen.

Perampanel carries a black box warning that some patients, including those without preexisting psychiatric illness, can develop psychosis or behavioral changes that include suicidal and homicidal ideation. It also has potential for abuse given that very high doses produce euphoric and dissociative effects similar to ketamine, earning it a schedule III classification by the U.S. Drug Enforcement Agency.

Drug Interactions

Phenytoin, oxcarbazepine, and eslicarbazepine induce CYP enzymes, increasing the metabolism of commonly used anesthetic agents, including midazolam, fentanyl, alfentanil, and aminosteroidal muscle relaxants. All drugs in this class enhance the CNS depressant effects of agents used in the perioperative period.[177]

Drugs of Abuse

The abuse of legal and illicit substances remains an intractable problem in modern society. The number of Americans abusing or dependent on ethanol exceeds 17 million and an estimated 24 million are current users of illicit drugs. Drugs of abuse are used for their pleasurable effects, which are due to activation of the mesolimbic dopaminergic reward system, either directly or indirectly. Anesthesiologists often see acutely intoxicated patients during anesthesia for trauma. In the elective setting, many patients abuse drugs chronically and if acutely intoxicated or withdrawing should have their procedures postponed.

The social history is often unreliable in detecting substance abuse. A history of alcohol abuse in younger patients should raise concerns over concurrent use of illicit substances. For nonurgent procedures in which suspicion is high, urine drug screening is useful. Routine drug screens do not test for designer drugs unless regional prevalence makes this cost-effective. It is important to understand how these substances adversely interact with anesthetic agents and to recognize withdrawal syndromes.

Ethanol

Ethanol (C_2H_5OH) has been consumed since prehistoric times. It is produced for human consumption by fermentation. Historically, it was thought that ethanol acted by perturbing the neuronal lipid membrane. More recent evidence suggests that there are multiple sites of action, including $GABA_A$ and glycine receptor potentiation and NMDA glutamate receptor inhibition.[178] Ethanol is rapidly absorbed into the bloodstream and metabolized by alcohol dehydrogenase in the liver to acetaldehyde. Acetaldehyde might mediate some of the neurologic and the changes in dopaminergic transmission that lead to alcoholism. This unstable intermediate is metabolized to acetic acid by aldehyde dehydrogenase. Ethanol is also oxidized by CYP 2E1 in the liver. This pathway is minor except under conditions of chronic consumption, in which CYP 2E1 is dramatically upregulated.

Acutely intoxicated patients have decreased anesthetic requirements, whereas chronic abusers can have higher requirements, partly owing to CYP induction. Perioperative concerns for the alcoholic patient include cardiomyopathy, alcoholic hepatitis, cirrhosis, and varices. Postoperatively generalized grand mal withdrawal seizures can occur around 24 to 36 hours after abstinence. Within 72 hours of cessation, delirium tremens occur in around 5% to 10% of alcoholics and is characterized by confusion, hallucinations, agitation, and autonomic hyperactivity. Treatment and prophylaxis are with the benzodiazepines. The older chronic alcoholic is also at an increased risk for postoperative cognitive dysfunction.

Cocaine

Since the time of the Incas, cocaine has been used as a stimulant. Originally consumed by chewing the leaves of the South American plant *Erythroxylum coca,* it was popularized in Europe and North America by its use in Coca-Cola and Vin Mariani. Modern pharmaceutical techniques allowed purification of the active ingredient in the 1880s, and cocaine hydrochloride was marketed as a panacea for a wide range of illnesses. Identification of the anesthetic properties of the drug saw its widespread use for local and regional anesthesia (see Chapter 20). Early experimenters including Freud and Halsted often self-administered to study the drug but succumbed to its addictive potential. With increasing evidence of problems associated with abuse, cocaine fell out of favor for medicinal use and was banned from distribution in 1914. It remains the second most commonly abused illicit substance, with around 1.5 million adults in the United States reporting recent use.

Cocaine produces intense euphoria and feelings of increased energy. The drug acts by blocking the reuptake of the neurotransmitters dopamine, serotonin, and norepinephrine into nerve terminals, thereby increasing the synaptic concentrations of these neurotransmitters. Effects on dopaminergic neurons are thought to be responsible for the high addictive potential of this drug.[179]

Cocaine is usually consumed orally or by snorting. The alkalinized form ("crack cocaine") can be injected, smoked, or snorted and has even greater addictive potential owing to very rapid absorption with high peak plasma levels. The elimination half-life is 0.5 to 1.5 hours and metabolism is by liver and plasma cholinesterases.

The sympathetic effects of cocaine can precipitate vasoconstriction or vasospasm in arteries supplying the brain and heart, leading to strokes and myocardial infarction or ischemia. Higher doses lead to ventricular arrhythmias and death. Users who smoke crack cocaine can induce asthma or develop pulmonary hemorrhages. Several serious complications are associated with anesthesia in the setting of acute cocaine use. Patients can become severely hypertensive, particularly during laryngoscopy.[180] Direct-acting vasodilators including nitroglycerin and hydralazine or calcium channel blockers are appropriate for treatment and prophylaxis although they worsen preexisting tachycardia. Caution should be exercised in the use of β-blockers, in that unopposed α-receptor action can worsen hypertension and lead to myocardial ischemia. The induction agents, ketamine and etomidate, can exacerbate the underlying hemodynamic abnormalities. Halothane should be avoided in that it sensitizes the myocardium to catecholamines, with a potential for arrhythmias.

Chronic cocaine users can develop intraoperative hypotension that is unresponsive to ephedrine that will usually respond to direct acting vasoconstrictors such as phenylephrine. Physical and psychological dependence to the drug develops, and abrupt cessation perioperatively is associated with a non–life-threatening withdrawal syndrome characterized by depression and fatigue.

Amphetamines

Amphetamine derivatives from the plant *Ephedra sinica* have been used for medicinal purposes for millennia. Modern pharmaceutical processes allowed the synthesis of amphetamine in 1887. Other members of the class, methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) were first synthesized in the early 20th century. Methamphetamine was used widely by the German military during World War II as a stimulant to prevent fatigue. Over the past 2 decades, methamphetamine ("crystal meth") abuse has become a vast social problem, particularly in the American Midwest. MDMA (ecstasy) was first used as an appetite suppressant before finding use in psychotherapy circles during the 1970s. The euphoric and energizing effects of the drug led to use in the club and bar scene. Although classified as Schedule 1 in the United States in 1984, usage spread to the mainstream and around the world, with ecstasy being among the top four most widely consumed illicit substances.

The basic amphetamine structure is composed of a phenethylamine backbone with a methyl group attached to the alpha carbon. Substitutions generate the related compounds, methamphetamine and MDMA. Methamphetamine abusers commonly administer the drug intravenously, by smoking, or by snorting. Less commonly it is taken orally. MDMA is usually taken orally but can be snorted or delivered rectally. Metabolism of the amphetamines is by CYP 2D6 in the liver. The elimination half-life is 6 to 10 hours for MDMA and 10 to 15 hours for methamphetamine.[180] The effects of amphetamines are mediated by enhanced neuronal release of dopamine, serotonin, and norepinephrine in specific regions of the brain.

Abuse of methamphetamine is associated with cognitive impairment, psychosis, Parkinson disease, extensive dental disease, and hypertension. Amphetamine and methamphetamine have high addictive potential, particularly when administered intravenously or by smoking. Idiosyncratic effects of MDMA include severe hyperthermia that can lead to rhabdomyolysis and disseminated intravascular coagulation. On occasion, patients present with seizures or obtundation caused by severe hyponatremia. Ecstasy is commonly adulterated with other agents, leading to a wide range of other adverse effects.

In the setting of acute intoxication, amphetamines increase volatile anesthetic requirements and reduce the duration of thiopental. These agents have unpredictable effects on the response to sympathomimetic drugs. Hypertensive effects akin to those seen with cocaine can be observed and are managed similarly. Severe hyperthermia is treated by supportive measures. It is unclear if dantrolene or clozapine are useful in this setting. Postoperatively discontinuation of amphetamine and methamphetamine can lead to a withdrawal syndrome similar to that seen with cocaine.

Emerging Developments

Ketamine in the Treatment of Depression

Ketamine was first used as a general anesthetic in the late 1960s and its unique properties have ensured its continued presence within the group of essential intravenous anesthetics. While anesthesiologists are familiar with ketamine's action as a general anesthetic, the drug has recently become the focus of much interest within the field of psychiatry as a potential treatment for depression.

Traditional antidepressants have an efficacy of only 60% to 70% in the treatment of mood disorders and are associated with prolonged delay of onset of action and high remission rates.[181] The search for novel antidepressants has proved unrewarding in recent years; thus it was not surprising that promising results from preclinical and clinical studies with ketamine would generate considerable excitement.

The effectiveness of some NMDA antagonists in animal models of depression led to the conduct of a small randomized controlled trial of ketamine in the treatment of severe unipolar or bipolar depression in 2000.[182] Seven patients received 0.5-mg/kg intravenous ketamine infusions or placebo at two different time points. Immediately after receiving ketamine, patients demonstrated clinically significant improvements in depression rating scores—effects that persisted up to 72 hours after administration.

This initial study prompted the conduct of large numbers of open-label trials demonstrating a 25% to 78% reduction in depressive symptom severity.[183] The difficulty of blinding patients to ketamine treatment has led to a paucity of placebo-controlled, double-blind randomized clinical trial data. Systematic reviews[181,183] of the available high-quality trial data have concluded that ketamine does have a rapid antidepressant effect but it remains unclear whether this is durable. Promisingly, most of these studies have been conducted in patients with severe or treatment refractory depression.

The psychotomimetic properties of the drug have led to fears of abuse potential in this patient population. Other practitioners deem the intravenous administration of ketamine impractical and

have trialed the use of oral ketamine therapy despite a bioavailability of 23% by this route.[184]

The recognition that not all NMDA antagonists are effective as antidepressants emphasizes that considerable work remains to be done to elucidate the mechanisms of ketamine in mood disorder treatment. A recently published study[185] has shown that metabolism of R-ketamine to 2R/6R-hydroxynorketamine is essential for antidepressant effects in a mouse model. These effects appear to be independent of NMDA receptor inhibition and instead rely on early and sustained activation of AMPA receptors, implicating a novel mechanism and suggesting new avenues for next-generation rapid-acting antidepressants.

Key Points

- Neuropharmacologic drugs represent the most prescribed class of agents, with more than 750 million prescriptions written in the United States in 2016. The pharmacology and clinical significance of these drugs in the perioperative setting are often underappreciated.
- The underlying mechanisms for most of the drugs remains elusive, although theories for many converge in effects centered in serotonergic, noradrenergic, and dopaminergic pathways; other receptor groups important to anesthetic pharmacology, including GABA, acetylcholine, and glutamate receptors, are also frequently implicated.
- A number of psychopharmacologic agents are potent inducers or inhibitors of specific cytochrome P450 isoenzymes and thus have the potential to alter the metabolism of many drugs used in the perioperative period.
- Many antipsychotic and mood stabilizer drugs have a narrow therapeutic index with multiple warnings in the product labeling. Pharmacologic and physiologic changes in the perioperative period have the potential to alter plasma concentrations and therapeutic/toxic effects.
- Several psychopharmacologic agents are associated with effects on cardiac conduction, seizure threshold, CNS depression, autonomic and serotonergic activation, the neuroendocrine response to stress, bleeding tendency, and other parameters relevant to anesthetic care. Interaction between some drugs, such as meperidine with monoamine oxidase inhibitors, can be severe or fatal.
- Neuroleptic malignant syndrome (NMS), which can be triggered by many antipsychotics, very closely resembles malignant hyperthermia (MH) and is treated similarly. Patients with a history of NMS should be regarded as MH-susceptible.
- Most psychopharmacologic drugs, including the commonly prescribed antidepressants and anxiolytics, cause changes in receptor expression and function and are associated with withdrawal syndromes if discontinued abruptly. Psychopharmacologic agents should almost always be continued during the perioperative period.
- Levodopa for Parkinson disease should be continued perioperatively and consideration given to enteral administration for longer procedures.
- The decision to continue anticholinesterase therapy for myasthenia gravis should be individualized. These agents interact with neuromuscular blockers and inhibit metabolism of ester-type local anesthetics and succinylcholine.
- Substance abuse is common in patients undergoing anesthesia for emergency procedures. Acute intoxication can lead to adverse interactions with anesthetic agents and vasoactive drugs.
- An emerging development in the field is the use of ketamine as a treatment for refractory depression. Data supporting the application of the technique are mixed and thus the therapy must still be considered in development.

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Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA*. 2010;303:47–53. Confirming a 2008 study using previously unpublished data from the FDA that suggested antidepressants might be ineffective in patients with mild to moderate baseline symptoms, this large and controversial meta-analysis casts doubt on the utility of widespread antidepressant use and suggests that only patients with severe baseline symptoms will benefit. (Ref. 35).

Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988;45:789–796. This large muticenter trial demonstrated the efficacy of clozapine in otherwise treatment-resistant schizophrenia, setting a path for FDA approval despite the risk of agranulocytosis associated with the drug. (Ref. 90).

Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353:1209–1223. This study broke ground in evaluating the effectiveness of the second-generation antipsychotics compared with the first-generation agents. Efficacies were similar, but the clinical course was dominated by a 74% rate of discontinuation. (Ref. 92).

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Melvin MA, Johnson BH, Quasha AL, et al. Induction of anesthesia with midazolam decreases halothane MAC in humans. *Anesthesiology*. 1982;57:238–241. This study established an interaction between the benzodiazepines and volatile anesthetics at a time when the mechanisms for neither were well elucidated, and formed a foundation for predicting how nonanesthetic sedatives would affect anesthetic management.

Wong DT, Horng JS, Bymaster FP, et al. A selective inhibitor of serotonin uptake: Lilly 110140, 3-(p-trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine. *Life Sci*. 1974;15:471–479. Principally of historical import, this paper represents the initial description of an SSRI, describing the drug that would come to be named fluoxetine and be marketed under the name Prozac. (Ref. 34).

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13

Autonomic Nervous System: Physiology

JOEL O. JOHNSON

CHAPTER OUTLINE

Historical Considerations

Anatomy and Physiology
- Sympathetic Nervous System
- Parasympathetic Nervous System

Cellular Physiology
- Preganglionic Neurons
- Postganglionic Neurons
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  - *Enteric Nervous System*
- Second Messengers in the Autonomic Nervous System
  - *Adrenal Medulla*

Autonomic Nervous System Reflexes
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  - *Autonomic Dysreflexia*
  - *Thermogenesis Reflex*
- Cardiac Reflexes
  - *Baroreceptor Reflex*
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  - *Bainbridge Reflex*
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  - *Oculocardiac Reflex (Trigeminal Nerve–Mediated Reflexes)*

Anesthesia, Disease, and the Autonomic Nervous System
- Effects of Anesthetics on the Autonomic Nervous System
- Autonomic Failure
  - *Diabetes Mellitus*
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Emerging Developments
- The Role of the Autonomic Nervous System in Obesity and Inflammation
- Sacral Nerves Part of Sympathetic System

Historical Considerations

A specialized taxonomy of the autonomic nervous system (ANS) has been developing since the time of Galen (AD 130–200). In the early 1900s, Langley first referred to the ANS.[1] He used the term *sympathetic nervous system* (SNS) as described by Willis in 1665, and introduced the second division as the *parasympathetic nervous system* (PNS) in 1921.[2] Although Langley initially described only the visceral motor system (efferent fibers), the existence of visceral reflex arcs necessitated the inclusion of the sensory (afferent) portions of the ANS.[3] Early anesthesia textbooks did not contain explicit information dealing with the ANS, but dealt with the practice of anesthesia, elucidating basic considerations of pharmacology and anesthetic technique. The evolution of the comprehensive anesthesia textbook has led to extensive chapters on the ANS.[3,4]

The ANS maintains cardiovascular, thermal, and gastrointestinal homeostasis. A firm understanding of the basic anatomy and physiology of the ANS forms an important foundation for the practice of anesthesiology. ANS structure, function, and reflexes are critical to the support of the circulation under anesthesia. This chapter reviews anatomy and physiology of the ANS relevant to anesthesia.

Anatomy and Physiology

ANS anatomy is composed of central control and feedback areas, sensory receptors, peripheral effectors, and reflex conduction pathways. In addition, complex interactions occur between the ANS and the endocrine system (see Chapter 36).[4] The renin-angiotensin system, antidiuretic hormone, glucocorticoid and mineralocorticoid responses, and insulin interact via an increasing number of receptor subtypes to maintain physiologic homeostasis (Fig. 13.1).

There are no distinct centers of autonomic function in the cerebral cortex. However, input from various sensory systems can affect higher cortical centers, be processed, and result in efferent autonomic activity. Tachycardia and peripheral vasoconstriction heralding a "fight-or-flight" response or a vasovagal response (fainting) are well-known examples of this higher cortical sensory processing.[5] External stimuli representing a threat or danger are detected by the senses of hearing, touch, smell, or sight. These signals are sent to the brainstem, where reflex responses are processed in the hypothalamus and the limbic forebrain. Higher cortical centers provide descending input to the paraventricular nucleus of the hypothalamus, which has projections to sympathetic and parasympathetic nuclei. Chronic stress alters these structures and their function, leading to both sensitization and habituation of the stress response.[6,7]

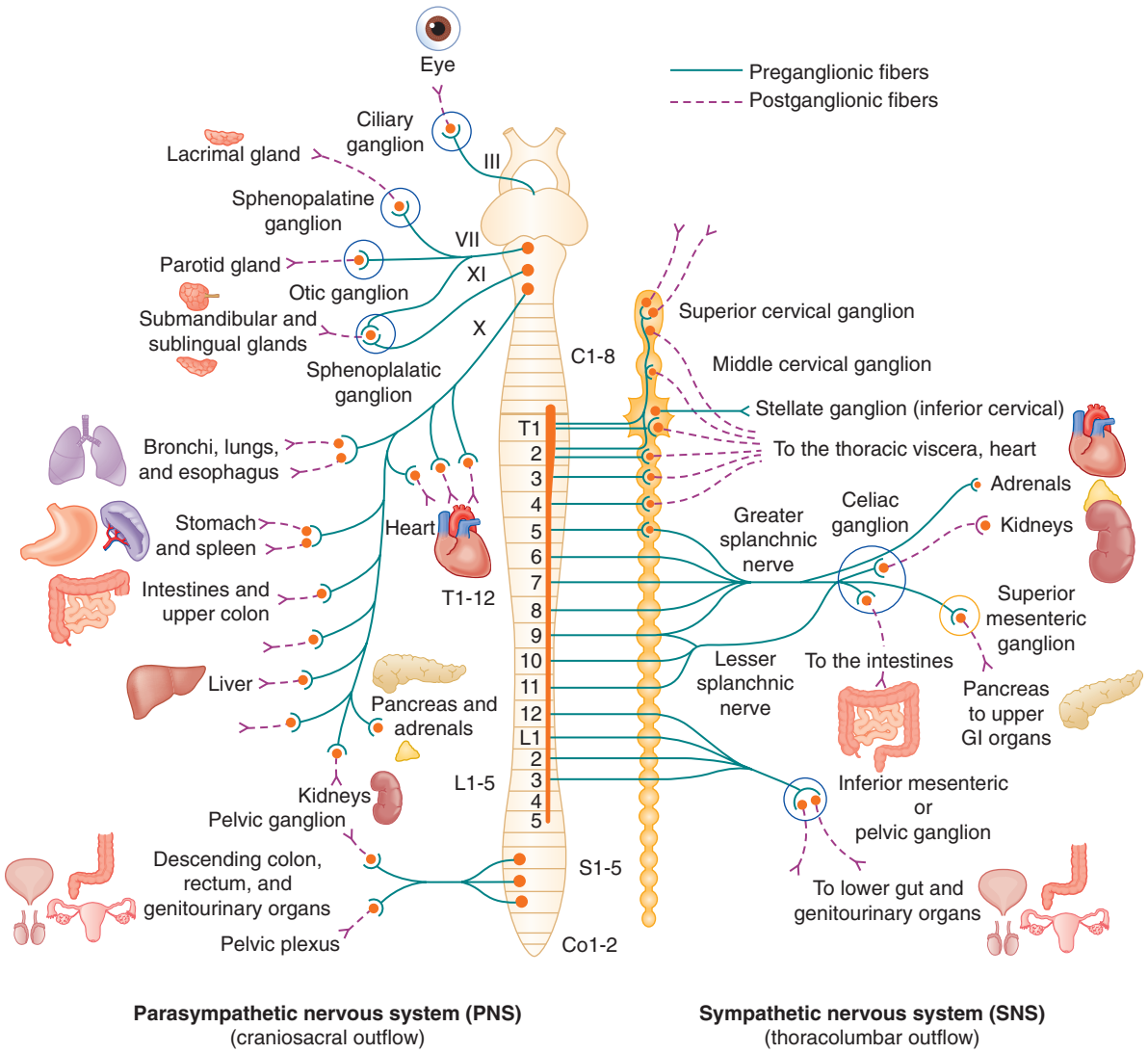
The hypothalamus is the midbrain center that processes sympathetic and parasympathetic functions, temperature regulation, fluid regulation, neurohumoral control, and stress responses. Hunger, sleep, and sexual function are also regulated by the hypothalamus, dependent on both cortical input and complex feedback control. The anterior hypothalamus controls temperature, while the posterior hypothalamus is involved in water regulation. The

Abstract

This chapter presents a concise description of the autonomic nervous system (ANS) with a focus on clinical elements related to anesthesiology. Beginning with a review of the anatomic divisions of the sympathetic (SNS) and parasympathetic (PNS) systems, the narrative links these structures to the interplay between the seemingly antagonistic physiologic actions of the two divisions. A close look at ANS cellular physiology reveals the receptor and effector mechanisms responsible for these differential effects, leading the reader to understand where anesthetic pharmacology might affect cardiovascular, pulmonary, gastrointestinal and humoral systems. Well-known ANS reflexes that are seen during the conduct of an anesthetic highlight the interaction between the SNS and the PNS. A review of the effect of anesthetics and ANS disease outlines the importance of the ANS in anesthetic practice. Emerging developments, including a radical change in the anatomic structure of the ANS, concludes the chapter.

Keywords

autonomic nervous system
sympathetic nervous system
parasympathetic nervous system
autonomic reflexes
disease states



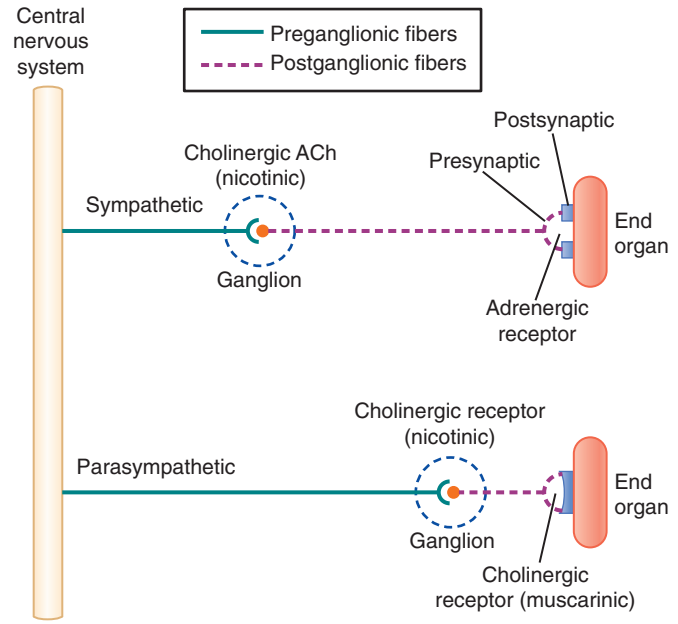
• **Fig. 13.1** Schematic representation of the autonomic nervous system consisting of the parasympathetic nervous system *(PNS, left)* and the sympathetic nervous system *(SNS, right)*.

hypothalamic-pituitary axis is a part of the ANS that ultimately regulates long-term blood pressure control and stress responses.[7]

The output centers of the ANS reside in the medulla oblongata and the pons of the brainstem. Immediate control of blood pressure, heart rate, cardiac output, and ventilation is organized and integrated in specific nuclei. Tonic impulses from nuclei such as the nucleus tractus solitarius maintain blood pressure and respond to afferent signals from the sensory side of the ANS. These afferent impulses from the vagus (X) and glossopharyngeal (XI) nerves result in vasodilation and bradycardia (see the section on ANS reflexes).

The ANS is anatomically and functionally divided into two complementary systems, the SNS and the PNS (see Fig. 13.1). The peripheral SNS is controlled by the thoracolumbar segment of the spinal cord, while PNS control arises from the brainstem nuclei and sacral segments (see Fig. 13.1). Activation of the SNS produces diffuse physiologic responses, while the PNS exerts local control of innervated organs.[8] Both systems have efferent pathways through peripheral ganglia; the SNS ganglia are located close to the thoracolumbar spine, and the PNS ganglia are situated near or inside the innervated organs (see Fig. 13.1; Fig. 13.2). Ganglia serve as synaptic relay stations, and in the SNS coordinate an efferent mass action response through signal amplification. Thus one preganglionic SNS fiber can activate 20 to 30 postganglionic sympathetic neurons and their fibers. In contrast, PNS preganglionic fibers terminate in ganglia located in proximity to the innervated organs and affect only one to three postganglionic neurons.[2] The close proximity of PNS ganglia to their effector organs is the anatomic basis of the more focused and specific responses elicited by PNS activation.

Most organs are affected by both the SNS and the PNS. Different organs have their resting tone dominated by the SNS or the PNS, and this ratio can change depending on pathophysiologic states and also can change over the lifetime of an individual. For instance, newborns are dominated by parasympathetic responses; hence bradycardia can be seen in 20% of unpremedicated infants during stressful situations such as anesthetic induction and airway manipulation, while it is uncommon in adults.[9] As another example, vasoreactivity of the major blood vessels, arteries, and arterioles is primarily responsive to the SNS, while PNS cardiovascular effects reside mainly at the level of the heart. The differential effects of



• **Fig. 13.2** Differences between the location of the ganglia in the sympathetic and parasympathetic branches of the autonomic nervous system. The 22 paired sympathetic ganglia are located close to the vertebral column in the sympathetic chain. The unmyelinated postganglionic fibers innervate their respective organs. The exception is the adrenal gland, where the sympathetic preganglionic nerve fibers travel directly to the adrenal medulla. The parasympathetic preganglionic fibers travel directly to the organ of innervation to synapse with postganglionic neuronal cell bodies. *ACh,* Acetylcholine.

the ANS in various organs and organ systems are summarized in Table 13.1.

In general, the SNS modulates the activity of vascular smooth muscle, cardiac muscle, and various glands (especially the adrenal gland); this modulation is critical for the fight-or-flight response. In contrast, the PNS modulates "rest-and-digest" functions such as salivation, lacrimation, urination, digestion, defecation, and sexual arousal.

Sympathetic Nervous System

The SNS is formed from preganglionic fibers in the thoracolumbar segments (T1-L3) of the spinal cord arising from the intermediolateral gray column (see Fig. 13.1). These myelinated fibers enter the paravertebral ganglia and travel a variable distance up or down the sympathetic chain to synapse with the neuronal cell bodies of postganglionic sympathetic neurons. The unmyelinated postganglionic fibers then innervate their respective organs. An exception to this rule is the adrenal gland, where the preganglionic fibers do not synapse in the thoracic ganglia, but course through the sympathetic chain into the adrenal medulla. The chromaffin cells in the adrenal medulla are derived from neuronal tissue and essentially function as the postganglionic cells.

The stellate ganglion consists of postganglionic neurons that provide sympathetic innervation to the head and neck. Preganglionic fibers from the first four or five thoracic segments form this ganglion as well as the superior and middle cervical ganglia. Local anesthetic injected in the vicinity of the stellate ganglion blocks the sympathetic fibers coursing to the ipsilateral head and neck and may result in Horner syndrome, characterized by ptosis, miosis, enophthalmos, and anhydrosis on the affected side.[10] This syndrome might be seen as a direct effect of a stellate ganglion block or be experienced as a side effect of a brachial plexus block owing to its close proximity to the stellate ganglion.[10] Similarly, blockade of the lumbar plexus produces a sympathectomy in the lower extremities, and peripheral nerve block often produces a sympathectomy in the affected limb because the postganglionic sympathetic nerve fibers travel along the somatic nerves.

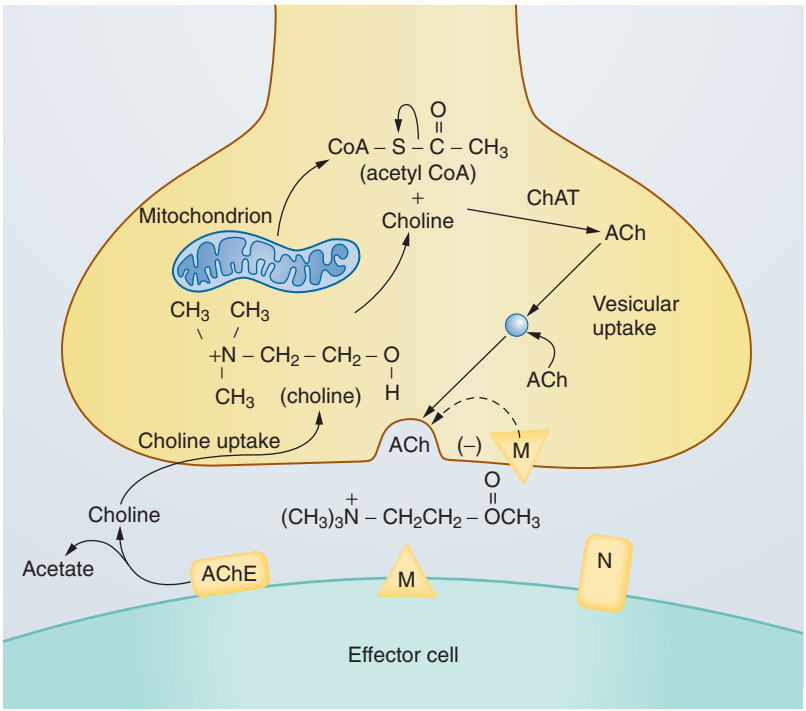
TABLE 13.1 Autonomic Nervous System Receptor Types and Subtypes

Receptor	Effector	Response to Stimulation
Sympathetic Nervous System		
α_1	Smooth muscle (vascular, iris radial, ureter, trigone, bladder sphincters)	Constriction
α_2	Presynaptic SNS nerve endings	Inhibition of NE release
	Brain	Neurotransmission
β_1	Heart	Increase rate, contractility, conduction
	Adipose tissue	Lipolysis
β_2	Blood vessels	Dilation
	Bronchioles	Dilation
	Kidney	Renin secretion
	Liver	Gluconeogenesis, glycogenolysis
	Endocrine pancreas	Insulin secretion
	Uterus	Relaxation
D_1	Blood vessels	Dilation
D_2	Presynaptic SNS nerve endings	Inhibition of NE release
Parasympathetic Nervous System		
M_1	Skeletal prejunctional nerve endings	Facilitate ACh release
M_2	Lung–presynaptic PNS nerve endings	Inhibits ACh release
	Visceral organs	Increase
M_3	Lung smooth muscle, postsynaptic	Bronchoconstriction
N_1	PNS and SNS ganglion	Ganglionic blockade
N_2	Skeletal muscle	Muscle contraction

ACh, Acetylcholine; *D,* dopamine; *M,* muscarinic; *N,* nicotinic; *NE,* norepinephrine; *PNS,* parasympathetic nervous system; *SNS,* sympathetic nervous system.

Parasympathetic Nervous System

Preganglionic fibers in the PNS arise from the midbrain, medulla oblongata, and sacral segments of the spinal cord. Cranial nerves II, VII, IX, and X carry preganglionic parasympathetic fibers directly



• **Fig. 13.3** The cholinergic synapse. Acetylcholine *(ACh)* is produced in the presynaptic terminal by the combination of acetyl coenzyme A *(CoA)* and choline through the action of choline acetyltransferase *(ChAT).* This neurotransmitter is stored in vesicles located in the presynaptic terminal and released upon nerve stimulation. ACh can bind to either nicotinic *(N)* or muscarinic *(M)* postsynaptic receptors to elicit an effector response (after summation in the postsynaptic membrane). In addition, ACh interacts with presynaptic muscarinic receptors to provide negative feedback on ACh release. ACh is broken down in the synapse by acetylcholine esterase *(AChE),* and choline is taken up into the presynaptic terminal to be reused.

to ganglia located near or directly in innervated organs. The sacral segments S2-S4 provide innervation to the rectum and genitourinary tissues (see Fig. 13.1).

The vagus nerve (X) is the major carrier of parasympathetic neuronal traffic. These preganglionic fibers affect the heart, lungs, and abdominal organs with the exception of the distal portion of the colon. A combination of the distal location of the ganglion and the smaller two- to threefold amplification factor between preganglionic and postganglionic fibers causes parasympathetic effects to be specific to each organ.

Cellular Physiology

Preganglionic Neurons

Synaptic transmission through ANS ganglia is similar in both the SNS and the PNS. Preganglionic neurons in both the SNS and PNS are cholinergic. Acetylcholine (ACh) is stored in synaptic vesicles and released by a calcium ion (Ca^{2+})-dependent process upon nerve terminal depolarization (Fig. 13.3). ACh then interacts with postsynaptic receptors to depolarize the postsynaptic membrane. The principal ganglionic receptors are excitatory nicotinic ACh receptors, related to the ACh receptors at the neuromuscular junction (see Chapter 21). Thus many neuromuscular blocking agents have cardiovascular side effects mediated by their actions at the level of ANS ganglia. Recent advances in the pharmacology of these drugs have been directed at decreasing these ganglionic actions (see Chapter 22).

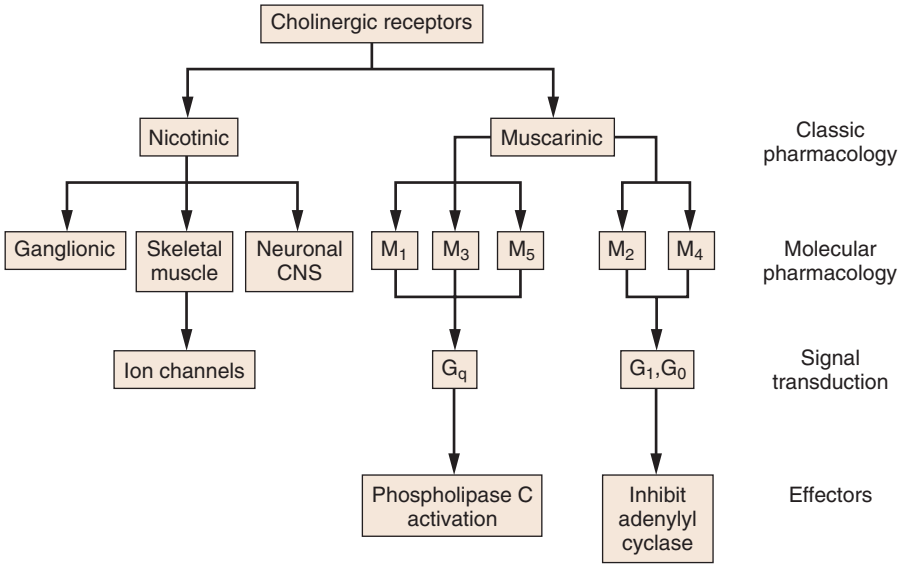
There are two distinct nicotinic receptor types, designated neuronal and muscle nicotinic ACh receptors (Fig. 13.4).[11] Neuronal ACh receptors expressed in the autonomic ganglia are composed of $\alpha_3\beta_4$ subunits and are blocked by older neuromuscular blockers (e.g., gallamine), leading to ganglionic blockade. The neuromuscular junction has muscle nicotinic ACh receptors (composed of $\alpha\beta\delta\varepsilon$ subunits in adults) that are blocked selectively by the newer neuromuscular blocking agents, resulting in few side effects. Volatile anesthetics and ketamine are potent inhibitors both at $\alpha_4\beta_2$ in the central nervous system (CNS) and ganglionic $\alpha_3\beta_4$ receptors.[11] The development of neuromuscular blocking agents has been focused on reduction of muscarinic side effects and elimination of ganglionic blockade. Structure-activity relationships indicate that the presence of quaternary ammonium moieties facilitates binding at the ACh site, whereas interionic distances may play a role in diminishing ganglionic as well as muscarinic cross-reactivity.[12]

Both nicotinic and muscarinic agonists and blockers interact at the level of the ganglia, the effects of which summate to either excite or inhibit the postganglionic neuron, and subsequently inhibit the effector organ. Thus the ganglionic synapse serves complex integrative and processing functions during normal physiology and while under the influence of anesthetic agents.

Postganglionic Neurons

Sympathetic Nervous System

Epinephrine, norepinephrine, and dopamine are the classic neurotransmitters of sympathetic synaptic transmission released from

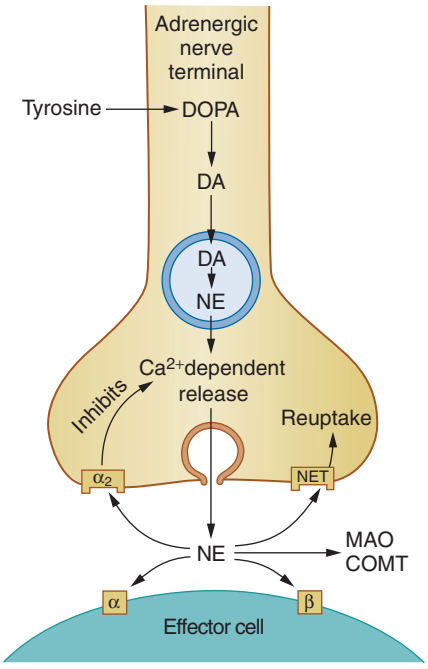


• **Fig. 13.4** Classification of cholinergic receptors. Receptor classification is pharmacologic or based on second messenger signal transduction. *CNS,* Central nervous system.

postganglionic neurons (Fig. 13.5); they interact with adrenergic receptors to effect sympathetic physiologic responses. As shown in Fig. 13.6, these neurotransmitters and their receptors can be characterized at different levels. Building on the original observation by Ahlquist, adrenergic "receptors" are of two different types (α and β) classified in terms of the overall physiologic response they elicit (the "classic pharmacology" approach).[13] Modern pharmacology further categorizes these receptors in terms of their molecular biology (e.g., DNA sequence and protein structure). From a mechanistic perspective, these receptors can also be classified in terms of how their signals are transduced (i.e., which G-protein subtype is involved) and how the response is effected (i.e., what ion channels or enzymes are involved).

For example, norepinephrine released from sympathetic postganglionic neurons stimulates both α- and β-adrenergic receptors, eliciting classic adrenergic responses. α_2 Receptors located presynaptically, provide a negative feedback loop to modulate further release of neurotransmitter (see Fig. 13.5). The postsynaptic receptors regulate effector cells through second-messenger signaling. The various and widespread physiologic actions of adrenergic and dopaminergic receptors are summarized in Table 13.1.

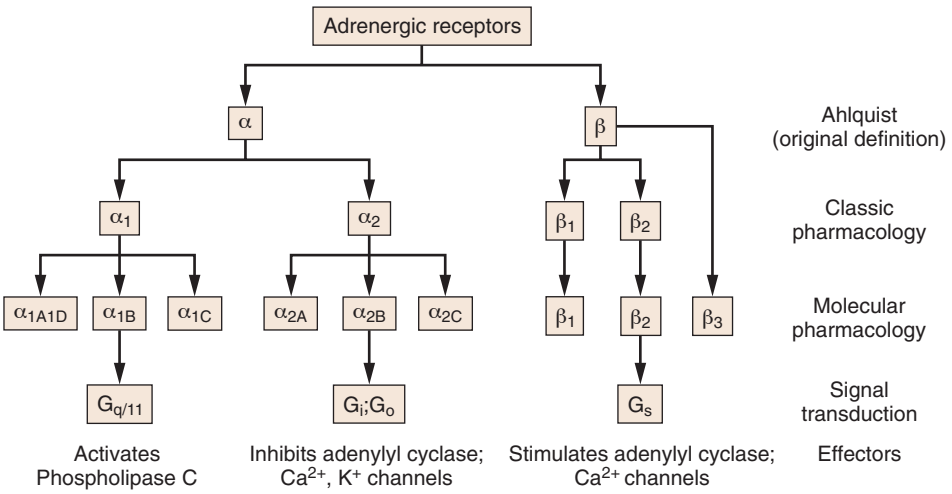
Synthesis of the adrenergic neurotransmitters takes place in the presynaptic varicosities of postganglionic sympathetic neurons. The steps in the enzymatic synthesis of norepinephrine are depicted in Fig. 13.5. The neurotransmitters are stored and released from synaptic vesicles, and reuptake into presynaptic nerve endings assists in the termination of transmitter action. In addition, diffusion of transmitters away from the synaptic cleft and metabolism by monoamine oxidase and catechol-*O*-methyl transferase quickly terminate the action of norepinephrine.



• **Fig. 13.5** The adrenergic presynaptic terminal. Tyrosine is converted to dihydroxyphenylalanine *(DOPA)* by tyrosine hydroxylase. DOPA decarboxylase produces dopamine *(DA)* in the cytoplasm, which is taken up into synaptic vesicles. Inside the synaptic vesicles, DA is converted to norepinephrine *(NE)* by dopamine β-hydroxylase. When NE is released from the presynaptic site by calcium *(Ca^{2+})*-dependent exocytosis, the released neurotransmitter interacts with the effector cell adrenergic receptors and receptors located on the presynaptic membrane. Presynaptic α_2 receptors inhibit further NE release. Presynaptic β receptors enhance NE reuptake, the major factor in removal of NE from the synaptic cleft. NE synthesis is controlled by a negative feedback loop at the level of tyrosine hydroxylase (not shown). Small amounts of NE escape into extraneuronal tissues, where it is inactivated by monoamine oxidase *(MAO)* and catechol-*O*-methyltransferase *(COMT). NET,* norepinephrine transporter.

Parasympathetic Nervous System

ACh is the primary neurotransmitter at the postganglionic effector sites of the PNS. The postsynaptic receptors for ACh are classified as nicotinic or muscarinic. As with the adrenergic receptors, cholinergic receptors can be classified in terms of classic



• **Fig. 13.6** Classification of adrenergic receptors. Receptor classification is pharmacologic or based on second-messenger signal transduction. *Ca^{2+},* Calcium ion; *K^{+},* potassium ion.

TABLE 13.2 Homeostatic Balance Between the Parasympathetic and Sympathetic Nervous Systems by Organ System

Organ System	Effector	SNS Stimulation	PNS Stimulation
Cardiovascular	Sinoatrial node	Increase heart rate	Decrease heart rate
	Atrioventricular node	Increase conduction velocity	Decrease conduction velocity
	His-Purkinje fiber	Increase automaticity, conduction	None or minimal
	Myocardial tissue	Increase contractility	None or minimal
	Coronary arterioles	Constriction (α_2), dilation (β_2)	Dilation and constriction
Gastrointestinal	Salivary glands	Little increase in secretion	Stimulates secretion
	Gall bladder	Relaxation	Contraction
	Smooth muscle	Inhibits	Stimulates
	Sphincters	Constricts	Relaxes
Ophthalmologic	Iris	Mydriasis	Miosis
	Ciliary muscle	Relaxation (for far vision)	Contraction (for near vision)
Pulmonary	Bronchial smooth muscle	Relaxation	Contraction
Genitourinary	Bladder walls	Relaxes smooth muscle	Smooth muscle contraction
	Bladder sphincter	Contraction	Relaxation
	Ductus deferens, seminal vesicle, prostatic and uterine musculature	Contraction of smooth muscle	Vasodilation and erection
Thermal regulation	Blood vessels	Constriction	Dilation
	Sweat glands	Diaphoresis (postganglionic sympathetic fibers are cholinergic)	Little effect

PNS, Parasympathetic nervous system; *SNS,* sympathetic nervous system.

pharmacology, molecular biology, and/or cellular mechanisms (see Fig. 13.4). Nicotinic receptors, which function at the neuromuscular junction, are also present in autonomic ganglia (see earlier text).

Muscarinic receptors mediate the majority of PNS physiologic effects (Table 13.2). After release into the synaptic cleft, the action of ACh is quickly terminated by the extracellular enzyme acetylcholinesterase (AChE) through hydrolysis (see Fig. 13.3). AChE is postsynaptically membrane-bound; hydrolysis of ACh produces choline and acetate. Choline is taken up by the presynaptic nerve endings to be reused, while acetate diffuses away from the synaptic cleft.

There are five distinct subclasses of muscarinic receptors, three of which have pharmacologic significance in the PNS, designated M_1, M_2, and M_3.[14] M_1 receptors exist in autonomic ganglia and the CNS and are present in the airway. M_1, M_2, and M_3 receptors have effects on the airway smooth muscle with the majority of receptors being M_2 and M_3. M_2 receptors are located presynaptically and function as part of a negative feedback loop to limit release

of ACh. M_3 receptors are located postsynaptically and mediate bronchoconstriction.

Enteric Nervous System

The gastrointestinal tract is innervated by sympathetic and parasympathetic efferents arising from preganglionic and postganglionic sites. These neural inputs, along with visceral afferents, interact with intrinsic neural elements (often referred to as the enteric nervous system) to control gut function. The SNS contributes nerve fibers from cell bodies located within the prevertebral sympathetic ganglia and from celiac, inferior mesenteric, and pelvic ganglia. Vagal (parasympathetic) innervation consists of both sensory and motor fibers. The vagal efferents end on smooth muscle within the walls of the gut, interacting with the intrinsic myenteric ganglion to control motility (see Chapter 31). Efferent outflow from the sympathetic and the parasympathetic systems modulate blood flow, secretory activity, and motility.[15,16] Vagal afferent traffic responds to normal gut function, whereas sympathetic afferents respond to painful stimuli such as distention and injury.

Anesthetic effects on the enteric nervous system can be divided into direct pharmacologic effects on the intestinal smooth muscle and effects resulting from spinal or epidural anesthesia. Muscarinic cholinergic receptors in the gut can be modulated by AChE inhibitors and anticholinergics used for reversal of neuromuscular blockade.[17] Postoperative ileus can be decreased by the use of thoracic epidural anesthesia.[18] Autonomic dysfunction causing gut dysmotility occurs because the SNS exerts more influence in the postoperative period than the parasympathetic system. This inhibitory sympathetic reflex can be interrupted by division of the splanchnic nerves, destruction of afferent sensory nerves, or chemical sympathectomy via thoracic epidural anesthesia. The clinical result of thoracic epidural anesthesia has been shown to be a shortened time to resolution of postoperative ileus.[18]

Second Messengers in the Autonomic Nervous System

The interaction of neurotransmitters with their postsynaptic receptors results in signal transduction, which translates receptor binding into an effector cell response. In the adrenergic system, transduction is mediated by G proteins, which then regulate adenylyl cyclase and phospholipase C to generate second messengers and/or directly modulate various ion channels (see Chapter 1). In contrast, nicotinic ACh receptor binding leads to opening of its intrinsic ion channel, which results in changes in the cell electrical potential. Muscarinic ACh receptors are G-protein–coupled receptors similar to adrenergic receptors. Second-messenger responses to muscarinic receptor stimulation depend on the effector site and the muscarinic receptor subtypes expressed (see Table 13.2).

Adrenal Medulla

The paired adrenal medullae are specialized portions of the SNS. Chromaffin cells are homologous to the sympathetic ganglion neurons and are similarly derived from the neural crest. The adrenal medulla can be thought of as a functional sympathetic ganglion in direct communication with the systemic circulation. Stimulation of the SNS results in the release of epinephrine and norepinephrine from the medulla into the bloodstream, eliciting a diffuse (nontargeted) sympathetic response from various effector organs expressing adrenergic receptors. In this way, the adrenal gland represents the general effector of the SNS; stimulation results in a 20- to 30-fold amplification essential to the stress response.[19]

Autonomic Nervous System Reflexes

The ANS maintains homeostasis using the SNS and PNS as counteracting regulators (see Table 13.2). The relative tone of each of the two subsystems varies with age, sex, organ system, and environmental effects such as stress.[20] The challenge facing anesthesiologists is to maintain homeostasis while the ANS is modulated by medications, coexisting disease, surgical stimulation, and anesthetic drugs. Understanding of the pathways of ANS reflexes, and the anesthetic/surgical circumstances under which they are accentuated or attenuated, provides a conceptual framework for maintaining homeostasis during anesthesia and critical care.

Central Nervous System Reflexes

Cushing's Triad

Cushing's triad is the physiologic association of increased intracranial pressure, bradycardia, and hypertension.[21] Intracranial hypertension leads to sympathetically mediated increases in blood pressure; the increase in vascular tone results in bradycardia. Activation of parasympathetic medullary centers via the baroreceptor reflex (see later text) slows the heart but does not overcome sympathetically mediated hypertension. The result is a homeostatic increased blood flow to the brain.

Autonomic Dysreflexia

Historically termed *autonomic hyperreflexia,* this condition results from chronic disruption of efferent impulses down the spinal cord, as seen in spinal cord trauma or tumor impingement.[22] Autonomic hyperreflexia is uncommon if the level of disruption is below T5. Inciting stimuli such as bladder distention, bowel distention, or surgical stimulation can produce an exaggerated sympathetic response. This occurs because there is a loss of normal inhibitory impulses from areas above the level of the lesion. A portion of the exaggeration in the response is due to adrenergic receptor supersensitivity secondary to denervation. Management of the quadriplegic or high paraplegic patient consists of either spinal or general anesthesia combined with careful manipulation of blood pressure.[23]

Thermogenesis Reflex

Autonomic control of thermoregulation in mammals consists of reflex pathways from sensory cells originating in diverse tissues, including the skin, core organs, and the CNS. These signals are processed by the hypothalamus, which maintains body temperature within a narrow range of a few tenths of a degree around 37°C. Daily circadian rhythms result in a sinusoidal variation of about 1°C. The output of the hypothalamus controls effector responses, including peripheral vasculature action (vasodilation or vasoconstriction), sweating, and shivering.[24]

The preoptic area in the anterior hypothalamus receives thermal afferent signals from peripheral receptors as well as sensors located in the core (spinal cord, some organs). Efferent traffic goes to the principal thermoregulatory effectors: (1) cutaneous blood vessels, which vasoconstrict to reduce heat loss and vasodilate to facilitate heat loss; (2) brown fat and skeletal muscle for thermogenesis and shivering; and (3) sweat glands to provide for evaporative heat loss.[25]

Sweating is controlled by cholinergic fibers that can be blocked by muscarinic antagonists such as atropine or by peripheral nerve block.[26] Shivering can be blocked by the use of neuromuscular blockers and is diminished in old age and neuromuscular diseases. Shivering does not occur in newborns and is limited in infants.

Nonshivering thermogenesis occurring in newborns and infants is modulated by norepinephrine from adrenergic nerve terminals. Vasoconstriction is controlled by the ANS at the level of the arteriovenous shunts and is the result of sympathetic nerve traffic and not circulating catecholamines.

All general anesthetics impair thermogenesis reflexes. The sweating threshold is slightly increased and vasoconstriction and shivering thresholds are decreased markedly. These effects of anesthetics can lead to hypothermia during surgery if heat loss through radiation, conduction, convection, and evaporation is not minimized.[27]

Cardiac Reflexes

Baroreceptor Reflex

Stretch receptors in the walls of the carotid artery (carotid sinus) and aorta sense an increase in pressure (either endovascular or external, such as carotid massage). Afferent impulses are carried via the nerve of Hering and the vagus nerve to the medulla. In the medulla the excitatory baroreceptor inputs interact at the nucleus of the solitary tract to disinhibit inhibitory interneurons, which then send increased signals to the rostral ventrolateral medulla and onward to the intermediolateral nucleus.[28] A decrease in heart rate, blood pressure, myocardial contractility, and total peripheral vascular resistance is mediated by efferent vagal activity (see Chapter 24). This effect is seen during anesthesia when phenylephrine, an α_1-receptor agonist, is administered intravenously, causing a rise in blood pressure and a fall in heart rate. Halothane attenuates this reflex.[29]

Chemoreceptor Reflex

Central chemoreceptors are sensitive to increases in arterial carbon dioxide and decreases in arterial pH. Hypercarbia elicits a rapid and vigorous increase in minute ventilation (see Chapter 29). Volatile anesthetics, opioids, and nitrous oxide attenuate this response in a dose-dependent fashion. Even subanesthetic concentrations of volatile anesthetics have an effect on the ventilation response; thus patients given halogenated agents in the operating room can continue to have an impaired response to hypercarbia in the postanesthesia care unit.[30] Peripheral chemoreceptors are present in the carotid body; volatile anesthetics also produce dose-dependent attenuation of the ventilatory response to hypoxia mediated by these receptors.[31] Hypoxia elicits afferent impulses from the carotid and aortic bodies through the nerve of Hering and the vagus to the nucleus tractus solitarius, increasing respiratory rate, tidal volume, and thus minute ventilation. Sympathetic activation causing increased heart rate and cardiac output can also occur.[32]

Bainbridge Reflex

An increase in central venous pressure activates stretch receptors in the atria. Afferent impulses through the vagus nerve have an impact on cardiovascular centers in the brain, which then inhibit tonic parasympathetic output, resulting in tachycardia.[33] The Bainbridge reflex can be seen during childbirth when autotransfusion increases central venous pressure.[34] Steep Trendelenburg positioning, such as that seen with laparoscopic hysterectomy, may also precipitate this reflex.

Bezold-Jarisch Reflex

This cardiac reflex is characterized by hypotension, bradycardia, and peripheral vasodilation (see Chapter 10). The Bezold-Jarisch reflex occurs in response to noxious stimuli detected in the ventricle; historically this was studied using *Veratrum* alkaloids administered intravenously. Chemoreceptors located in the ventricles respond to myocardial ischemia, resulting in an increase in blood flow to the myocardium and a decrease in the work of the heart. This appears to be a cardioprotective reflex, as coronary vasodilation occurs. The pathway for this cardioprotective reflex begins with receptors in the ventricles of the heart, which detect mechanical and chemical stimuli. Afferent unmyelinated C-fibers travel through the vagus to enhance the baroreceptor reflex mechanisms, inhibit sympathetic output, and inhibit vasomotor tone, leading to peripheral vasodilation. The significance of this reflex in the presence of anesthetics continues to be debated, particularly in relation to regional anesthesia. As a cardioinhibitory reflex, the Bezold-Jarisch reflex might be functioning in parallel with the baroreceptor reflex but is probably not a predominant cause of physiologic change in humans.[35]

Valsalva Maneuver

Forced expiration against a closed glottis leads to multiple ANS-mediated responses. Increased intrathoracic pressure leads to a decrease in venous return, causing an abrupt decrease in cardiac filling and blood pressure. The baroreceptor response leads to an increase in heart rate and inotropy through sympathetic stimulation. Upon glottic opening, the increase in venous return leads to an increase in blood pressure (contractility is still increased). This is detected by the baroreceptors, causing a parasympathetically mediated decrease in heart rate.[36]

Oculocardiac Reflex (Trigeminal Nerve–Mediated Reflexes)

The trigeminal nerve (V) is associated with several autonomic reflexes; the best known is the oculocardiac reflex. Pressure on the globe or pulling on the extraocular musculature elicits afferent signals in the short and long ciliary nerves. These signals converge on the Gasserian ganglion, causing a parasympathetic response, notably severe bradycardia. Release of the stretch results in a return of normal heart rate. This muscarinic receptor–mediated response can be blocked with glycopyrrolate or atropine or by retrobulbar nerve block. In addition to the oculocardiac reflex, parasympathetic activation has been reported during intranasal stimulation and is an important part of the diving reflex.[37,38] During anesthesia, the trigeminal-mediated reflex may often be terminated by cessation of the stimulation.

Anesthesia, Disease, and the Autonomic Nervous System

Effects of Anesthetics on the Autonomic Nervous System

General anesthetics tend to suppress the ANS, as they do the CNS. Many specific drugs used in anesthesia directly or indirectly interact with systems, organs, and receptors of the ANS, which then modify the function of the ANS. For instance, administration of the α_2-agonist clonidine decreases the dose of halothane required to produce general anesthesia.[39] Dexmedetomidine, an agonist of α_2 receptors in the CNS, is often used as an anesthetic adjunct to augment both sedation and analgesia.[40]

Anesthetics depress the ANS, in part by attenuating homeostatic reflexes and by decreasing the normal variability in measurements seen owing to the balance between the sympathetic and

parasympathetic systems. Heart rate variability, pulse-to pulse interval, and pulse plethysmography amplitude have been used to characterize the state of the ANS.[41,42] Administration of a potent opioid such as fentanyl decreases normal beat-to beat variability, depresses sympathetic tone, and promotes vagal activation.[43] Potent inhaled anesthetics such as desflurane depress the ANS as measured by heart rate variability.[44] Xenon, an anesthetic that has less hemodynamic depression than potent inhaled agents, causes increased parasympathetic and decreased sympathetic activity compared with total intravenous anesthesia with propofol.[45] Thus, although inhaled anesthetics have variable effects on the ANS, depression of the SNS appears to dominate.

General anesthesia and regional anesthesia also have differential effects on the ANS. The balance of sympathetic with parasympathetic tone in the upper body (unaffected by a lumbar epidural block) and the lower body, or the change in the balance between the intraoperative and postoperative state can have consequences in critical cardiac patients.[46] ANS dysfunction in the intensive care unit complicates the perioperative course in the surgical patient.[47]

Autonomic Failure

Aging, diabetes mellitus, and dysautonomia can result in failure or dysfunction of the ANS that affects perioperative management.

Aging

The cardiovascular effects of aging are characterized by hypertension and orthostatic hypotension, two conditions regulated by the ANS.[48] In addition, loss of temperature control can lead to heat stroke or hypothermia. All of these conditions lead to an inability of the older patients to adequately adapt to environmental stress. While the amount of circulating epinephrine and the number of β-adrenergic receptors are not reduced in older adults, the amount of norepinephrine is increased. This leads to a cyclic decline in responsiveness of adrenergic receptors as circulating plasma norepinephrine increases and receptors downregulate, requiring more stimulation.[48] Because older adults have decreased levels of plasma renin and aldosterone and increased levels of atrial natriuretic factor, they are prone to salt-wasting and hypovolemia.[49] The resultant labile blood pressure, particularly with orthostatic changes, makes pharmacologic management challenging. For instance, β-adrenergic agonists have a markedly decreased effect on heart rate, cardiac output, and vasodilation as a result of reduced affinity of the β-adrenergic receptor and a decline in the efficacy of second-messenger coupling.[48]

Temperature regulation in older patients is also altered as a consequence of changes in the ANS, and as a result of reduced ability of the body to respond physiologically with shivering and vasoconstriction. Older patients have reduced muscle mass so they are unable to generate heat effectively. They also have reduced subcutaneous fat (even though total fat as measured as a proportion of body weight is increased), leading to a decrease in thermal insulation.[50] Thermoregulatory control of skin blood flow in the elderly is also altered as a result of changes in the ANS. Reflex vasoconstriction and vasodilation are impaired because of diminished sympathetic output and reduced vascular responsiveness.[51] As a consequence, older adults can experience more stress related to hypothermia and hyperthermia.

Diabetes Mellitus

Autonomic neuropathy is common among diabetic patients. Between 20% and 40% of insulin-dependent diabetic patients have significant peripheral neuropathy, characterized by labile blood pressure, thermoregulatory deficits, and gastroparesis (possibly vagal nerve dysfunction).[52] This constellation of problems can require modification of the typical anesthetic plan, including pretreatment to mitigate the consequences of aspiration of stomach contents, cardiovascular support, and proactive efforts to prevent hypothermia. Perhaps in part because of autonomic dysfunction, diabetic patients experience more stress and are at increased risk for perioperative complications.[53]

Autonomic Dysautonomia

Dysautonomia can occur as a result of a genetic defect (e.g., familial dysautonomia, Shy-Drager syndrome), viral infection (Guillain-Barré syndrome), malignancy (Lambert-Eaton syndrome), or diseases of unknown etiology (Parkinson disease). Orthostatic hypotension, supine hypertension, and a decreased beat-to-beat variability in heart rate are common signs. This can lead to rapid changes in blood pressure and an exaggerated response to sympathomimetic drugs under anesthesia as the result of an alteration in adrenergic receptor number or function.[54]

Emerging Developments

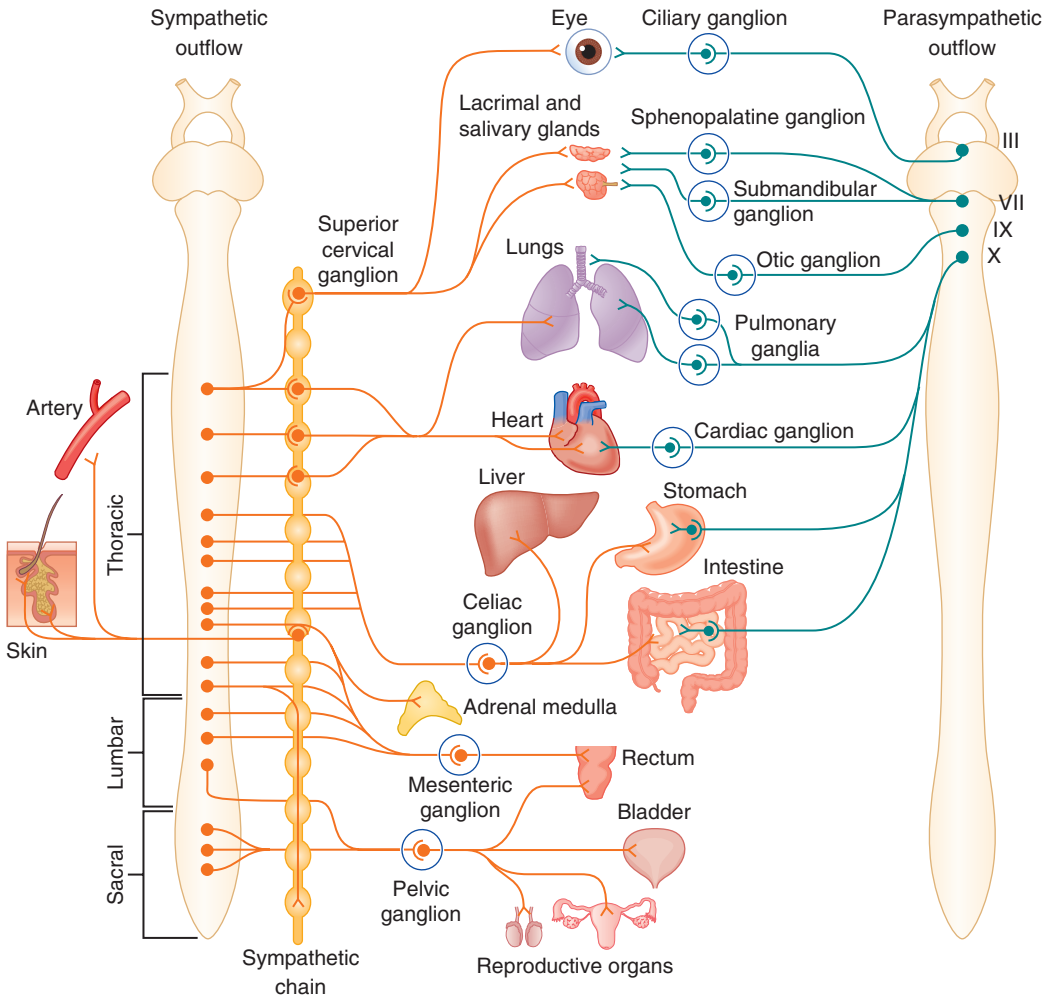
The Role of the Autonomic Nervous System in Obesity and Inflammation

Obesity has been associated with chronic neuroinflammatory changes in the hypothalamus, impairing neuroendocrine and autonomic control of elements related to occurrence of metabolic syndrome. In particular, chronic hypothalamic inflammation results in an upregulation of sympathetic activity, glucose intolerance, insulin resistance, and β-cell dysfunction. The increase in sympathetic activity leads to obesity-related hypertension and a sympathetically mediated modulation of visceral adipose tissue.[55]

Metabolic syndrome is associated with high rates of cardiovascular, pulmonary, and renal perioperative adverse events. Research relating to anesthetic care of the patient with metabolic syndrome is currently lacking; recognition of patient characteristics (central obesity, atherogenic dyslipidemia, hyperglycemia) and the associated heightened sympathetic activity will alert the practitioner to the added risks.[56]

Sacral Nerves Part of Sympathetic System

Recent investigations may lead to a simplification of the long-held anatomic structure of the ANS. Using a mouse model, Espinosa-Medina and colleagues demonstrated that the genetic signature of the sacral outflow tract neurons was better characterized as being of sympathetic origin, rather than parasympathetic.[57] The genetic makeup of sacral preganglionic neurons shares features with the thoracic (sympathetic) preganglionic neurons and both neuron types appear to have arisen from similar progenitor cells. There is anatomic evidence that both thoracic and sacral preganglionic cell types occupy sites in the mediolateral region of the spinal cord and exit the spinal cord from a ventral position (compared with the dorsal exit sites of preganglionic parasympathetics of the cranial nerves). The complex neurotransmitter phenotypes and pharmacologic responses of the sacral section of the spinal cord also appear to be primarily of sympathetic origin. This leads to a revised depiction of the anatomy of the ANS that is elegant and easier to understand (Fig. 13.7).



• **Fig. 13.7** Anatomic structure of the autonomic nervous system based on recent findings indicating that the sacral neural output is sympathetic in both phenotype and pharmacology.

Key Points

- The ANS maintains cardiovascular, metabolic, thermal, and gastrointestinal homeostasis.
- Central control of the ANS is primarily mediated in the hypothalamus and medulla oblongata.
- Emerging from the spinal cord, the SNS acts primarily by the effector neurotransmitter norepinephrine to increase critical organ blood flow (i.e., muscles, heart, brain) in response to external challenges. The distribution of sympathetic ganglia close to the CNS facilitates a rapid amplification of this generalized fight-or-flight response.
- Emerging from select cranial and sacral nerves, the PNS acts primarily by the effector neurotransmitter acetylcholine (and muscarinic cholinergic receptors) to modulate activities that occur when the body is at rest (e.g., salivation, urination, defecation, sexual function). The distribution of parasympathetic ganglia close to effector organs facilitates the more focused rest-and-digest functions of the parasympathetic system.
- The adrenal medulla is functionally a sympathetic ganglion in direct communication with the systemic circulation that contributes to the amplification of the fight-or-flight response by delivering epinephrine and norepinephrine throughout the body.
- ANS reflexes (e.g., baroreceptor reflex, oculocardiac reflex) have important implications for anesthetic management.
- Anesthetics generally depress the ANS, in part by attenuating homeostatic reflexes.
- Autonomic dysfunction associated with aging, diabetes, obesity, and other disease states can have important implications on anesthetic management, especially as it relates to the support of the circulation during anesthesia.
- New studies have questioned the craniosacral location of the PNS, outlining a simpler concept that the PNS arises from the cranial nerves, while the SNS is represented in the spinal cord, thoracic to sacral.

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14

Autonomic Nervous System Pharmacology

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CHAPTER OUTLINE

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Inhibition of Synthesis, Storage, and Release of Norepinephrine

Parasympathetic Pharmacology
- Cholinergic Receptors
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Emerging Developments
- Active Emergence and Enhanced Recovery Using CNS Stimulants

The autonomic nervous system (ANS) maintains homeostasis by integrating signals from peripheral and central sensors to modulate organ perfusion and function. Autonomic "tone" maintains cardiac muscle, visceral organs, and vascular smooth muscle in a state of intermediate function. From this state, rapid increases or decreases in autonomic outflow can adjust blood flow and organ activity in response to the environment. The rapidity of the ANS response is impressive considering that neurotransmitters must be released from terminals, cross a synaptic cleft to an effector site, bind to a receptor, and initiate an intracellular event. For example, in just a few seconds, ANS activation can double heart rate (HR) and arterial blood pressure (BP). In a nearly similar time frame it can cause sweating, nausea, loss of bladder control, and fainting. The sympathetic nervous system (SNS) has been called the "fight-or-flight" response system and is activated under stress. In contrast, the parasympathetic nervous system is responsible for "rest and digest." The anatomy and physiology of the ANS are discussed in Chapter 12.

In the perioperative and intensive care settings, multiple factors disrupt the typically tight ANS control of organ and vascular homeostasis. Thus pharmacologic manipulation of the ANS is commonplace in these settings. For example, both general and regional anesthesia have powerful influences on normal ANS function. When an inhaled anesthetic acts to directly relax vascular smooth muscle and lower BP, the ANS reacts to counteract hypotension via baroreflex adjustments of ANS activity. However, a second

effect of volatile anesthetics is to impair baroreflex function. The net effect of these influences requires treatment of unwanted hypotension with sympathomimetic or vagolytic drugs. Laryngoscopy and tracheal intubation or surgical incision powerfully activate the SNS; adrenergic receptor blocking drugs are used to dampen these responses.

Historical Perspective

The sympathomimetic properties of the ma huang plant were appreciated in China as early as 3000 BC. Ma huang was used as a diaphoretic, circulatory stimulant, antipyretic, and sedative for cough.[1] Ephedrine, the main alkaloid of ma huang, was isolated in 1886.[2] Over the next 25 years, adrenal extracts were described and analyzed and the term *sympathomimetic* was coined. Adrenergic receptors were identified and subdivided into two primary types (α and β) according to their responses to epinephrine and norepinephrine.[3] The β receptors were further divided into β_1, β_2, and β_3 receptors based on their actions at receptors and sensitivities to inhibitors.[4–6] The α receptors were similarly subdivided into α_1 andα_2 receptors, but they have been further subdivided into α_{1a}, α_{1b}, α_{1d}, α_{2a}, α_{2b}, and α_{2c} receptors based on their pharmacology and associated second-messenger systems.[7,8]

The history of parasympatholytic drugs dates back to ancient times when *Mandragora*, the mandrake plant, was used for wounds and sleeplessness. Henbane, which contains atropine, was used in ancient Egyptian times as a mydriatic. In the Middle Ages, henbane extract was used to enhance the inebriating qualities of beer and by "witches" to produce flushed skin and vivid hallucinations.

Muscarine, the first parasympathomimetic drug, derives from the fungus *Amanita muscaria* and was described in 1869. It was found to bind receptors that would be called *muscarinic* and had the same effect on the heart as did stimulation of the vagus nerve. Originally discovered by Loewi, the "heart-inhibiting" substance that decreased HR and contractility was acetylcholine (ACh).[9] Muscarinic receptors are activated by ACh and are thus called *cholinergic*.

Structure and Mechanism of Adrenergic Receptors

The basic catecholamine structure consists of an aromatic phenylethylamine with two hydroxyl groups. The name *catecholamine* derives from the molecule 3,4-dihydroxylphenyl, known as *catechol*. Epinephrine and norepinephrine have a chiral center at the hydroxyl group on the β- carbon, where the L-isomer is active, while dopamine has no chiral center (Fig. 14.1). Intravenous formulations of epinephrine and norepinephrine consist of the L-isomer; a racemic formulation of epinephrine is available for inhalation.

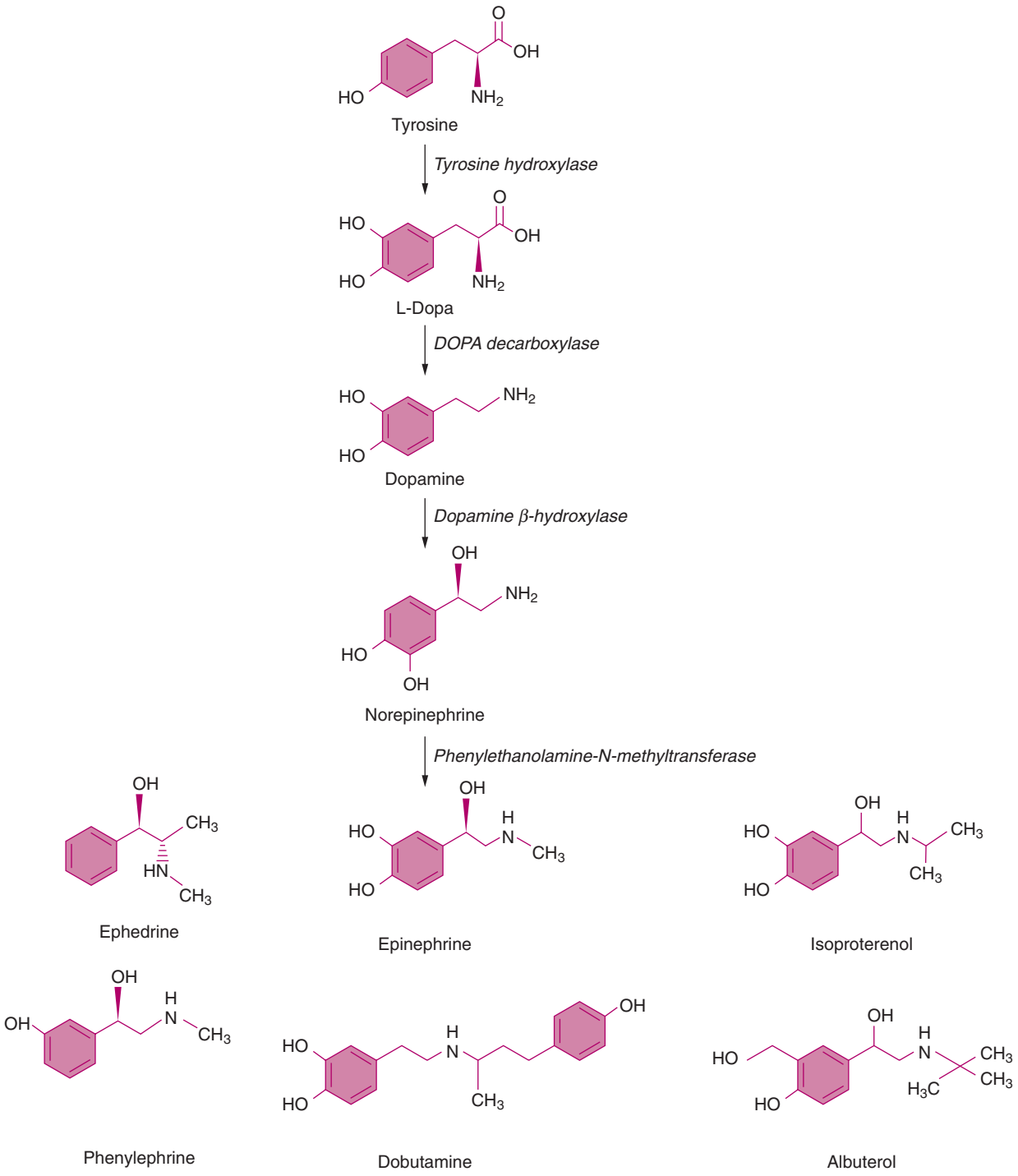
Epinephrine and norepinephrine are predominantly charged molecules at physiologic pH owing to their amine moiety and are unable to cross lipid cellular membranes on their own (although they can cross via transporters). Their actions are mediated following signal transduction by transmembrane receptors that initiate intracellular signaling events. Adrenergic receptors are coupled to guanine nucleotide binding proteins (G proteins) that couple the receptor to an effector system (see Chapter 1). Adrenergic G-protein–coupled receptors (GPCRs) are classified according to their actions on adenylyl cyclase and their sensitivity to pertussis toxin. The structure of the β-adrenergic receptor is consistent with most GPCRs, with seven transmembrane segments.[10] The signaling cascade of β_1- andβ_2-adrenergic receptors begins with ligand binding to the amino terminus of the receptor on the extracellular surface, then proceeds to the intracellular carboxyl terminal loop of the receptor coupling to G_s-proteins, which stimulate adenylyl cyclase to convert adenosine triphosphate (ATP) to the second-messenger cyclic adenosine monophosphate (AMP). The resulting phosphorylation by cyclic AMP (cAMP)-dependent protein kinase produces cellular responses.[11,12] The atomic resolution structure of the β_2-receptor bond to G_s has recently been determined and shows the involvement of the amino- and carboxy-terminal alpha helices of G_s as the main interaction between the two proteins. The activated receptor demonstrates outward movement of the sixth transmembrane segment and the presence of a second intracellular loop between the β_2-adrenergic receptor/G_s complex. The receptor is stabilized extracellularly by fusion of the amino terminus to T4 lysozyme, and intracellularly by numerous interactions with G_s. The Gβ and Gγ subunits of G_s do not directly interact with the β_2-adrenergic receptor.[13]

The α_2 receptors are coupled to G_i-proteins to inhibit adenylyl cyclase. The α_1 receptors are coupled to G_q-proteins activating phospholipase C that hydrolyzes phosphatidylinositol diphosphates (PIP_2) to the second messengers inositol trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 activates calcium ion (Ca^{2+}) release from intracellular stores via IP_3 receptors, while DAG activates lipid mediated signaling pathways including members of the protein kinase C family.[14]

Dopamine receptors also are GPCRs and are classified as D1-type (D1 and D5) and D2-type (D2, D3, and D4) receptors.[15] These receptors are located throughout the central nervous system (CNS), on SNS postganglionic nerve terminals, on afferent and efferent arterioles of the nephron, and in the adrenal glands. D1-like receptors stimulate adenylyl cyclase via G_s, and D2-like receptors inhibit adenylyl cyclase via G_i. D1-receptors are postsynaptic and stimulation mimics β_2 effects, leading to regional vascular dilation. D2-like receptors occur at presynaptic and postsynaptic sites. Presynaptic D2-like receptor activation inhibits norepinephrine release from sympathetic terminals, an effect similar to the presynaptic effects of ACh and α_2-agonists. Postsynaptic sites mimic α1 and α_2 vasoconstriction on blood vessels, but this action is relatively weak.

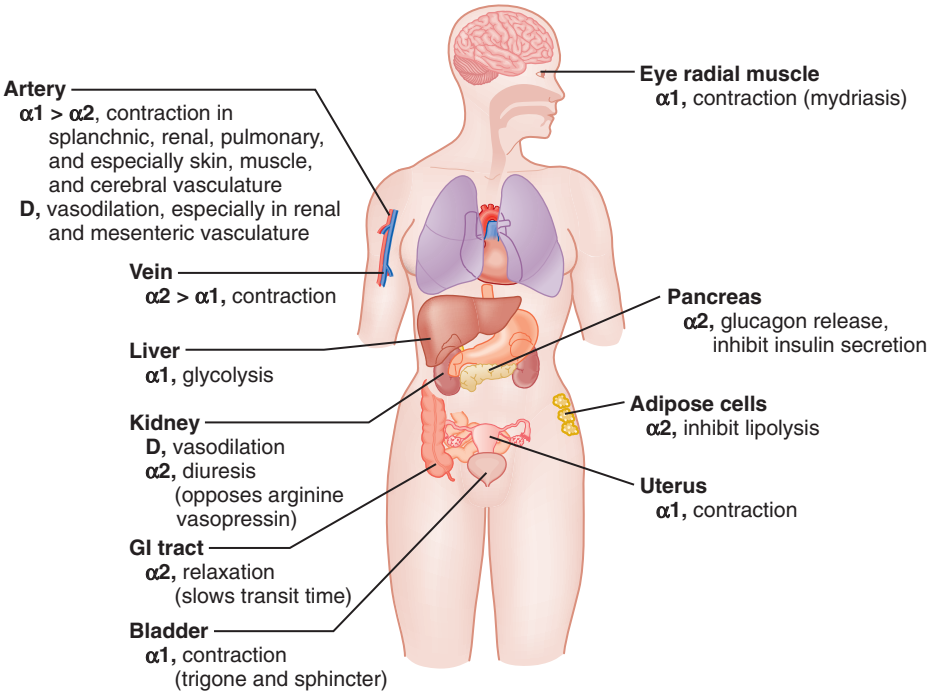
The α_1 adrenoceptors are activated by the selective α_1-receptor agonists phenylephrine and methoxamine and are inhibited by low concentrations of the antagonist prazosin. The α_1-receptors are widely distributed, and when stimulated mediate primarily arterial and venous vascular constriction (Table 14.1). The α_2-adrenoceptors are activated by the selective α_2-receptor agonists clonidine and dexmedetomidine and are blocked by the antagonist yohimbine; they exist as three subtypes: α_{2a}, α_{2b}, and α_{2c}.[16] The α_2 receptors are located presynaptically on sympathetic neurons where they inhibit the release of norepinephrine. Postsynaptic α_2 receptors are located on blood vessels and in tissues, including liver, pancreas, platelets, kidney, adipose tissue, and the eye (Fig. 14.2). Within the CNS, receptors in the locus coeruleus likely account for the sedative properties of α_2 agonists, and receptors in the medullary dorsal horn area for the reduction in sympathetic outflow.[17] The α_2 receptors are also on the vagus nerve and in the intermediolateral cell column and the substantia gelatinosa. The dorsal horn of the spinal cord contains α_{2a} adrenoceptors colocalized with opioid receptors that modulate afferent pain signals.

Both β_1- and β_2-adrenergic receptors are characterized by their stimulation by epinephrine and norepinephrine and are heavily expressed in myocardial tissue, including atria, ventricular papillary



• **Fig. 14.1** Biosynthesis and structures of the catecholamines, and their structures compared to common adrenergic drugs. Stereochemical structure is indicated as shown; isoproterenol, dobutamine, and albuterol are racemates.

muscle, sinoatrial and atrioventricular nodes, left and right bundles, and Purkinje fibers. They have inotropic (increased contractility), chronotropic (increased HR), and dromotropic (increased conduction velocity) effects (Fig. 14.3). Activation of $\beta_1$receptors increases renin and aqueous humor production. The β_2-receptors are the major β receptors in arterioles and the only β receptors in the vena cava, aorta, and pulmonary artery.[18] Activation of β_2 receptors leads to uterine smooth muscle relaxation and relaxation of vascular smooth muscle, including splanchnic, muscular, and renal vasculature, resulting in a reduction in diastolic pressure and decreases in systemic vascular resistance. Activation of β_2 adrenoceptors causes relaxation of bronchial smooth muscle and increased liver glycogenolysis. β_2 Receptor activation also reduces the plasma [potassium ion (K^+) concentration by promoting uptake into skeletal muscle



• **Fig. 14.2** Predominant physiologic effects of α_1-adrenergic and dopamine (D) receptors.

TABLE 14.1 Relative Adrenergic Drug Effects on Peripheral Resistance and Capacitance Vessels[a]

	VASOCONSTRICTION	
	α_1 Arterial	α_1 Venous
Norepinephrine	+++++	+++++
Phenylephrine	++++	+++++
Epinephrine	0/++++[b]	0/++++[b]
Dopamine	0/++++[c]	+++
Methoxamine, metaraminol	+++++	++++
Ephedrine	++	+++
Dobutamine	+/0	?
Isoproterenol	0	0

[a]Drugs are listed in descending order of potency within each vascular region.
[b]Dose-dependent; β effects of epinephrine predominate at low doses.
[c]Dose-dependent; dopamine and β effects predominate at low doses.

and reducing aldosterone secretion, leading to renal losses of K^+ (see Fig. 14.3). The β_3 receptors are expressed in visceral adipocytes, gallbladder, and colon. Their activation mediates lipolytic and thermogenesis in brown and white adipose tissue.[19]

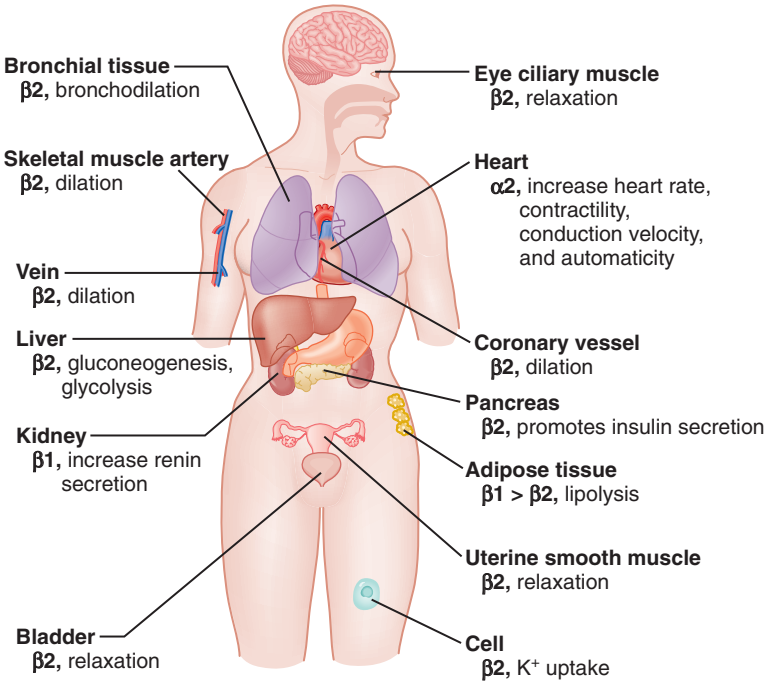
Endogenous Catecholamines

The biosynthesis of the naturally occurring catecholamines (epinephrine, norepinephrine, and dopamine) begins with the conversion of tyrosine to 3,4-dihydroxyphenylalanine (DOPA) (see Fig. 14.1). The rate-limiting step in catecholamine synthesis is conversion of tyrosine to DOPA by the enzyme tyrosine hydroxylase.

Epinephrine

Epinephrine, also known as adrenaline, is an endogenous monoamine with broad clinical applications. Epinephrine is present in chromaffin cells in the adrenal medulla, where it is synthesized, stored, and released upon sympathetic stimulation. On average, 80% of the secreted catecholamine in the adrenal medulla is epinephrine and 20% is norepinephrine. The normal resting rate of secretion by the adrenal medulla is about 0.2 μg/kg per minute of epinephrine and about 0.05 μg/kg per minute of norepinephrine. These rates are sufficient to support arterial BP fully if the SNS is denervated. Because of slow removal from the circulation, the effects of secreted epinephrine and norepinephrine on organ function last 5 to 10 times longer than the effect from a burst of sympathetic activity to an organ or vascular bed. Epinephrine has a large β-receptor effect that increases cardiac function (i.e., HR and contractility) far more than norepinephrine (Table 14.2). The β-receptor effect also constricts precapillary blood vessels and large veins. Epinephrine has a weaker effect on blood vessels in skeletal muscle than norepinephrine because of the greater affinity of epinephrine for β_2- (relaxation) than α_1-receptors (contraction). The β effects of epinephrine can increase the metabolic rate to twice normal and promote glycogenolysis in liver and muscle, thereby raising blood glucose levels.

Infusions of epinephrine have dose-dependent actions at α and β receptors. Low doses (2–10 μg/min) predominantly stimulate β_1 and β_2 receptors (see Table 14.2). At higher doses of epinephrine (>10 μg/min), α receptors are activated, leading to vasoconstriction of the skin, mucosa, and renal vascular beds. Blood flow



• **Fig. 14.3** Predominant physiologic effects of β_1- and β_2-adrenergic receptor activation.

TABLE 14.2 Relative Potency of Common, Naturally Occurring, and Synthetic Adrenergic Agonists

	RECEPTORS						
Sympathomimetics	**α_1**	**α_2**	**β_1**	**β_2**	**D1**	**D2**	**Dose Dependence[a]**
Phenylephrine	+++++	?	±	0	0		++
Norepinephrine	+++++	+++++	+++	0	0		+++
Epinephrine	++++	+++	++++	++	0		++++
Ephedrine	++	?	++++	++	0		++
Dopamine	+ to +++++	?	++++	++	+++	?	+++++
Dobutamine[b]	0 to +	?	++++	++	0		++
Isoproterenol	0	0	+++++	+++++	0		0
Dexmedetomidine	+	+++++	0	0	0		
Clonidine	++	+++++	0	0	0		
Fenoldopam	0	0	0	0	+++++		

[a]α, β, or D.
[b]Dobutamine is a racemic mixture; (–)dobutamine is a potent α_1 agonist, and (+)dobutamine is a potent α_1 antagonist, reducing its net vascoconstrictor effect.

redistribution occurs away from these circulations, reversing many of the β_2 effects to vasodilate. Further stimulation of α receptors decreases skeletal muscle and splanchnic blood flow and inhibits insulin secretion.

Epinephrine has broad clinical effects and its use has often been supplanted by more selective synthetic adrenergic agonists. However, epinephrine is still commonly added to local anesthetics to prolong their duration of action. Epinephrine is also indicated in anaphylactic shock, localized bleeding, bronchospasm, and stridor related to laryngotracheal edema. Subcutaneous doses of 0.2 to 0.5 mg can be used in early anaphylaxis to stabilize mast cells and reduce degranulation. Epinephrine also stimulates cellular K^+ uptake via β_2 receptors and for short periods can be used to treat life-threatening hyperkalemia.

Norepinephrine

Norepinephrine is the principal endogenous mediator of SNS activity secreted from postganglionic terminals to act on adrenergic effector organs. Intravenous administration (4–12 μg/min) results in dose-dependent hemodynamic effects on α_1 and β adrenoceptors (see Table 14.2). Compared with the effects of epinephrine, norepinephrine has a greater effect at α_1-receptors and no effect on β_2 receptors, thereby creating greater arterial and venous vascular constriction than epinephrine (see Table 14.1). In lower doses, β_1 actions predominate, and BP increases due to augmented cardiac output. Larger doses of norepinephrine stimulate the α_1 receptors and result in arterial and venous smooth muscle contraction in hepatic, skeletal muscle, splanchnic, and renal vascular systems. At these larger doses, HR and cardiac output can decrease via baroreflex mechanisms.

Intravenous administration of norepinephrine is most often used therapeutically for treatment of profound vasodilation, as in septic shock unresponsive to fluid administration. It increases BP, left ventricular stroke work index, cardiac output, and urine output. When given to patients already exhibiting marked vasoconstriction, further increases in vascular resistance can lead to compromised limb and organ blood flow, resulting in ischemia. Norepinephrine is less arrhythmogenic than epinephrine. Its effect on pulmonary α_1 receptors combined with its effect to increase venous return can result in pulmonary hypertension and right heart failure. To minimize this effect during open heart surgery, it can be given directly into the left atrium along with a selective pulmonary vasodilator such as prostaglandin E_1.

Dopamine

Dopamine is an endogenous catecholamine that is also involved in central and peripheral neural transmission. Dopamine is synthesized from tyrosine and is the immediate precursor to norepinephrine (see Fig. 14.1). Parenteral administration of dopamine does not cross into the CNS; therapy of Parkinson disease requires use of the precursor L-DOPA that can cross the blood-brain barrier. When dopamine is used for hemodynamic support and maintenance of adequate perfusion during shock, it must be given via continuous infusion because of rapid metabolism. At low infusion rates (1–3 μg/kg per minute), vasodilation of coronary, renal, and mesenteric vasculature occurs and renal blood flow, glomerular filtration, and Na^+ excretion increase owing to D1-like receptor agonism (see Fig. 14.2). Although this "renal dose" of dopamine was purported to improve kidney function in patients at risk for acute renal failure, meta-analysis has failed to show improvement in renal dysfunction or mortality.[20] At doses of 3 to 10 μg/kg per minute, β_1-receptor stimulation leads to positive inotropic and chronotropic effects, and at presynaptic terminals promotes the release and inhibits the reuptake of norepinephrine. At higher doses (>10 μg/kg), α_1-receptor activation causes peripheral vasoconstriction and can reduce renal blood flow.

Metabolism of Catecholamines

The catecholamines are metabolized by catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO). COMT is an intracellular enzyme located in postsynaptic neurons. MAO is concentrated in the mitochondria of nerve terminals, resulting in a constant turnover of norepinephrine even in the resting nerve terminal. Metabolites can be detected in urine as metanephrines or vanillylmandelic acid. Urine collections and analysis can be useful to follow progress in treatment of pheochromocytoma. There are two primary termination routes for norepinephrine released from nerve terminals: simple diffusion (and metabolism in plasma, kidney, or liver) and reuptake into noradrenergic nerve terminals (which can be blocked by cocaine and most tricyclic antidepressants). Synthetic sympathomimetic drugs that mimic endogenous catecholamines can have longer durations of action because of their resistance to metabolism by MAO or COMT.

Synthetic Catecholamine-Like Drugs

Synthetic catecholamines, which are also included as sympathomimetic drugs, are a mainstay of critical care and perioperative medicine for support of the circulation. Depending on their selectivity and potency for different subtypes of α, β, and dopamine receptors, their route of administration, their lipid solubility, and their metabolism, sympathomimetic drugs can be used to achieve a variety of clinical effects. Certain drugs also have indirect sympathomimetic action; these include ephedrine, tyramine, and the amphetamines. They cause release of norepinephrine from its storage vesicles in the sympathetic nerve endings, thereby increasing synaptic concentration and postsynaptic effects.

D1-Receptor Agonists

Fenoldopam is a synthetic, selective D1-agonist without significant D2-, α-adrenergic, or β_2-adrenergic effects (see Table 14.2 and Fig. 14.2).[21] It is 10-fold more potent than dopamine at the D1 receptor. The principal use of fenoldopam is to manage hypertension in doses of 0.1 to 0.8 μg/kg per minute, with upward titration in 0.1-μg/kg per minute steps as needed. A low-dose infusion of fenoldopam (~0.1–0.2 μg/kg per minute) produces renal vasodilation and increases renal blood flow, glomerular filtration rate, and Na^+ excretion without changes in systemic BP. A renal protective effect has been observed in aortic and cardiac surgery involving cardiopulmonary bypass.[22,23] When compared with dopamine in acute early renal dysfunction, fenoldopam is more effective at reversing renal hypoperfusion.[24] A meta-analysis indicated that fenoldopam reduces both the need for renal replacement therapy and in-hospital death in cardiovascular surgery.[25]

α_1-Receptor Agonists

Agonists of α_1 adrenoceptors exert vasoconstrictor actions on arteries and veins, leading to BP increase and redistribution of blood flow (see Fig. 14.2).[26] In healthy individuals, cardiac output is maintained because of increased preload. HR typically slows via the baroreflex response to increased BP. Myocardial blood flow and oxygen delivery can be improved owing to the longer diastolic filling time from the lower HR and from improved diastolic coronary blood flow because of the increased aortic BP. In patients with impaired ventricular function, increases in afterload can impair myocardial function. Topical use of α_1 agonists can be used for vasoconstriction (e.g., on nasal mucosa).

Phenylephrine

The effects of phenylephrine were described in the 1930s, and it was first used to maintain BP during spinal anesthesia.[27] It is a nearly pure α_1-selective agonist, only affecting β receptors at very high doses (see Table 14.2). It has similar potency to norepinephrine for α_1 receptors but has a longer duration of action. Phenylephrine

produces greater venoconstriction than arterial vasoconstriction and therefore increases venous return and stroke volume. Cardiac output typically does not change owing to baroreflex slowing of HR. Phenylephrine can be useful as a bolus or continuous infusion for treatment of hypotension, and can be used to reverse unwanted right-to-left shunt in tetralogy of Fallot. Newer evidence suggests that phenylephrine is not detrimental to fetal oxygen delivery in pregnant patients who are hypotensive after neuraxial blockade. However, although not harmful, it still might be inferior to ephedrine in maintaining placental blood flow during cesarean delivery.[28,29] A 0.25%, 0.5%, or 1% phenylephrine solution can be used topically as a nasal decongestant; 2.5% or 10% phenylephrine solutions are used to produce mydriasis when administered into the eye. Both these routes can raise BP. Rarely more serious side effects such as pulmonary edema and adverse cardiac events result. Thus α_1-adrenergic antagonists, such as phentolamine or tolazoline, or direct vasodilating drugs, such as hydralazine or nicardipine, should be available. β-Blockers are contraindicated to treat a hypertensive crisis from phenylephrine (such as an accidental overdose). β-Blockers in this situation can reduce myocardial contractility and produce acute pulmonary edema in the face of high afterload.[30]

Methoxamine

First described in 1948 and used to maintain BP during spinal anesthesia, methoxamine has a longer duration of action, more arterial vasoconstriction, and less venoconstriction compared with phenylephrine.[31] It is not typically used to support BP acutely because it can increase afterload and has a long half-life. Doses of 1 to 5 mg every 15 minutes are described. Untoward hypertension can occur following its use to treat regional anesthetic-induced hypotension because sympathetic tone returns as the spinal anesthetic recovers before the action of methoxamine dissipates.

Midodrine

Midodrine is an orally absorbed α_1 agonist with a half-life of about 3 hours and duration of action of 4 to 6 hours. It is used to treat dialysis-related hypotension or autonomic failure resulting in postural hypotension, but hypertension is a possible effect when patients are supine.

α_2 Receptor Agonists

Agonists of α_2 receptors such as clonidine were originally used as antihypertensive agents because of their central effect to decrease sympathetic outflow from the CNS and to reduce presynaptic norepinephrine release. The α_2 receptor mediates sedation and hypnosis, sympatholysis, neuroprotection, diuresis, and inhibition of insulin and growth hormone secretion.[32–34] Rapid intravenous administration of α_2 agonists such as dexmedetomidine can transiently increase BP through vasoconstriction at postsynaptic α_{2b} receptors on arteries and veins. This receptor subtype might also account for their antishivering effect. Postsynaptic α_2 receptors exist in a number of other tissues and organs, including liver, pancreas, platelets, kidney, fat, and eye (see Fig. 14.2).

Within the CNS, a large density of α_2 receptors is located in the medullary dorsal motor complex and in the locus coeruleus. The locus coeruleus is an important modulator of wakefulness and the major site of the sedative/hypnotic actions of the α_2 agonists. Among the many desirable properties of α_2 agonists that promote their use in the perioperative period are anxiolysis, sedation, reductions in minimal alveolar concentration (MAC) of volatile anesthetics, reduced chest wall rigidity from opioids, reduction in intraoperative BP variability from intubation, extubation and surgical stress response, and reductions in postanesthetic shivering.[35] A meta-analysis found that α_2-receptor agonists reduce perioperative cardiac mortality and ischemia, a benefit likely attributable to reduced sympathetic outflow and reduced shivering.[36] Side effects include sedation, dry mouth, and bradycardia via reduced sympathetic "tone" and a slight vagomimetic effect. It is likely that some of the effects from α_2-receptor agonists are from actions at nonadrenergic imidazoline receptors.

TABLE 14.3 Classification of α-Receptors and the Relative α1/α2 Selectivity

	ORDER OF SELECTIVITY	
	Agonists	**Antagonists**
α_1 ↕ β_1	Methoxamine Phenylephrine Norepinephrine Epinephrine Dopamine Clonidine (220:1) Dexmedetomidine (1620:1)	Prazosin Phenoxybenzamine Phentolamine Tolazoline Yohimbine

Clonidine

Clonidine, first synthesized in the 1960s, has an onset time after oral administration of 30 to 60 minutes, with a half-life of 6 to 24 hours. The α_2-:α_1-receptor affinity is ~220:1 (Table 14.3). It is available in 100-, 250-, and 300-μg tablets for oral administration, a transdermal patch releasing 150 to 200 μg over 24 hours, and an injectable solution of 150 μg/mL. Oral dosing is typically every 8 hours. Clonidine should not be withheld before surgery because acute withdrawal can result in rebound hypertension.[37] Neuraxial administration can be used to lessen the requirement for opioids when treating acute and chronic pain. Epidural clonidine is indicated for treatment of severe cancer pain (0.5 μg/kg per hour). When given in this manner, bradycardia and sedation can occur but respiratory drive is maintained. Clonidine also is beneficial in the treatment of opioid withdrawal in an intensive care unit (ICU) setting.[38]

Dexmedetomidine

Dexmedetomidine is highly selective for α_2 adrenoceptors (see Table 14.3), with an α_2-: α_1-receptor affinity of 1620:1. Intravenous administration in the ICU setting is useful for continuous sedation and analgesia while sparing respiratory drive. Sedation is described as "arousable sedation" much like natural sleep, consistent with effects on central sleep mechanisms. Patients receiving dexmedetomidine for postsurgical pain have slower early postoperative HRs and require 50% less morphine in the postanesthesia care unit.[39] In a prospective randomized study, dexmedetomidine initiated at the end of coronary artery bypass surgery and continued into the ICU resulted in reduced use of analgesics, β-blockers, diuretics, antiemetics, and epinephrine, and achieved adequate sedation compared with propofol sedation.[40] In the ICU setting following cardiac surgery, the combination of opioid/dexmedetomidine sedation resulted in less delirium compared with opioid/benzodiazepine sedation.[41,42] Recommended dosage is a 1-μg/kg loading dose given

over 10 to 20 minutes followed by a 0.2- to 0.7-μg/kg per hour infusion. Hypotension and bradycardia are common side effects, and bradyarrhythmias and sinus arrest are rare but potential serious adverse events. Newer applications for dexmedetomidine include pediatric sedation for hospital procedures, treatment of emergence agitation, and sedation in the ICU setting. Additionally, the FDA approved the use of dexmedetomidine for MAC sedation in 2010.[43]

β_1-Receptor Agonists

Isoproterenol

Isoproterenol, the isopropyl derivative of norepinephrine, was the first synthetic β-receptor agonist in clinical use. It is given parenterally because of its short duration of action (<1 hour).[44] It has almost purely β-receptor activity, with minimal α-receptor affinity. It is nonselective for β_1 and β_2 receptors (see Table 14.2). Isoproterenol produces positive chronotropic and inotropic cardiac effects via β_1-adrenoceptor stimulation, and bronchodilation and vasodilatation in vascular smooth muscle through β_2 activation. Large doses cause tachycardia and decrease diastolic BP, which reduces coronary blood flow and thus can compromise myocardium at risk or worsen dysrhythmias. Dobutamine is a common substitute for isoproterenol owing to lesser effects on HR, thereby preserving diastolic filling time and coronary blood flow and reducing myocardial oxygen demand. The emergence of phosphodiesterase inhibitors to improve myocardial performance has also reduced the need for isoproterenol as an inotropic agent.[45] The β_2 response from isoproterenol can be used for bronchodilation, although other β_2 drugs are more typically used. Isoproterenol has been used to manage heart failure secondary to bradycardia, cor pulmonale, pulmonary hypertension, as a chemical "pacer" in third-degree heart block, and in torsades de pointes ventricular tachycardia.

Dobutamine

Dobutamine is a synthetic catecholamine obtained by substitution of a bulky aromatic group on the side chain of dopamine. Dobutamine is a racemic mixture of the (+) and (−) isomers. The (−) isomer acts on α_1-adrenergic receptors and increases vascular resistance, and the (+) isomer is a potent β_1-adrenergic receptor agonist and a potent α_1-adrenergic receptor antagonist that blocks the effects of (−) dobutamine (see Table 14.2). Compared with dopamine, dobutamine has less notable venoconstriction and is less likely to increase HR and more likely to decrease pulmonary vascular resistance. The most prominent effects with increasing infusion rates of dobutamine (2–20 μg/kg per minute intravenously) are a progressive increase in cardiac output, decrease in left ventricular filling pressure, minor increases in HR until higher doses are given, and decreases or no change in systematic vascular resistance. However, when dobutamine is given to patients using β-blockers, systemic vascular resistance can increase, leading to increases in BP from the unmasked α_1-effect. Dobutamine has minimal β_2 effects. Thus it often improves cardiac output without major adverse effects on the myocardial oxygen supply/demand ratio because afterload is maintained, thereby improving coronary blood flow.[46] It enhances automaticity of the sinus and atrioventricular nodes and facilitates intraventricular conduction. It does not affect dopamine receptors. Dobutamine is prepared in 5% dextrose in water because it is inactivated in alkaline solutions. Tachyphylaxis can occur with infusions longer than 72 hours. Dobutamine is often used for nonexercise cardiac stress testing and for the treatment of acute heart failure, especially in patients being weaned from cardiopulmonary bypass.

Selective β_2-Receptor Agonists

Selective β_2-receptor agonists are indicated in the treatment of acute asthma and chronic obstructive pulmonary disease. These agents work by reducing bronchial airway resistance via smooth muscle relaxation. By changing the catechol ring (3,4-dihydroxylphenyl) to a resorcinol ring (3,5-dihydroxylphenyl), there is improved bioavailability as the result of the reduced action of COMT. Further substitutions on the amino group increase β-receptor activity, reduce α-receptor activity, and increase the duration of action by decreasing metabolism by MAO.

Metaproterenol (orciprenaline), albuterol, salmeterol, and isoetharine (isoetarine) are inhaled, thereby reducing their systemic side effects. These reach therapeutic concentrations in the bronchi with minimal activation of cardiac and peripheral β_2 receptors. In addition to bronchodilation, therapeutic effects include suppression of release of leukotrienes and histamine from mast cells and decreased microvascular permeability. However, at higher concentrations all currently used β_2-selective agonists also stimulate β_1 receptors, which increases the risk for arrhythmias (predominantly atrial fibrillation). Other potential adverse effects, particularly when given orally or parenterally, are skeletal muscle tremor, tachycardia, mismatching of pulmonary ventilation and perfusion, and pulmonary edema. Long-term use can lead to tolerance, bronchial hyperreactivity, and hyperglycemia in diabetic patients.

Terbutaline and Ritodrine

Terbutaline can be administered orally, subcutaneously, or by inhalation. It is rapidly effective by the latter two routes and its effects persist for 36 hours, in part owing to its structure with a resorcinol ring preventing COMT action. A subcutaneous dose of 0.25 mg can be useful to treat status asthmaticus. Terbutaline is used primarily long term for obstructive pulmonary disease, and acutely for status asthmaticus, bronchospasm, and acute anaphylactic shock, where it does not have the cardiac stimulating effects of epinephrine.

Terbutaline and ritodrine are also tocolytic drugs used to manage premature labor contractions through relaxation of the myometrium via their β_2 effect. Ritodrine is usually started intravenously and is continued orally if tocolysis is achieved. It is metabolized in the liver to inactive conjugates, and about half the drug is excreted unchanged in the urine. Albuterol is similar to terbutaline, although it cannot be given subcutaneously. Use of β_2 agonists has been associated with hypokalemia as well as tachyphylaxis. The mechanism of hypokalemia involves an insulin-mediated increase in uptake of extracellular K^+ and/or increased sodium-potassium adenosine triphosphatase activity.[47] Angina, cardiac arrhythmias, hyperglycemia, hypokalemia, and pulmonary edema with normal pulmonary capillary wedge pressures have been attributed to terbutaline and ritodrine therapy.[48]

Indirect-Acting Sympathomimetics

Some of the synthetic catecholamine-like drugs have an indirect sympathomimetic action. These drugs include ephedrine, tyramine, and the amphetamines. Because their effects are to cause release of norepinephrine from synaptic vesicles in sympathetic nerve endings, care must be taken when they are administered to patients taking tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs).[49] The TCAs inhibit catecholamine reuptake and the MAOIs inhibit catecholamine breakdown. MAOIs in combination with serotonin reuptake inhibitors can also lead to

neuromuscular and autonomic hyperactivity and altered mental status (serotonin syndrome).[50]

Ephedrine

Ephedrine is one of the most commonly used noncatecholamine sympathomimetic drugs in the perioperative period. Ephedrine is a natural product of the ephedra plant *(Ephedra sinica),* and is a mixed-acting, noncatecholamine sympathomimetic with both direct and indirect stimulating effects on α- and β-adrenergic receptors. It acts indirectly by competing with norepinephrine for local reuptake into synaptic vesicles, resulting in elevated concentrations of norepinephrine at receptor sites. Intravenous effects resemble those of epinephrine, albeit with a less potent but longer-lasting effect. It causes increases in HR, cardiac output, and BP that last 10 to 15 minutes. Tachyphylaxis owing to catecholamine depletion can occur with repeat doses.

Ephedrine relaxes bronchial smooth muscle, increases trigone and sphincter muscle tone in the urinary bladder, and has a stimulatory effect on the CNS that increases MAC. Uterine and placental artery blood flow are not adversely affected when ephedrine is used to sustain BP during spinal anesthesia for cesarean section, and umbilical artery vascular resistance remains unchanged. This is due to an effect of ephedrine to cause venoconstriction, thereby improving preload, cardiac output, and uterine blood flow.

Amphetamine and Other Central Nervous System Stimulants

Amphetamine and methamphetamine are powerful stimulants of the CNS, in addition to having peripheral α and β actions common to indirect acting sympathomimetics. They cause release and inhibit reuptake of stimulatory neurotransmitters in the cortex, motor nuclei, and reticular activating system. Acute effects include wakefulness, alertness, mood elevation, decreased sense of fatigue, and increased initiative, self-confidence, euphoria, and elation. Peripheral indirect activity leads to acute increases in BP with reflex bradycardia; large doses can cause arrhythmias. Chronic use leads to a decrease in BP because the metabolites are false neurotransmitters. Even though therapeutic use has declined, their respective methylenedioxy derivatives (3,4-methylenedioxyamphetamine [MDA] and 3,4-methylenedioxymethamphetamine [MDMA]) remain popular illicit recreational drugs. Treatment of acute intoxication consists of acidification of urine to enhance elimination, administration of sedatives, and control of cardiovascular side effects. Dantrolene is indicated to prevent hyperthermia.

Methylphenidate (Ritalin, Methylin) is structurally related to amphetamine but has milder CNS-stimulating activity and less effect on motor function. It is used to treat narcolepsy and attention deficit/hyperactivity disorder. Side effects of insomnia, anorexia, weight loss, suppression of growth, and abdominal pain have been described in children. Overdose causes symptoms similar to those of overdose with amphetamine, including restlessness, agitation, irritability progressing to confusion, aggressive behavior, delirium, and paranoid delusions.

False Transmitters and Monoamine Oxidase Inhibition

MAOIs are powerful drugs used to treat depression and Parkinson disease. They include phenelzine, iproclozide, isocarboxazid, tranylcypromine, selegiline, rasagiline, and moclobemide. MAO catalyzes the oxidation of monoamines such as norepinephrine, serotonin (MAO-A), phenylethylamine (MAO-B), and dopamine (MAO-A,B). Dietary amines (e.g., tyramine derived from fermentation processes in cheese, wine, and beer) can cause a hypertensive reaction in patients taking MAOIs. In the presence of MAOIs, tyramine displaces norepinephrine from synaptic vesicles, leading to profound hypertension. When an indirect-acting sympathomimetic drug such as ephedrine is administered, an exaggerated BP increase can occur, especially in the first weeks of therapy with an MAOI. With long-term use, there is downregulation of adrenergic receptors, and TCAs and selective serotonin reuptake inhibitors are usually continued through the perioperative period given their rapid excretion and long latency period for effectiveness.[51] MAOIs require discontinuation before surgery to allow restoration of enzyme activity. Irreversible MAOIs should be discontinued 2 weeks before surgery or switched to a reversible MAOI (moclobemide), which needs to be stopped only 24 hours before surgery.[52] Because dopamine is a substrate for MAO, it should be administered at much lower doses in patients taking an MAOI or TCA. Use of meperidine with an MAOI can lead to hypertension, convulsions, and coma. Because of their risk for lethal dietary and drug interactions, MAOIs are generally used only when patients are unresponsive to first-line antidepressants.

Ergot Alkaloids

Poisoning caused by the fungus *Claviceps purpurea* on wheat or rye in the Middle Ages was associated with mental disturbances and severe, painful peripheral vasoconstriction frequently leading to gangrene of the extremities. Often termed *St. Anthony's fire,* this effect is from ergot alkaloids that stimulate contraction of a variety of smooth muscles, both directly and indirectly via adrenergic and serotonergic receptors. Contraction of vascular smooth muscle leads to coronary, cerebral, and peripheral vasoconstriction. In clinical practice, the ergot alkaloids are taken orally and are slowly absorbed from the gut with bioavailability of approximately 10%; they are hepatically metabolized and eliminated primarily in the bile. The oral dose of ergotamine to treat an acute migraine is 2 mg, followed by a 1-mg dose every half hour to a maximum of 6 mg. The intramuscular dose is 0.5 mg, repeated every half hour to a maximum of 3 mg. Intramuscular administration of ergonovine is used to enhance postpartum uterine contractions. The usual dose of 0.2 mg can be continued up to a week postpartum as an oral preparation. Ergot alkaloids are contraindicated in patients with sickle cell disease, peripheral and coronary artery disease, thyrotoxicosis, and porphyria.

Other Sympathomimetic Drugs

Pseudoephedrine and phenylpropanolamine are commonly used as oral preparations to treat nasal congestion via vasoconstriction. These sympathomimetic drugs are similar to ephedrine in releasing norepinephrine and epinephrine but have fewer CNS effects. Several drugs are used primarily as vasoconstrictors via α_1-receptor agonism for local application to the nasal mucous membranes or to the conjunctiva, including propylhexedrine, tetrahydrozoline, oxymetazoline, naphazoline, and xylometazoline. Their systemic absorption is minimal compared with topical phenylephrine solutions. Cocaine is another sympathomimetic still used clinically for its analgesic and vasoconstrictive properties. Intranasal cocaine with a topical local anesthetic has been shown to provide adequate pain control during repair of nasal fractures.[53] However, given the

potential for abuse and toxicity, the aforementioned topical drugs have largely replaced the use of cocaine-containing topical solutions for vasoconstriction.

Vasopressin

Vasopressin, commonly known as arginine vasopressin (AVP), is an endogenous hormone that regulates urine volume and plasma osmolality. Although not a sympathomimetic, it too is used as a potent vasoconstrictor that preserves splanchnic perfusion.[54,55] It acts on V2 receptors on the collecting ducts to promote water reabsorption and concentration of urine. Higher concentrations of AVP can occur via a baroreflex response to hypotension and will act on $V1_a$ receptors located on vascular smooth muscle to promote vasoconstriction via a phosphoinositol pathway. Vasopressin is available in an aqueous solution of 20 units/mL. Vasopressin is no longer recommended as an alternative to a first or second dose of epinephrine during resuscitation from cardiac arrest, but it can be useful in small doses to treat refractory intraoperative hypotension in patients using angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. Doses of 1 to 8 units are typical. Vasopressin also has been cited as a useful pharmacologic aid in hemorrhagic shock because of its augmentation of the neuroendocrine stress response and can reverse severe hypotension, restore cardiovascular function, and decrease catecholamine requirements.[56–59] Furthermore, use of vasopressin can be an effective strategy in persistent hypotension that had been resistant to fluids and exogenous catecholamines.[59]

Adrenergic Blocking Drugs

Sympatholytic drugs oppose the effects transmitted by postganglionic fibers of the SNS. Most drugs of this class act postsynaptically to compete reversibly with agonists for α- and β-adrenergic receptors. Adrenergic activity can be disrupted at several points in the stimulatory process, as follows:

1. Blockade of α receptors, resulting primarily in dilation of vascular tissue; examples are phenoxybenzamine and phentolamine.
2. Blockade of β-receptors, the major pharmacologic target being the heart and vascular smooth muscle. Propranolol blocks β_1- and β_2-receptors; atenolol and metoprolol block mainly β_1 receptors.
3. Blockade of sympathetic activity by drugs that block transmission of nerve impulses through autonomic ganglia at nicotinic receptors; hexamethonium blocks both sympathetic and parasympathetic transmission through the ganglia.
4. Inhibition of synthesis and storage of norepinephrine in sympathetic nerve endings; examples are reserpine and α-methyldopa.
5. Blockade of release of norepinephrine from sympathetic endings; an example is guanethidine.

α-Antagonists

The "α-blockers" play an important role in regulating the activity of the SNS both peripherally and centrally. Blockade of α_2-adrenergic receptors with selective antagonists such as yohimbine can potentiate release of norepinephrine to activate both α_1 and α_2 receptors. Antagonists of α_1-adrenergic receptors such as prazosin also stimulate release of norepinephrine, but the α_1-receptor effect is blocked.

Phenoxybenzamine

Phenoxybenzamine is an irreversible, noncompetitive blocker of α-adrenergic receptors (see Table 14.3). It forms a covalent link with the α receptor such that recovery of receptor function requires synthesis of new receptor molecules with a half-life of 18 to 24 hours. The consequent reduction in peripheral vascular tone leads to orthostatic hypotension and is accompanied by baroreflex-mediated sympathetic activation resulting in increases in HR and cardiac output. Phenoxybenzamine may also improve cardiac output by other mechanisms. It blocks presynaptic inhibitory α_2 receptors in the heart and decreases elimination of myocardial norepinephrine by inhibition of reuptake. Overdoses are treated with norepinephrine when unopposed β_1-receptor effects are present. Epinephrine is not recommended for this purpose in that its β_2 effects lead to further hypotension. Oral doses of phenoxybenzamine are used to manage pheochromocytoma or urinary retention caused by neurogenic bladder or benign prostatic hypertrophy. For adults, initial dosing is 10 to 20 mg bid for pheochromocytoma and 10 to 20 mg per day for relief of obstruction in neurogenic bladder.

Phentolamine and Tolazoline

Phentolamine and tolazoline are competitive, nonselective α-receptor antagonists (see Table 14.3). Although these drugs have cardiovascular effects similar to those of phenoxybenzamine, α-blockade is short-lived and the effects are reversible with α-receptor agonists. Phentolamine and tolazoline can be used to treat hypertensive crisis caused by ingestion of tyramine-containing substances in patients taking MAOIs or owing to clonidine withdrawal. Phentolamine can be given as a 5- to 15-mg intravenous bolus and has an onset in 12 minutes and duration of 10 to 30 minutes. The recommended dose of tolazoline for treatment of neonatal persistent pulmonary hypertension is a 0.5 to 2 mg/kg loading dose administered over 10 minutes followed by 0.5 to 2 mg/kg per hour. The use of these antagonists to treat pulmonary hypertension has fallen out of favor with the advent of newer agents (see Chapter 26). Phentolamine can be infiltrated into tissues to reduce the vasoconstriction from accidental extravasation of norepinephrine.

Prazosin

Prazosin is the prototype of a family of α-adrenergic drugs that contain a piperazinyl quinazole nucleus. Prazosin has a very high affinity for most subtypes of α_1-receptors (see Table 14.3). Its α_{1B}-receptor antagonism results in dilation of arteries and veins with a decrease in peripheral vascular resistance and venous return and cardiac filling. The unexpectedly blunted reflex HR response to the hypotensive effect of prazosin might be due to a CNS effect to suppress sympathetic outflow. Prazosin is given orally (15 mg); the starting dose to treat hypertension is usually 0.5 mg at bedtime. The effects of a single dose last about 10 hours.

Doxazosin, Terazosin, Tamsulosin

Doxazosin has hemodynamic effects similar to prazosin, but its duration is about three times longer. Terazosin is less potent than prazosin but has higher bioavailability, so its effects last longer. Selectivity of α_{1A}-subtype over $\alpha 1_B$-subtype receptors for relaxation of bladder neck, prostate capsule, and prostatic urethra make doxazosin and tamsulosin useful for treating benign prostatic hypertrophy with little effect on BP.

β-Antagonists

The β-adrenergic receptor blockers have a range of lipid solubilities that influence their absorption and distribution (Table 14.4). The prototype drug propranolol, developed in the early 1960s, has

TABLE 14.4 β-Adrenergic Blocking Drugs

Drug	Receptor Selectivity	ISA	Plasma Half-Life (hr)	Oral Availability (%)	Lipid Solubility	Elimination	Oral Dose	IV Dose
Propranolol	$\beta_1\beta_2$	0	3–4	36	+++	Hepatic	40–320 mg	0.5–1 mg to maximum 3 mg
Metoprolol	β_1	0	3–4	38	+	Hepatic	100–400 mg	5 mg q2 min to 15 mg total
Atenolol	β_1	0	6–9	57	0	Renal	50–100 mg	2.5 mg over 2.5 min q5 min to 10 mg or 0.15 mg/kg over 20 min
Esmolol	β_1	0	9 min	–	?	RBC esterase	NA	50–100 mg Bolus, 0.05–0.3 mg/kg per minute infusion
Timolol	$\beta_1\beta_2$	0	4–5	50	+	Hepatic > renal	15–45 mg; 60 mg maximum	Ophthalmic preparation for glaucoma, 0.25–0.5 mg/mL
Carvedilol	$\alpha_1\beta_1\beta_2$		2–8			Hepatic	12.5–50 mg	NA
Labetalol	$\alpha_1\beta_1\beta_2$		~6			Hepatic	400–1200 mg	5–20 mg IV q5–10 min to maximum 300 mg; start infusion at 2 mg/min

ISA, Intrinsic sympathomimetic activity; *NA*, not applicable; *RBC*, red blood cells.

high lipid solubility and attains high brain concentrations. The lipid-insoluble β-blockers such as atenolol are less well absorbed orally, have fewer CNS side effects, and are excreted primarily via the kidneys (with prolonged excretion in renal failure). β_2-Blockade can cause bronchospasm and peripheral vasoconstriction; this can be problematic in patients with chronic obstructive pulmonary disease, reactive airway disease, and peripheral vascular disease.

Modifications of the molecular structure of β-blockers can lead to a range of desired pharmacodynamic effects, including enhanced selectivity for β_1-receptors, partial agonist activity at β_2-receptors (known as intrinsic sympathomimetic activity, ISA), α_1-receptor antagonism, and/or quinidine-like membrane stabilizing activity. ISA from drugs such as pindolol leads to less reduction of HR, cardiac output, and peripheral blood flow and reduced risk of bronchoconstriction. Most β-adrenergic antagonists do not block α-adrenergic receptors. Two exceptions are labetalol and carvedilol, which have both nonselective β-receptor antagonist and α-receptor antagonist activity. Blockade of stimulatory presynaptic β_2-receptors reduces release of norepinephrine and contributes to the hypotensive effect of β-receptor antagonists.

The β-receptor antagonists have a number of predictable side effects. They can lead to profound bradycardia, asystole and heart failure. They inhibit gluconeogenesis; in diabetic patients receiving β-blockers, the common signs of hypoglycemia such as tremors and tachycardia can be masked. Hypoglycemia-induced perspiration, mediated by cholinergic mechanisms, can remain the only warning sign in these patients. Blockade of peripheral β_2-receptors can precipitate Raynaud vascular spasm in susceptible patients. The use of β-blockers to attenuate adrenergic crisis can worsen hypertension (from β_2-receptor blockade) if α-receptor blockade is not adequate due to unopposed α effects. Combination of β-blockers with non-dihydropyridine calcium channel blockers can significantly reduce cardiac conduction, and when also combined with H_2-receptor blockers, severe negative inotropism can result.

Even though myocardial depression from volatile or intravenous anesthetics is additive with that of pure β-blockers, perioperative use of β-blockers reduces morbidity and mortality in patients with documented coronary artery disease and in patients at high risk for coronary artery disease.[60–65] However, there has been some controversy regarding β-blockade with metoprolol in particular. The Perioperative Ischemic Evaluation (POISE) trial showed that while those starting metoprolol in the perioperative period experienced fewer myocardial infarctions, this group also had more deaths and nonfatal cerebrovascular accidents. A meta-analysis has shown significant heterogeneity across studies, suggesting that the benefits and risks of initiating a perioperative β-blockade should be carefully weighed for each patient.[65] Clinically both partial and pure antagonists are used in the treatment of hypertension and tachyarrhythmias, and both decrease mortality after myocardial infarction. Sudden withdrawal of β-receptor blockers can lead to rebound adrenergic effects, including tachycardia, hypertension, arrhythmias, myocardial ischemia, and infarction. The enhanced adrenergic state occurs 2 to 6 days after withdrawal.[66] This has led to the current recommendation to continue β-blockers in the perioperative period to avoid withdrawal.[51]

Esmolol

Esmolol is a selective β_1-adrenoceptor antagonist with a rapid onset of 90 seconds. Owing to rapid hydrolysis by red blood cell esterase, it has a short duration of action with a half-life of only 9 to 10 minutes (see Table 14.4). Esmolol is not metabolized by plasma cholinesterase. The brevity of esmolol makes it useful as a bolus of 1 to 2 mg/kg to reduce cardiac effects from transient β-adrenergic stimulation in the perioperative period and as an infusion in critically ill patients in whom it can be withdrawn quickly if adverse cardiac effects (congestive heart failure, bradycardia, hypotension) occur. As an infusion for supraventricular tachycardia or hypertensive crisis, a loading dose of 500 μg/kg over 4 minutes followed by a 50- to 300-μg/kg per minute infusion results in steady-state concentrations in 5 minutes.[67,68] β_1-Selectivity allows esmolol to be used safely in patients with bronchospastic and vascular disease.

Labetalol

Labetalol is a mixture of four stereoisomers that block α_1, β_1, and β_2 receptors, and is therefore considered a mixed antagonist (see Table 14.4). It is considered a peripheral vasodilator that does not cause reflex tachycardia.[69] It has an $\alpha:\beta$ antagonistic potency ratio of 1:7 when given intravenously and a ratio of 1:3 after oral administration. It is lipid soluble and has substantial first-pass hepatic metabolism. The peak hypotensive effect from intravenous labetalol occurs within 5 to 15 minutes and the duration of action is 4 to 6 hours. It can be used to treat hypertension in pregnancy. Despite HR slowing from labetalol, the decreased afterload helps maintain cardiac output. It may be given in 5- to 10-mg bolus doses at 5-minute intervals to control a hypertensive crisis. Uterine blood flow is not affected, owing in part to preserved cardiac output.

Metoprolol and Atenolol

Metoprolol is cardioselective with a ratio of 30:1 in affinity for β_1 and β2-receptors (see Table 14.4). It is lipid soluble and has a high first-pass hepatic metabolism resulting in the need for high oral doses (100–200 mg/day) compared with intravenous doses of 2.5 to 5 mg, titrated to effect. It is roughly half as potent as propranolol, and maximum β_1-blockade effect is achieved at 0.2 mg/kg. Atenolol is also β_1 selective, is lipophilic and has an elimination half-life of 6 hours. Even so, the effect of an oral dose of 25 to 100 mg lasts 24 hours. In a recent study, perioperative blockade with atenolol resulted in a reduced short- and long-term mortality in high-risk patients undergoing noncardiac surgery compared with metoprolol.[70] The differences might be explained by the longer metabolic half-life of atenolol and a lower chance of missing a dose and/or experiencing a "withdrawal" sympathetic response when compared with metoprolol.

Inhibition of Synthesis, Storage, and Release of Norepinephrine

α-Methyldopa is one of a group of antihypertensive drugs called *false neurotransmitters* that replace norepinephrine in the synaptic vesicles located in postganglionic nerve endings of the SNS. It is metabolized to α-methyldopamine and then to α-methylnorepinephrine, which are less potent at adrenergic receptors than dopamine and norepinephrine, thus accounting for some of their antihypertensive effects. Central effects of the metabolites result from action on α_2 receptors to decrease sympathetic outflow and to reduce anesthetic requirements by 20% to 40%. *Reserpine* prevents uptake of norepinephrine into vesicles, thereby inhibiting storage of dopamine and norepinephrine. *Guanethidine* acts by reducing norepinephrine release from sympathetic terminals and by depleting norepinephrine storage. It does not have sedating effects because it does not cross the blood-brain barrier. Side effects from the false transmitters include orthostatic hypotension, drowsiness, diarrhea, bradycardia, hepatitis, and autoimmune hemolytic anemia. Thus their use as antihypertensive drugs has fallen out of favor.

Parasympathetic Pharmacology

Cholinergic Receptors

The neurotransmitter ACh acts at distinct receptor types: nicotinic and muscarinic. The naturally occurring substances, muscarine and nicotine, were originally used to define and name the two receptor families. They have distinctly different tissue locations (see Chapter 13). Muscarinic receptors are GPCRs with a typical seven-transmembrane configuration. There are five subtypes, M_1-M_5. The odd-numbered subtypes are defined by *Pertussis* toxin insensitivity, coupling to G_q/G_{11} protein and stimulating phospholipase C to alter one or more ion channels. This effect generally leads to depolarization or increased excitability.[71,72] The even-numbered subtypes M_2 and M_4 are *Pertussis* toxin–sensitive, are coupled to the G_i/G_0 protein, and inhibit adenylyl cyclase to initiate a presynaptic inhibitory effect. Muscarinic subtypes M_1 and M_4 are found primarily in brain; M_3 and M_4 are found in lung, gastrointestinal tract, and glandular tissue; and M_2 receptors are located in cardiac tissue. Muscarinic receptor activation by ACh at the postsynaptic junction in heart and smooth muscle leads to bradycardia, salivation, bronchoconstriction, miosis, and increased gastrointestinal motility and secretion (Table 14.5). In addition, "adrenergic" muscarinic receptors are located on presynaptic sympathetic terminals in the cardiovascular and coronary systems, and their activation reduces norepinephrine release. In brain, release of ACh is subject to substantial ongoing autoinhibition as a result of coactivation of presynaptic muscarinic receptors on cholinergic terminals.

Nicotinic receptors activate postganglionic junctions of both the sympathetic and parasympathetic nervous systems (see Chapter 13). Nicotinic receptors are also located at the neuromuscular junction (see Chapter 21). Nicotinic cholinergic receptors are heteropentameric ligand-gated ion channels that allow depolarizing inward flow of monovalent cations.[73] The nicotinic receptor agonists consist primarily of the depolarizing neuromuscular-blocking drugs (e.g., succinylcholine [suxamethonium], hexamethonium) and can

TABLE 14.5 Antimuscarinic Drugs

Drug	IV	IM	CNS[a]	GI Tone	Gastric Acid	Airway Secretions[b]	Heart Rate
Atropine	15–30 min	2–4 hr	++	—	–	–	+++[c]
Scopolamine	30–60 min	4–6 hr	+++[a]	–	–	———	+0[c]
Glycopyrrolate	2–4 hr	6–8 hr	0	——	——	——	+0

CNS, Central nervous system; *IV*, intravenous; *IM*, intramuscular; *GI*, gastrointestinal.
[a]CNS effect often manifest as sedation before stimulation.
[b]Secretions may be reduced by inspissation.
[c]May decelerate initially.

simultaneously stimulate autonomic ganglia. The neuromuscular-blocking drugs are considered in Chapter 19.

Muscarinic Receptor Agonists

Muscarinic agonists are divided into two general groups:

1. The choline esters (ACh, methacholine, carbachol, bethanechol) and alkaloids (pilocarpine, muscarine, arecoline) that act directly on muscarinic receptors
2. Acetylcholinesterase inhibitors or anticholinesterases (physostigmine, neostigmine, pyridostigmine, edrophonium, echothiophate) that act indirectly by inhibiting ACh hydrolysis

The anticholinesterase drugs are frequently used to reverse the action of nondepolarizing neuromuscular-blocking drugs (see Chapter 22), to improve neuromuscular function in myasthenia gravis, and for colonic pseudo-obstruction. Newer drugs have been designed to improve cognitive function in Alzheimer disease.

Owing to rapid hydrolysis, direct-acting agonists such as ACh have few clinical applications, with the exception of topical application to produce miosis. Longer activity of the direct-acting agonists can be achieved by methylation of the choline moiety as noted with the synthetic drug methacholine. This modification prevents significant nicotinic receptor effects and slows acetylcholinesterase metabolism (Table 14.6). Carbachol and bethanechol are long-acting synthetic parasympathetic agonists; the carbamic-linked ester moiety significantly reduces metabolism. Carbachol has significant nicotinic activity at autonomic ganglia. Bethanechol is similar to methacholine and is highly specific for muscarinic receptors. It is used orally or parenterally, has only minimal cardiac negative chronotropic and inotropic effects, and is useful therapy for postoperative urinary retention and neurogenic bladder from spinal cord injury.

Pilocarpine is a tertiary amine alkaloid with actions similar to methacholine (see Table 14.6). Clinical use includes treatment for xerostomia and glaucoma, where it is used as a topical drug to produce miosis and reduce intraocular pressure. Pilocarpine has minimal nicotinic effects unless given systemically, in which case hypertension and tachycardia can result.

Echothiophate, a long-acting irreversible anticholinesterase, is instilled into the eye to reduce resistance to aqueous humor outflow and lower intraocular pressure. Echothiophate is absorbed into the circulation and therefore can prolong the duration of succinylcholine because of a reduction in cholinesterase levels. The action of ester-based local anesthetics can also be lengthened in patients receiving echothiophate through slower metabolism of the local anesthetic. Enzyme activity might not return to normal for 4 to 6 weeks after discontinuation of long-term therapy.

Muscarinic Receptor Antagonists

Anticholinergic drugs (atropine, scopolamine, glycopyrrolate) competitively inhibit the action of ACh by reversibly binding at muscarinic receptors. Nicotinic ACh receptors are not affected by doses that are usually used. The naturally occurring anticholinergic drugs atropine and scopolamine are tertiary amines derived from the belladonna plant. Low doses of atropine and scopolamine (up to 2 μg/kg) have typically undesired effects within the CNS to augment vagal outflow, which can result in bradycardia.[74]

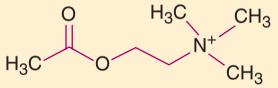
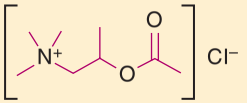
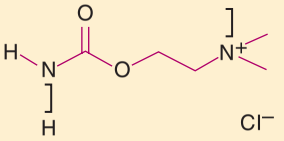
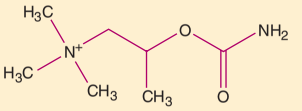
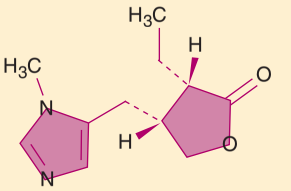
At usual clinical doses (0.5–1 mg), atropine acts at peripheral muscarinic receptors to block the action of ACh, thereby increasing HR, producing mydriasis (pupil dilation) and cycloplegia (paralysis of accommodation), and inhibiting salivary, bronchial, pancreatic, and gastrointestinal secretions (see Table 14.5). It reduces gastric secretion of acid, mucin, and proteolytic enzymes, slows gastric emptying, reduces lower esophageal tone, and slows gastric motility. Atropine reduces the activity of sweat glands and thus evaporative heat loss, even in small doses. It relaxes bronchial smooth muscle, reduces airway resistance, inhibits mucociliary clearance in the airways, and thickens bronchial secretions.[75] Atropine and scopolamine are tertiary amines that cross the blood-brain barrier and the placenta. There is no harmful effect on the fetus. Their central effects might account for their antiemetic properties and control of nausea triggered by the vestibular apparatus.[76] Scopolamine skin patches are used to control motion sickness and postoperative nausea and vomiting (see Chapter 34). Atropine can block presynaptic muscarinic receptors on adrenergic terminals, leading to a sympathomimetic effect. These drugs should be used with caution in patients with cardiac tachyarrhythmias or severe coronary artery disease, and are contraindicated in narrow-angle glaucoma because they can increase intraocular pressure. They are considered safe when given parenterally to patients with the more common open-angle glaucoma.

Scopolamine in the usual clinical doses of 0.3 to 0.6 mg displays stronger antisialagogue and ocular activity, but is less likely than glycopyrrolate or atropine to increase HR (see Table 14.5).[77] Scopolamine crosses the blood-brain barrier more effectively than atropine and is commonly associated with amnesia, drowsiness, fatigue, and non–rapid eye movement sleep. One limitation imposed by the central actions of higher doses of scopolamine (and atropine) is an infrequent side effect termed the *central anticholinergic syndrome*. The origin of the syndrome is due to blockade of the abundant muscarinic ACh receptors in the CNS, which leads to agitation, disorientation, delirium, hallucinations, and restlessness. It can manifest as somnolence and should be considered in the differential diagnosis of delayed awakening from anesthesia. Physostigmine is a tertiary amine anticholinesterase that crosses into the CNS and can be administered in intravenous doses of 15 to 60 mg/kg for the treatment of central anticholinergic syndrome.

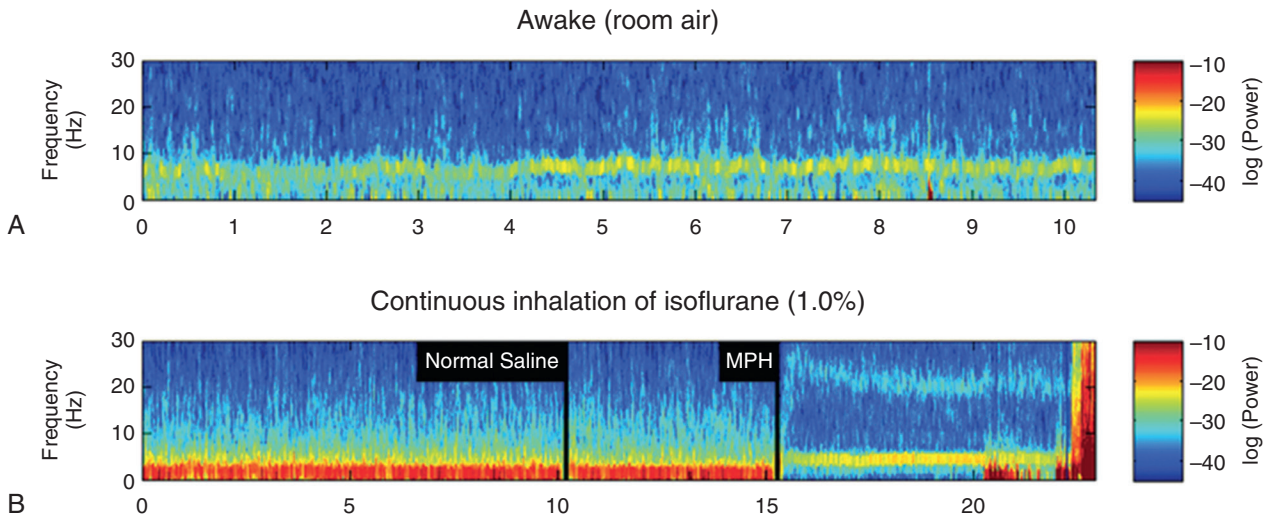
Glycopyrrolate is a synthetic quaternary amine that does not cross into the CNS and does not produce the CNS side effects noted with atropine and scopolamine (see Table 14.5). It is more potent and longer-acting at peripheral muscarinic receptors than atropine. It is used clinically as an antisialagogue to treat bradycardia and to inhibit cardiac muscarinic receptor side effects when anticholinesterase agents are used to reverse the effects of muscle relaxants. The antisialagogue dose of 0.004 mg/kg can last up to 8 hours. The recommended dose to reverse neuromuscular blockade is 0.2 mg for every 1 mg of neostigmine. The vagal blocking effect lasts 2 to 3 hours. Similar to atropine, low doses can cause initial bradycardia.

Inhalation of anticholinergics is the most effective route of administration when bronchodilation without systemic side effects is desired. Ipratropium, a derivative of methylatropine, is an inhaled anticholinergic that inhibits muscarinic receptor subtypes with a peak effect of 30 to 60 minutes and a duration of action of 3 to 6 hours.[78] Low doses of ipratropium decrease airway size via preferential blockade of neuronal M_2-muscarinic receptors. However, following large ipratropium doses, bronchodilation results from blockade of M_3-muscarinic receptors on airway smooth muscle. Ipratropium, unlike atropine, does not affect mucociliary clearance of respiratory secretions. In chronic obstructive pulmonary disease, ipratropium is beneficial in improving pulmonary function, and tachyphylaxis with long-term use has not been demonstrated.[79] In acute asthma exacerbations, ipratropium can provide additional benefit when used with inhaled β_2-agonists.

TABLE 14.6 **Comparative Muscarinic Actions of Systemic Direct Cholinomimetic Agents**

	Acetylcholine	Methacholine	Carbamylcholine	Bethanechol	Pilocarpine
					
Esterase Hydrolysis	+++	+	0	0	0
Eye (topical)					
Iris	++	++	+++	+++	+++
Ciliary	++	++	+++	+++	++
Heart					
Rate	−−	−−	−	−	?
Contractility	−	−	−	−	
Conduction	−−	−−	−	−	
Smooth Muscle					
Vascular	−−	−−	−	−	−−
Bronchial	++	++	+	+	++
GI motility	++	++	+++	+++	++
GI sphincters	−−	−	−−	−−	++
Biliary	++	++	+++	+++	++
Bladder					
Detrusor	++	++	+++	+++	++
Sphincter	−−	−	−−	−−	++
Exocrine Glands					
Respiratory	+++	++	+++	++	+++
Salivary	++	++	++	++	+++++
Pharyngeal	++	++	++	++	++++
Lacrimal	++	++	++	++	++++
Sweat	++	++	++	++	+++++
GI acid, secretions	++	++	++	++	++++
Nicotinic actions	+++	+	+++	−	+++

GI, Gastrointestinal; +, stimulation; −, inhibition.



• **Fig. 14.4** Spectral analysis of electroencephalogram data reveals a shift in power induced by methylphenidate. Warm colors (*red*) represent higher power at a given frequency, whereas cool colors (*blue*) represent lower power. A representative spectrogram computed from a rat in the awake state shows predominance of θ power (4–8 Hz) (A). A representative spectrogram computed from a rat inhaling isoflurane (1.0%) shows predominance of δ power (<4 Hz) before and after administration of normal saline solution. However, administration of intravenous methylphenidate (5 mg/kg) promptly induced a shift in power to an active θ-dominant pattern similar to that observed during the awake state. This animal began to move vigorously approximately 5 minutes after methylphenidate administration, generating significant motion artifacts (*B*). (Adapted with permission from Solt K, Cotton JF, Cimenser A, et al. Methylphenidate actively induces emergence from general anesthesia. *Anesthesiolgy.* 2011;115:791–803.)

Emerging Developments

Active Emergence and Enhanced Recovery Using CNS Stimulants

Active emergence from anesthesia to avoid the numerous complications that can occur during emergence (e.g., emergence delirium, slow awakening, stage II adverse events) while also enhancing operating room turnovers and patient satisfaction is the goal of recent research efforts. This amounts to "turning on the lights" actively after an anesthetic is completed, rather than awaiting passive recovery from anesthesia. Mechanisms involved in emergence from anesthesia are not well understood but appear to be amenable to pharmacologic manipulation of the nervous system. Pharmacologic agents used in the treatment of attention deficit/hyperactivity disorder and used to treat narcolepsy can promote emergence for anesthesia. Dopamine is a neurotransmitter that elicits wakefulness. When a pharmacologic inhibitor of dopamine reuptake such as methylphenidate is given to rats anesthetized with propofol, a shift in the electroencephalogram to higher frequencies is observed along with a faster time to the righting reflex.[80] A similar effect can be seen in isoflurane-anesthetized rats where methylphenidate will shift the electroencephalogram to higher frequencies as noted in Fig. 14.4 and will shorten the time to emergence.[81] The effect of methylphenidate is inhibited by droperidol, an antagonist of the dopamine receptor.[81] Another research approach to further validate the role of dopamine in "active emergence" is to directly stimulate the ventral tegmental area containing dopamine neurons in rats anesthetized with isoflurane. This stimulus restores conscious behaviors and the righting reflex.[82] Modafinil is a Food and Drug Administration–approved schedule IV drug prescribed to improve wakefulness in patients with narcolepsy and has an off-label use to enhance cognitive function. Its precise mechanism of action is unknown but it has a weak atypical dopamine reuptake inhibitory effects. When given before surgery or after surgery, patient benefits of alertness and improved energy have been noted.[83,84] These studies in both rats and humans are leading to clinical trials to determine the efficacy and benefits of pharmacologic interventions to hasten emergence from anesthesia and improve early recovery.

Key Points

- The naturally occurring catecholamines epinephrine, norepinephrine, and dopamine are derived from the amino acid L-tyrosine. Their sites of action are on adrenergic and dopaminergic receptors.
- Adrenergic receptors have been subdivided based on their effector responses. β_1-receptors are localized in cardiac tissue and mediate increases in HR, contractility, and conduction velocity, whereas β_2-receptors are found on arterioles, vena cava, pulmonary artery, aorta, and uterine smooth muscle; both types mediate smooth muscle relaxation. The α_1-receptors mediate arterial and venous smooth muscle contraction. The α_2-receptors also mediate vascular constriction but have additional actions in the CNS to reduce sympathetic outflow and pain perception and to produce sedation.

- Dopamine is an endogenous catecholamine involved in neural transmission. Parenteral administration can be used for hemodynamic support and, depending on the infusion rate, activates D1 receptors to dilate renal and coronary vessels and β_1 receptors to cause chronotropic and inotropic effects, or, at high doses, activates α_1 receptors to mediate vasoconstriction. Fenoldopam is a synthetic selective D1 agonist used to treat hypertension or to improve renal function via selective vasodilation.
- Dexmedetomidine is a highly selective α_2 agonist used for sedation. It produces an "arousable" sedation much like natural sleep and is associated with less delirium compared with benzodiazepine sedation.
- Dobutamine is a racemic synthetic catecholamine. The (−) isomer acts on α_1 receptors to increase vascular resistance and the (+) isomer acts on β_1 receptors to increase contractility while antagonizing the increase in vascular resistance. It increases cardiac output, decreases pulmonary vascular resistance, and is unlikely to increase HR.
- Selective β_2 agonists are indicated for the treatment of acute asthma and chronic obstructive pulmonary disease by reducing smooth muscle tone and bronchial airway resistance. They are most commonly given via inhalation, and owing to structural changes that reduce metabolism, typically have a long duration of action.
- Ephedrine is a noncatecholamine sympathomimetic drug with both direct and indirect actions on α- and β-adrenergic receptors.
- Vasopressin is an endogenous hormone that acts on V1 and V2 receptors to promote water reabsorption and to preserve coronary, cerebral, and pulmonary blood flow while constricting splanchnic vessels during severe hypotension and shock.
- β-Adrenergic receptor blockers have a number of predictable effects to slow HR and inhibit gluconeogenesis. Their effects to reduce myocardial oxygen demand and myocardial infarction can be overshadowed in select circumstances by their association with a higher risk of stroke and death.
- Muscarinic receptor antagonists inhibit the action of ACh at muscarinic receptors to increase HR and pupil dilation and reduce production of secretions.
- Using CNS stimulants such as methylphenidate and modafinil as a means of increasing the rapidity of recovery from general anesthesia (and also enhancing recovery) is a topic of contemporary research interest.

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15

Thermoregulation: Normal Physiology, Anesthetic Effects, and Perioperative Considerations

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CHAPTER OUTLINE

Normal Physiologic Thermoregulation
Anesthetic Effects on Thermoregulation
Effects of Anesthetic Techniques and Agents
Consequences of Thermal Dysregulation Related to Anesthesia
Measuring Temperature Intraoperatively
Prevention and Correction of Intraoperative Hypothermia
Emerging Developments

Core body temperature is highly regulated in humans by the autonomic nervous system and the hypothalamus. General anesthesia, neuraxial anesthesia and analgesia, and drugs such as opioids all reduce the ability of the hypothalamus to regulate core temperature. Thus without intervention, hypothermia (and, less commonly, hyperthermia) is a common consequence of anesthetic management. In this chapter, we review normal thermoregulation, the mechanisms responsible for anesthesia-related hypothermia and hyperthermia, and the consequences of perioperative hypothermia. We use this framework to discuss methods to reduce, prevent, or correct perioperative hypothermia and hyperthermia.

Normal Physiologic Thermoregulation

Human body core temperatures are regulated by the hypothalamus in response to sensory inputs from the autonomic nervous system. Ambient and internal temperature is sensed by temperature-sensing elements in the skin and the dorsal root ganglia. The signals travel via ascending spinothalamic tracts and afferent somatosensory pathways, through the lateral parabrachial nucleus to the hypothalamus.[1,2] Exercise, nutrition, infection, hypothyroidism or hyperthyroidism, and drugs such as opioids and general anesthetic agents affect temperature thresholds through inhibitory postsynaptic signals in the hypothalamus.[3]

Core temperature in humans represents a balance between heat production via metabolism and heat loss mostly through the skin but also via gas exchange and urine output.[4,5] Basal heat production is about 0.83 kcal/kg per degree centigrade.[6,7] Well-perfused tissues are also generally the most metabolically active and produce the most heat.[8,9] Heat production is increased during exercise, mostly as a result of increases in muscle metabolism.[3] It is decreased during anesthesia owing to decreased metabolism, primarily in the brain, muscles, and heart.[10,11] Mechanical ventilation and neuromuscular blocking agents further reduce metabolic rate.[12,13]

There are four primary mechanisms for heat loss: radiation, convection, conduction, and evaporation (Fig. 15.1). Radiation makes the largest contribution.[14] Air movement displaces heat near the skin surface by displacing warm air with cooler air. Heat distribution from the core includes both blood-borne longitudinal convection and radial conduction into adjacent tissues.[15] Heat transfer to peripheral tissues is slower than core heat transfer because of the lower rate of perfusion. Longitudinal convection via the blood is the primary mechanism for peripheral redistribution of heat, although radial diffusion also contributes. Administration of intravenous fluids that are below core temperature increases heat loss via conduction because the administered fluid is warmed to body temperature by surrounding blood and tissues. Evaporation via intact skin and exhalation of warmed, humidified air dissipates less than 15% of the basal metabolic rate during normal circumstances but increases substantially during sweating.[16] The microenvironment around the skin surface influences heat loss through conduction, convection, and radiation.[17] Likewise, heat loss may be augmented by relatively cool operating rooms,[12,13] cool intravenous and irrigating fluids,[18] and evaporation from large surgical incisions.[19]

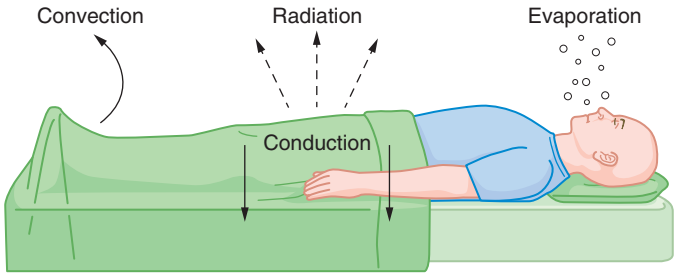
A useful model for understanding thermoregulation divides the human body into core and peripheral thermal compartments (Fig. 15.2). The core consists of the well-perfused organs—that is, the brain and those within the trunk—and makes up about 60% of body mass.[10] Because these organs are well perfused, heat distribution across the core is rapid and uniform. The hypothalamus normally regulates core temperature to the range of 36.5°C to 37.5°C.[3] In a given individual, core temperature varies with diurnal rhythms, cytokines produced during inflammation, and other stimuli. The peripheral compartment consists of the skin and subcutaneous

Abstract

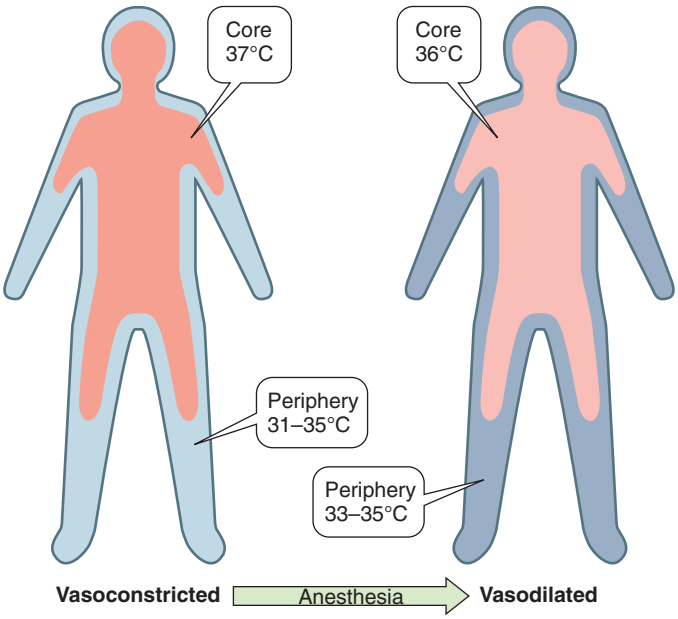
Core body temperature is highly regulated in humans by the autonomic nervous system and the hypothalamus. General anesthesia, neuraxial anesthesia and analgesia, and drugs such as opioids all reduce the ability of the hypothalamus to regulate core temperature. Intraoperative hypothermia is common and is caused by (1) redistribution of heat from the core to the periphery, (2) decreased metabolism, leading to decreased heat production, and (3) increased heat loss, primarily via radiation, convection, and in large, open surgeries, evaporation. Thus without intervention hypothermia (and, less commonly, hyperthermia) is a common consequence of anesthetic management. Although mild or moderate hypothermia may be protective in certain circumstances (e.g., after cardiac arrest), perioperative hypothermia is associated with multiple adverse outcomes, including increased postoperative discomfort and postanesthesia recovery time, blood loss and transfusion, cardiovascular morbidity, surgical site infection, deep vein thrombosis, and hospital length of stay. Intraoperative hypothermia can be prevented, mitigated, or corrected by preoperative and intraoperative active warming, which has also been shown to reduce complications.

Keywords

thermoregulation
core temperature
adverse effects of hypothermia
anesthetic-induced hypothermia
redistribution hypothermia
thermoregulatory vasoconstriction



• **Fig. 15.1** Mechanisms of intraoperative heat transfer include convection, radiation, evaporation, and conduction. Radiation makes the largest contribution to heat loss in anesthetized patients, with convective heat loss next in importance. Respiratory evaporation accounts for less than 10% of heat loss. With a large incision, however, evaporative heat loss can be substantial. Conductive heat loss plays almost no role in heat loss under anesthesia. (Adapted with permission from Sessler DI. Perioperative heat balance. *Anesthesiology.* 2000;92:578–596.)



• **Fig. 15.2** Redistribution hypothermia is responsible for the initial decrease in core temperature over the first 30 to 60 minutes after induction of general anesthesia. The degree of core temperature decrease is related to the degree of thermoregulatory vasoconstriction preoperatively. Preoperative active warming works by reducing thermoregulatory vasoconstriction, thereby reducing redistribution hypothermia. (Adapted with permission from Sessler DI. Temperature monitoring. In: Miller RD, ed. *Anesthesia.* 4th ed. New York: Churchill Livingstone; 1994:363–382.)

tissue, resting muscle, and the upper and lower extremities. The hypothalamus does not regulate peripheral temperature, but it does receive sensory temperature input from the periphery.[7] Peripheral temperature under normal circumstances is usually about 2°C to 4°C less than core temperature, largely as a result of peripheral vasoconstriction to regulate heat loss to the environment.

Exposure to a cold environment causes peripheral vasoconstriction. Peripheral vasoconstriction directly reduces heat loss, which helps to maintain the balance of heat production and heat loss. Peripheral vasoconstriction also causes redistribution of heat content (tissue temperature) from the periphery to the core,[20] thus immediately increasing core heat content while reducing peripheral heat content. This thermoregulatory response increases the core-to-peripheral temperature gradient, which may increase to more than 10°C in extreme circumstances.[21,22] Conversely, exposure to a hot environment or an increase in heat production, as with increased metabolism, induces thermoregulatory vasodilation to increase heat loss, as well as to transfer heat from the core to the periphery. Under these circumstances, the core-to-peripheral temperature gradient may be less than 2°C.

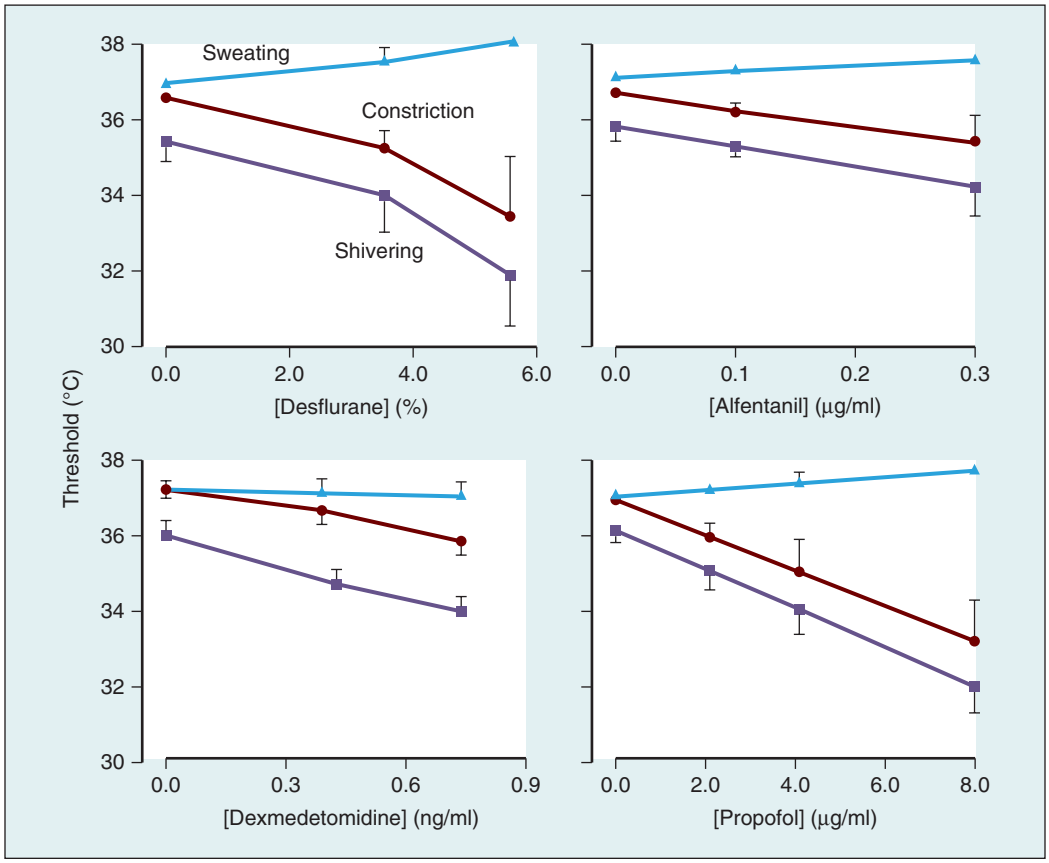
Hormonal, cytokine, and endocrine inputs to the hypothalamus define the core temperature set point, which varies diurnally and in response to fever triggers such as interleukin (IL)-2.[23,24] The hypothalamus integrates tissue and environmental temperature signals and maintains core temperature within a tight interthreshold range of about 0.2°C above or below the set point.[25] Modification of heat production (shivering, behavioral modification) and modification of heat loss (behavioral modification, vasoconstriction or vasodilation, and sweating) facilitate this tight temperature control.[3] Behavioral modification includes adding layers (e.g., clothing or covers) to reduce heat loss in response to cold exposure or a reduction in core temperature, and removing layers to increase heat loss in response to heat exposure or an increase in core temperature. It also includes reducing physical activity to reduce heat production or increasing physical activity, which may be voluntary or involuntary (shivering), to increase heat production.[26-28]

In summary, normal thermoregulatory mechanisms tightly control human body core temperature within a narrow interthreshold range of about 0.2°C. Next, we consider the important ways that anesthetic agents alter these mechanisms.

Anesthetic Effects on Thermoregulation

Intravenous and inhaled anesthetic agents, neuraxial anesthesia and analgesia, and opioids all blunt the hypothalamic responses to changes in core and environmental temperature, thus increasing the interthreshold range (i.e., the range of tolerated temperatures) in a dose-dependent manner (Fig. 15.3).[29] A major mechanism for this is through inhibition of changes in vascular tone. Virtually all anesthetic techniques and agents induce vasodilation. Vasoconstriction in response to a reduction in core temperatures is inhibited until the core temperature is decreased by ~3°C to 4°C. Anesthetic agents not only increase the interthreshold range but also inhibit or eliminate responses to changes in core temperature. General anesthesia prevents behavioral modification in response to core and environmental temperature changes while the patient is unconscious, and neuraxial anesthesia and opioids reduce temperature perception, thus making behavioral modification less likely. General anesthesia abolishes the shivering response and limits sweating. Mechanisms that cause increased heat loss to the environment include cutaneous vasodilation, surgical exposure (including radiative and evaporative heat loss), inhalation of dry, cold gases that are warmed and humidified in the lungs and exhaled, and administration of ambient temperature intravenous fluids. Anesthetic agents also reliably reduce the metabolic rate and thus heat production. Neuromuscular blocking agents compound the effects of anesthetic agents by further reducing metabolic heat production.[29]

As a result of the combination of reduction in heat production and reduced capacity to decrease heat loss leading to increased heat



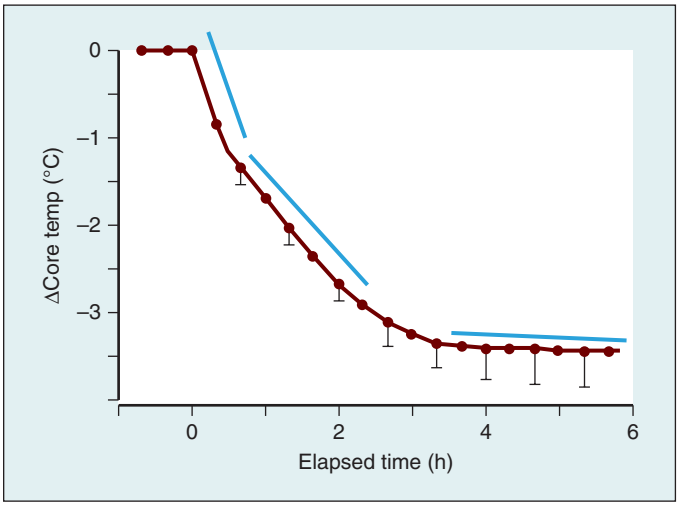
• **Fig. 15.3** Anesthetic agents and thermoregulation. Anesthetic agents with different mechanisms of action (desflurane, alfentanil, dexmedetomidine, and propofol) all inhibit thermoregulatory sweating, vasoconstriction, and shivering in volunteers in a dose-dependent fashion and with similar patterns, although to somewhat different degrees. The effect on vasoconstriction and shivering is much larger than that on sweating. (Used with permission from Sessler DI. The thermoregulation story. *Anesthesiology.* 2013;118:181–186.)

loss, in the absence of interventions to maintain normothermia, most patients exposed to general anesthesia become hypothermic, typically by 1°C to 3°C.[30] A 3°C reduction in mean body temperature translates to a heat "debt" of approximately 175 kcal in an average 70-kg patient, equivalent to about 3 hours of basal metabolic heat production.[11] Thus patients who become hypothermic intraoperatively may take hours to return to baseline thermal comfort.

Although core temperature is almost universally used as a measure of the state of thermoregulation of an individual, it does not accurately represent either total body heat content or mean body temperature because peripheral tissues are typically 2° to 4°C cooler than the trunk and the head.[10,31] This normal core-to-peripheral tissue temperature gradient is maintained by tonic thermoregulatory vasoconstriction of arteriovenous shunts in the fingers and toes[4,32] that maintain core temperature by reducing heat loss to the environment. Thus in addition to effects on normal thermoregulatory mechanisms, the direct vasodilation caused by all anesthetics causes dissipation of heat across the existing temperature gradients from the warmer core to the cooler periphery.[33] Despite the early decrease in core temperature within the first 30 minutes of anesthetic induction, body heat content during early anesthesia remains constant; that is, net heat exchange to the environment remains close to zero. The redistribution of core heat to the periphery contributes about 65% of the total decrease in core temperature during the first 3 hours of anesthesia.[10]

In the absence of interventions to minimize preinduction peripheral vasoconstriction or to add heat to the patient by active warming methods (these interventions are described in detail later), core temperatures under anesthesia typically decrease by 1°C to 1.5°C during the first hour.[6,7] This is followed by a slower linear phase of temperature decrease over the next 2 to 3 hours.[5] A plateau is then reached throughout the remainder of the procedure (Fig. 15.4).[26-28]

The initial large decrease is caused by redistribution of heat content as the result of vasodilation of previously constricted vessels. The linear phase results mainly from the decrease in metabolic rate induced by anesthesia, typically in the range of a 15% to 40% reduction.[10,11,34] In this phase, heat loss exceeds metabolic heat production, which leads to a slow, linear decrease in temperature. During this phase, patient factors such as basal metabolic rate and obesity, the type of operation, and ambient temperature all may affect the rate of decrease.[12,13] In a sufficiently long surgery (>4 hours) the linear phase is followed by a core temperature plateau, when heat loss and heat production reach equilibrium.[26,27,28]



• **Fig. 15.4** Hypothermia during general anesthesia. In the absence of active warming, hypothermia during anesthesia develops with a characteristic pattern. During the first hour, core temperature usually decreases 1°C to 1.5°C as a result of heat redistribution. This is followed by a slower, nearly linear decrease in core temperature as a result of heat loss. In the final phase, if the procedure is of sufficient duration, core temperature reaches a plateau and does not decrease further, as a result of reaching a steady state between heat production and heat loss, which may be facilitated by peripheral thermoregulatory vasoconstriction. (Used with permission from Kurz A, Sessler DI, Christensen R, et al. Heat balance and distribution during the core-temperature plateau in anesthetized humans. *Anesthesiology.* 1995;83:491–499.)

This state of equilibrium is also known as thermal steady state. Patients with sufficient initial body heat content remain relatively warm intraoperatively and tend to reach thermal steady state earlier. In patients in whom core temperature was maintained in the normal range preoperatively owing to thermoregulatory vasoconstriction, core temperature decreases by a greater amount and it takes longer to reach thermal steady state.[26-28] Core hypothermia in general or regional anesthesia is a function of the initial thermoregulatory state of the patient and the site, duration, and magnitude of surgery.

Although the core temperature plateau usually occurs at about the same time as the temperature becomes low enough to trigger thermoregulatory vasoconstriction (~34°C-35°C), vasoconstriction, surprisingly, only slightly reduces cutaneous heat loss.[35,36] The reason appears to be that constriction is largely restricted to arteriovenous shunts in the fingers and toes.[37] The distribution of heat to the periphery is influenced by peripheral blood flow, heat exchange between adjacent arteries and veins, and the core-to-peripheral temperature gradient. Once heat reaches the periphery it cannot travel back to the core against the temperature gradient. Reemergence of vasoconstriction restricts further redistribution from the core but cannot recover heat already lost to peripheral tissues. After vasoconstriction, cutaneous heat loss decreases as less heat flows peripherally from the core and peripheral tissues gradually cool. However, core temperature plateau appears well before a thermal steady state, suggesting that it is a constraint of centrally generated metabolic heat to the core, rather than a reduction in cutaneous loss. Cutaneous heat alterations therefore represent a more accurate measure of heat loss than changes in central body temperature because as mentioned redistribution is the determinant of heat balance.[38]

Thermoregulation under anesthesia is different in infants and children than in adults. Although respiratory losses are similar, infants have less mass with a high surface-area-to weight ratio. A greater fraction of their weight is distributed to their heads and torsos as opposed to their extremities.[39] With less overall mass, infants have lower metabolic heat production and cannot absorb much heat from the core. They typically lose heat from their thin scalps and skin as opposed to redistribution, which is most apparent during the linear phase of hypothermia.[3,12,13,40] Studies have also shown impaired thermoregulation in old age.[41]

As patients emerge from anesthesia postoperatively, they slowly regain thermoregulatory control and, in the absence of intraoperative active warming, regain core normothermia in about 2 to 5 hours.[42] Upon emergence, patients regain arteriovenous vasoconstriction and shivering and are able to decrease cutaneous heat loss,[36] constrain metabolic heat to the thermal core,[43] and increase metabolic heat production.[44] Recovery, however, may be limited by residual volatile anesthetics or opioids administered at the end of surgery.[26,27,45,46]

Effects of Anesthetic Techniques and Agents

General anesthesia decreases core temperature to a greater extent than neuraxial anesthesia. Patients under neuraxial anesthesia lose less heat from redistribution compared with those who have general anesthesia.[10,31,47,48] Although neuraxial anesthesia inhibits thermoregulation centrally,[49-51] more importantly, the inhibition of peripheral sympathetic motor nerves prevents thermoregulatory vasoconstriction and shivering.[52] Neuraxial anesthesia also has a lesser impact on reducing metabolic heat production.[10,31] As a result, patients under neuraxial anesthesia demonstrate a smaller initial reduction of core temperature related to redistribution and a slow, prolonged phase of linear hypothermia.[31]

Hypothermia during neuraxial anesthesia for small surgeries is usually mild because a passive plateau develops in well-insulated patients. Patients undergoing long operations under neuraxial anesthesia, on the other hand, are at risk of developing more severe hypothermia[53] comparable to that seen under general anesthesia.[54] Neuraxial anesthesia inhibits both autonomic thermoregulatory control and thermoregulatory shivering in response to hypothermia.[55,56]

Combined approaches, including anesthetic agents, analgesic/sedative agents, and/or neuraxial anesthesia/analgesia, produce a more pronounced inhibition of thermoregulation and a greater risk of perioperative hypothermia.[41] Heat redistribution may be increased because of differential and additive mechanisms. Heat may be lost at a higher rate during the linear phase. When the effects of regional anesthesia on vasoconstriction are superimposed on those of general anesthesia, vasoconstriction occurs at a lower core temperature.[57] Centrally initiated vasoconstriction will have a reduced effect on vascular tone in the lower extremities after neuraxial anesthesia.[58]

Although hypothermia is more common and appears to have more severe consequences, the disruption in thermoregulation induced by anesthesia may also lead to hyperthermia. In patients having superficial surgery of long duration in which almost all of the skin is covered by drapes, active warming can lead to hyperthermia owing to transfer of heat to the patient in excess of heat loss.[3] Adverse consequences of hyperthermia include increased heart rate and, if severe, neurologic consequences.

Consequences of Thermal Dysregulation Related to Anesthesia

Intraoperative core hypothermia was the norm in anesthesia management until at least the 1990s, and it was not thought to have adverse consequences. That view was incorrect, however. Even 0.5°C of hypothermia has adverse consequences, which include patient discomfort, prolonged duration (and cost) of immediate postoperative recovery in the postanesthesia care unit (PACU),[59] prolonged drug metabolism,[60] increased risk of blood loss and transfusion,[61] increased risk of cardiovascular and wound morbidity, and increased risk of deep vein thrombosis (Table 15.1 and Fig. 15.8).

Hypothermia may also have benefits for specific types of surgeries. Hypothermia reduces metabolism by about 7% per degree centigrade temperature reduction. A 1°C to 3°C reduction is protective in animal models of brain injury, but human trials have mostly shown no benefit. Hypothermia is commonly used for neuroprotection in cardiac surgery,[62-64] although there were no differences in mortality and hospital length of stay in coronary artery surgery patients kept hypothermic (34°C) versus normothermic (37°C) during cardiopulmonary bypass.[65] In traumatic brain injury, no benefit was found in a large, multicenter randomized, controlled trial of induced hypothermia.[66] In brain aneurysm clipping, intraoperative hypothermia was found to have no benefit in a large, multicenter randomized, controlled trial (Intraoperative Hypothermia for Aneurysm Surgery Trial [IHAST]).[67] In that trial, there was some benefit in patients in whom the aneurysm ruptured during surgery; this was offset by an increase in infectious complications, particularly because aneurysm rupture was rare. Patients rapidly cooled after cardiac arrest have improved outcomes, and induced hypothermia has now become standard of care.[68] Newborns with neonatal hypoxic-ischemic encephalopathy have also been shown to have improved outcomes with hypothermia.[69]

Although induced hypothermia may be beneficial in a few instances, adverse consequences are common and may be severe. Responses to decreased core temperature such as vasoconstriction and shivering are uncomfortable for patients,[70] increase oxygen consumption,[71] and may interfere with patient monitoring. Hypothermia is associated with increased cardiac morbidity in patients undergoing major vascular surgery.[72] Even mildly lowered temperatures reduce the function of enzymes of the coagulation cascade, including decreased levels of thromboxane B_2 and platelet surface P-selectin.[73,74] Prothrombin and activated partial thromboplastin times have been shown to be significantly prolonged at hypothermic temperatures (<35°C); temperatures less than 33°C produce a prolonged prothrombin time that is functionally equivalent to a 50% or more deficiency in factor V.[75-77] Compensatory vasoconstriction reduces both oxygen delivery and nutrient flow to peripheral tissues and affects coagulation, immune function, and the initiation phase of clot formation.[78,79] These effects on coagulation cause a concomitant increase in transfusion requirements in patients during surgery with higher blood loss such as hip replacement.[61]

Hypothermia reduces the motility of macrophages, chemotaxis, and the production of antibodies and antibacterial oxidant defenses.[80,81] Compensatory vasoconstriction decreases partial

TABLE 15.1 Major Consequences of Mild Perioperative Hypothermia in Humans

Consequence	Author	N	ΔT_{core} (°C)	Normothermic	Hypothermic	*P*
Surgical wound infection	Kurz et al.[85]	200	1.9	6%	19%	< 0.01
Duration of hospitalization	Kurz et al.[85]	200	1.9	12.1 ± 4.4 days	14.7 ± 6.5 days	<0.01
Intraoperative blood loss	Schmied et al.[21]	60	1.6	1.7 ± 0.3 l	2.2 ± 0.5 l	< 0.001
Allogeneic transfusion requirement	Schmied et al.[21]	60	1.6	1 unit	8 units	< 0.05
Morbid cardiac events	Frank et al.[72]	300	1.3	1%	6%	<0.05
Postoperative ventricular tachycardia	Frank et al.[72]	300	1.3	2%	8%	<0.05
Urinary excretion of nitrogen	Carli et al.[55]	12	1.5	982 mmol/day	1798 mmol/day	<0.05
Duration of vecuronium	Heier et al.[60]	20	2.0	28 ± 4 min	62 ± 8 min	< 0.001
Duration of atracurium	Leslie et al.[51]	6	3.0	44 ± 4 min	68 ± 7 min	< 0.05
Postoperative shivering	Just et al.[44]	14	2.3	141 ± 9 mL/min/m^2	269 ± 60 mL/min/m^2	< 0.001
Duration of postanesthetic recovery	Lenhardt et al.[93]	150	1.9	53 ± 36 min	94 ± 65 min	< 0.001
Plasma [norepinephrine]	Frank et al.[20]	74	1.5	330 ± 30 pg/mL	480 ± 70 pg/mL	< 0.05
Thermal discomfort	Kurz et al.[73]	74	2.6	50 ± 10 mm VAS	18 ± 9 mm VAS	< 0.001

N, Total number of subjects; ΔT_{core}, difference in core temperature between the treatment groups; *T*, temperature.
Only prospective, randomized human trials are included; subjective responses were evaluated by observers blinded to treatment group and core temperature. Different outcomes of the first three studies are shown on separate lines. VAS is a 100-mm-long visual analog scale (0 mm = intense cold, 100 mm = intense heat).[42]
Used with permission from Sessler DI. Complications and treatment of mild hypothermia. *Anesthesiology.* 2001;95:531–543.

pressure of oxygen in peripheral tissues. This decreases oxidative killing by neutrophils and reduces resistance to inoculation of bacteria, including *Escherichia coli*[82] and *Staphylococcus aureus*[83] in guinea pigs.[84] In a randomized, blinded, controlled trial in 200 colorectal surgery patients, patients randomly assigned to intraoperative core normothermia (36.6°C) achieved using intraoperative active warming versus core hypothermia (34.6°C; the control group), the surgical site infection rate was reduced by two-thirds in normothermic patients and their wounds made significantly more collagen.[85]

Although the majority of studies have investigated the adverse consequences of a 2°C core temperature differential on arrival in the PACU (~34.5°C vs. ~36.5°C), a recent retrospective, large database study at one institution demonstrated that, although hypothermia in the PACU is uncommon, intraoperative hypothermia remains common (67% of patients) and that both the degree and duration of intraoperative hypothermia predict adverse consequences, including prolonged hospital length of stay and transfusion requirement (see Table 15.1).[86] Thus consideration should be given not only to correcting hypothermia by the end of surgery but also to preventing it.

Measuring Temperature Intraoperatively

Preventing and correcting intraoperative temperature requires the core temperature to be measured. Temperature monitoring is a standard of care defined by American Society of Anesthesiologist practice guidelines: "Every patient receiving anesthesia shall have temperature monitored when clinically significant changes in body temperature are intended, anticipated or suspected."[61,87,88] Although measurement of core temperature is required, methods for measuring core temperature are variably reliable, and core temperature measurements do not provide information on thermal status and total body heat content.

Core temperature may be measured at many sites,[3,87] by using thermocouples, thermistors, and infrared sensors. There is a range of convenience and accuracy based on site and technology. The most reliable sites for measuring core temperature are the pulmonary artery, distal esophagus, nasopharynx, and tympanic membrane. Other generally reliable sites include the mouth, axilla, and bladder. Suboptimal sites include the forehead skin, infrared "tympanic" and "temporal artery" sensors, and rectal.[3]

Esophageal temperature measurements are commonly used intraoperatively because of their accuracy (provided they are advanced to the distal third of the esophagus)[89] and ease of use. The nasopharynx, axilla, and bladder are also reliable sites but may be limited by positioning.[3] Bladder temperatures are affected by urine flow. Axillary temperatures may be affected by forced-air warming.

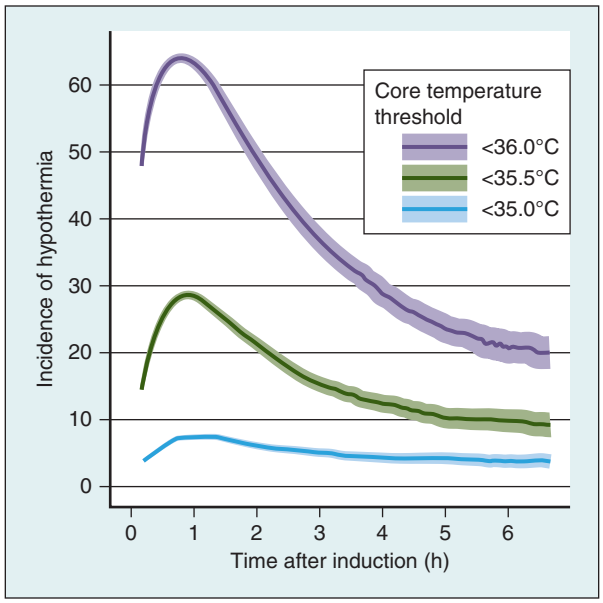
Although core temperature is useful, it does not provide information on heat content. A patient with a normal core temperature and minimal thermoregulatory vasoconstriction is quite physiologically different from a patient with a normal core temperature and severe thermoregulatory vasoconstriction and/or shivering. Therefore thermal comfort should also be assessed. Components include patient report of comfort, presence or absence of shivering, and assessment of peripheral temperature. Patients with a normal core temperature might benefit from active warming in the PACU if they report feeling cold, are shivering, or have obvious peripheral vasoconstriction because the adverse consequences are, at least in part, mediated by peripheral vasoconstriction and hypothermia of peripheral tissues.

Prevention and Correction of Intraoperative Hypothermia

Unless they are actively warmed, most anesthetized patients become hypothermic, defined as core temperature less than 36°C.[90] Because of the consequences and clinical burdens of hypothermia, anesthetists should aim to transport patients to the PACU with core temperatures of at least 36°C. Recent studies suggest avoiding intraoperative hypothermia should become a new practice standard. The reduction in metabolic rate and heat production induced by anesthesia has protective properties and is likely to be difficult to alter. Therefore the two primary ways by which perioperative hypothermia can be prevented or corrected are reducing heat loss and active warming.

Reduced heat loss can be achieved with a high ambient temperature and passive insulation. Reduced heat loss can be facilitated by keeping the preoperative holding room warm (at least 72°F). Some operating rooms have rapidly responsive thermostats; in that case, warming the operating room during induction, preparation, and draping and then reducing the temperature for surgeon comfort after the drapes are placed can be effective. Warm blankets are valuable for comfort in awake patients, although they are no more effective than unwarmed blankets in reducing heat loss (Fig. 15.5). Multiple layers similarly are not more effective than a single layer.[91] Because laundering blankets is relatively expensive and multiple layers of blankets my obscure the patient, making it more difficult to examine the patient, multiple blankets and routine replacement of blankets are not warranted.

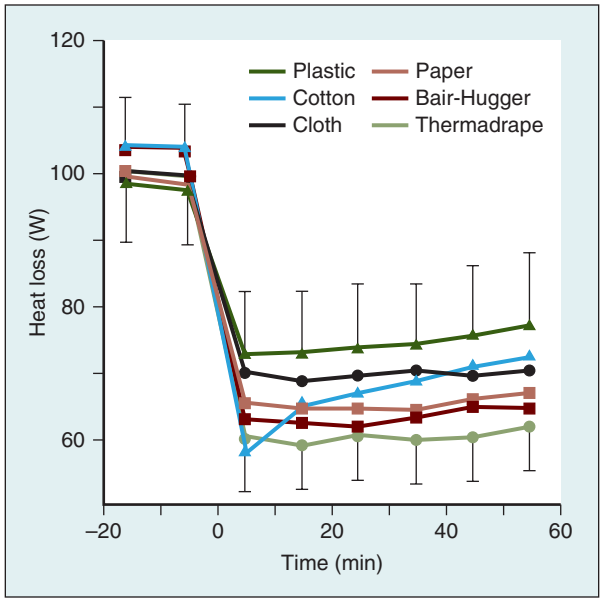
There are numerous methods and technologies for active warming, although not all are equally effective or safe. The goal of active warming is the transfer of heat to the patient without causing a burn. It can be achieved through a number of technologies,



• **Fig. 15.5** Insulating covers reduce heat loss but do not transfer heat. The magnitude of reduction is similar regardless of cover used. More layers or warmed layers also provide similar reduction in heat loss without transferring heat. (Used with permission from Sessler DI, McGuire J, Sessler AM. Perioperative thermal insulation. *Anesthesiology.* 1991;74:875–879.)

most introduced into practice in the 1980s and 1990s. These include forced-air warming, resistive heating, heating lamps, heated humidifiers, circulating water, warmed intravenous fluids, and warm fluid-containing plastic bottles. Circulating water, warmed fluids, heated humidifiers, and warmed plastic bottles may potentially cause burns, because the temperature of the water required to transfer heat actively is near the burning point for skin (>42°C-44°C). Skin warming with warmed fluid containers is discouraged by American Society of Anesthesiologists (ASA) guidelines because they have been responsible for the majority of thermal injuries as reported by the ASA.[48] Heated humidifiers have also caused burns. Circulating water blankets under the patient on the operating room table may increase the risk of pressure ulcers by increasing the metabolic rate and oxygen consumption in potentially poorly perfused skin at risk of unmet cellular demands. Warming intravenous fluids to 40°C to 42°C is effective in patients who are expected to receive more than 2 L of fluid. Patients with hypothermic trauma or hemorrhage benefit from fluid warming because of the required rapid infusion of fluids.

Skin surface active warming by forced air, resistive heating, or circulating water blankets that can be placed on the nondependent skin, on the other hand, is usually effective in transferring heat. Skin surface warmers work by increasing body heat content and decreasing the temperature gradient required for heat to flow between the core and the periphery.[48] This does not always adequately obliterate temperature gradients,[48] mainly because redistribution continues to decrease core temperature early during induction under general and regional anesthesia.[56] A retrospective analysis by Sun et al.[86] of 58,814 patients who were actively warmed during surgery demonstrated that temperatures were less than 36°C in 64% of patients and less than 35.5°C in 29% of patients 45 minutes after induction, despite more than 90% of those being normothermic by the end of the surgery (Fig. 15.6).

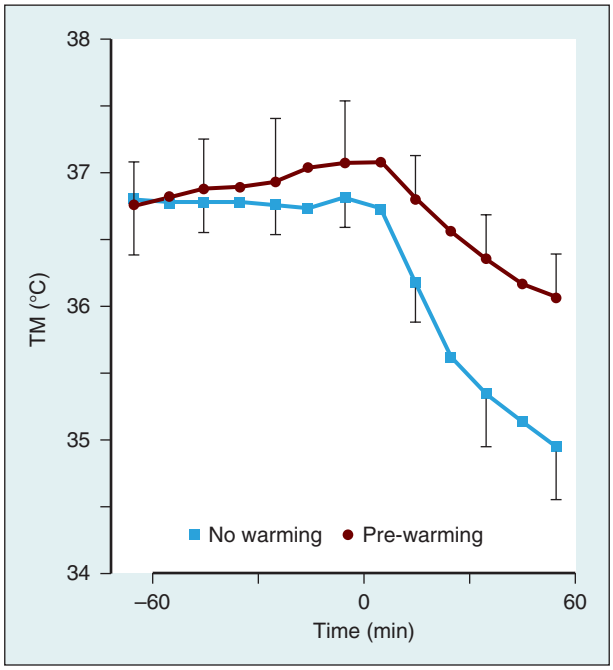


• **Fig. 15.6** The incidence of hypothermia as a function of time after induction, under progressive core temperature thresholds defining hypothermia. (Used with permission from Sun Z, Honar H, Sessler DI, et al. Intraoperative core temperature patterns, transfusion requirement, and hospital duration in patients warmed with forced air. *Anesthesiology. 2015*;122:276–285.)

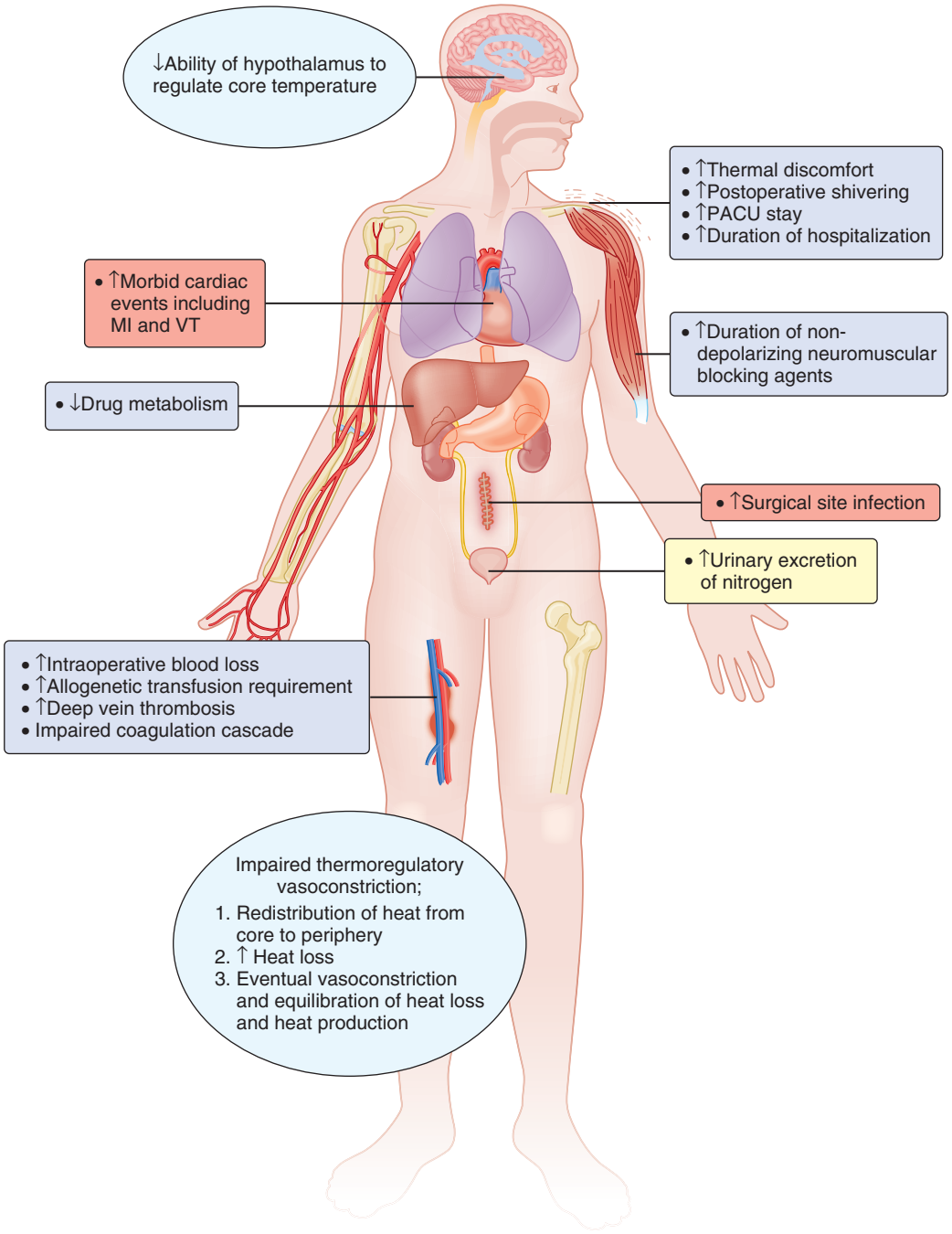
Using active warming in the preoperative holding area (prewarming) has been shown to prevent or reduce the decrease in core temperature that results from heat redistribution after induction (Fig. 15.7).[48,92] Prewarming may help prevent hypothermia during both general and neuraxial anesthesia and also helps reduce thermoregulatory shivering during neuraxial anesthesia or in the PACU.[48] Development and evaluation of prewarming protocols may improve patient outcomes by reducing perioperative hypothermia. Such protocols require policy and procedures, motivated staff, time, and patient education to be successful.

Emerging Developments

Perioperative hypothermia remains a common adverse effect of anesthesia for which more studies are needed to examine the effectiveness of preoperative warming in preventing intraoperative hypothermia and, specifically, initial core temperature redistribution. Health care centers are recognizing the adverse outcomes of hypothermia in patients beyond hospital length of stay and transfusion, including cardiac morbidity, surgical site infection, and deep vein thrombosis or pulmonary embolism (Fig. 15.8). Guidelines on monitoring and managing perioperative hypothermia are developing to establish a refined standard of care and reduce financial burdens.



• **Fig. 15.7** Prewarming minimizes redistribution hypothermia. During the preinduction period (–120 to 0 minutes), volunteers were either actively warmed or passively cooled (no warming). At induction of anesthesia (time = 0 minutes), active warming was discontinued and volunteers were exposed to the ambient environment. Initial tympanic membrane temperatures *(TM)* were similar before each preinduction treatment. During the 60 minutes after induction of anesthesia, core temperature (T) decreased less when volunteers were prewarmed ($\Delta T = -1.1°C \pm 0.3°C$) compared with when the same volunteers were not warmed ($\Delta T = -1.9 \pm 0.3°C$). These data indicate that redistribution hypothermia can be prevented by actively warming peripheral tissues before induction of anesthesia. Data are presented as mean ± SD. (Used with permission from Hynson JM, Sessler DI, Moayeri A, et al. The effects of preinduction warming on temperature and blood pressure during propofol/nitrous oxide anesthesia. *Anesthesiology.* 1993;79:219–228.)



• **Fig. 15.8** Schematic of anesthetic effects on thermoregulation and consequences of intraoperative hypothermia. Anesthetic effects are identified in *ovals,* whereas consequences are identified in *boxes.*

Key Points

- General anesthesia, neuraxial anesthesia and analgesia, and drugs such as opioids all reduce the ability of the hypothalamus to regulate core temperature.
- Intraoperative hypothermia is common and is caused by (1) redistribution of heat from the core to the periphery, (2) decreased metabolism leading to decreased heat production, and (3) increased heat loss, primarily via radiation, convection, and in large open surgeries, evaporation.
- Intraoperative hypothermia increases postoperative discomfort and post-anesthesia recovery time, blood loss and transfusion, cardiovascular morbidity, surgical site infection, deep vein thrombosis, and hospital length of stay.
- Intraoperative hypothermia can be prevented, mitigated, or corrected by preoperative and intraoperative active warming, which has also been shown to reduce complications.

Key References

Andrzejowski J, Hoyle J, Eapen G, et al. Effect of prewarming on post-induction core temperature and the incidence of inadvertent perioperative hypothermia in patients undergoing general anaesthesia. *Br J Anaesth*. 2008;101:627–631. This study provides evidence for a potential intervention to prevent intraoperative hypothermia: preoperative active warming. Warming before induction of anesthesia reduces thermoregulatory vasoconstriction and therefore reduces redistribution of heat from the core to the periphery after induction of anesthesia. Further studies are needed to define the most effective ways to prevent redistribution hypothermia. (Ref. 92).

Frank SM, Fleisher LA, Breslow MJ, et al. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events. A randomized clinical trial. *JAMA*. 1997;277:1127–1134. This is the first report of the increase in cardiovascular morbidity related to intraoperative hypothermia, as well as the reduction in cardiovascular morbidity from interventions to maintain perioperative normothermia. (Ref. 72).

Kurz A, Sessler DI, Lenhardt RA. Study of wound infections and temperature group: perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. *N Engl J Med*. 1996;334:1209–1215. This is the first randomized controlled trial of maintenance of perioperative normothermia. Maintenance of core normothermia through active warming in patients undergoing open colon surgery reduced surgical site infection by two-thirds compared with patients whose temperature was allowed to decrease ~2°C, which was standard of care at the time. (Ref. 85).

Sessler DI, Rubinstein EH, Moayeri A. Physiological responses to mild perianesthetic hypothermia in humans. *Anesthesiology*. 1991;75:594–610. This is an excellent summary of the literature on the physiological responses to perioperative hypothermia in humans. It includes the key references that describe redistribution hypothermia, mechanisms of heat loss, and effect of anesthetics on the interthreshold range for thermoregulatory vasoconstriction. (Ref. 45).

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Sun Z, Honar H, Sessler DI, et al. Intraoperative core temperature patterns, transfusion requirement, and hospital duration in patients warmed with forced air. *Anesthesiology*. 2015;122:276–285. Randomized controlled trials in perioperative normothermia compared groups with about a 2°C difference in core temperature on arrival in the PACU. Many patients in the "normothermic" group in these studies had a core temperature less than 36°°C intraoperatively, because induction causes vasodilation and redistribution of heat from the core to the periphery. Thus these studies looked at a larger temperature differential than would typically be seen in current practice, and intraoperative hypothermia was not considered. In the large database study by Sun et al., greater duration and degree of hypothermia were associated with increased hospital length of stay and transfusion requirements. This study opens a new avenue of research, focused on methods of preventing intraoperative hypothermia and resulting morbidity. (Ref. 86).

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16

Nociceptive Physiology

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CHAPTER OUTLINE

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Systems Physiology

Management of Perioperative Pain

Despite significant progress in our mechanistic understanding of the nociceptive system, inadequately treated perioperative pain remains a significant problem. A third of patients undergoing surgery continue to suffer from moderate to severe pain, resulting in personal suffering, protracted recovery including persistent pain after surgery, delayed hospital discharge, and increased morbidity and mortality.[1–3] Improving the management of postoperative pain remains an important clinical challenge. Although opioids are the most efficacious drugs, their pharmacologic profile does not allow adequate pain control in all patients. The occurrence of adverse effects can conflict with opioid dosing strategies required to alleviate pain. This has led to the widely embraced concept of multimodel analgesia, the combined use of different drug classes and regional anesthesia techniques, for the treatment of postoperative pain. The liberal use of opioids is also associated with significant abuse potential and drug diversion, which contributes to the current opioid epidemic in the United States, a serious public health issue costing many lives.[4] As such, identifying novel analgesic drug classes that exploit alternative targets in the nociceptive system remains a high priority.

This chapter primarily covers the fundamental neuroanatomy, molecular biology, and physiologic functions of the nociceptive system as they pertain to the processing of acute pain and the practice of anesthesia. The objective is to provide a framework that facilitates the understanding of current and novel analgesic drug targets and management strategies for the treatment of *acute pain*. Given the focus of this book on the practice of anesthesia rather than the management of *chronic pain,* functional alterations of the nociceptive system in the context of chronic pain are not discussed in depth. However, it is noteworthy that the protective function of postoperative pain can be lost, as pain becomes maladaptive in patients who develop persistent postoperative pain (PPP).[3,5]

Several clinical factors are associated with PPP, including type of surgery, severity of postoperative pain, young age, female sex, preexisting chronic pain conditions, and underlying psychosocial vulnerability.[3,6] However, the molecular mechanisms underlying PPP remain poorly understood. Polymorphism of certain genes, including genes coding for catecholamine-*O*-methyltransferase, Na_V 1.7, and K_V 1.9, have been linked to the propensity for developing chronic pain.[7] Whether these polymorphisms contribute to PPP in clinically relevant ways remains to be determined. Conceptionally, PPP reflects a shift in the balance between pronociceptive and antinociceptive processes, owing either to an exaggerated amplification of nociceptive input (central sensitization) or the deficient activation of endogenous central inhibitory pathways. Accordingly, several drugs classes counteracting central sensitization and/or enhancing central inhibitory control have been examined for reducing the incidence of PPP.[8–10] They include α_2-adrenergic agonists, calcium channel $\alpha_2\delta$ ligands (gabapentin and pregabalin), and *N*-methyl-D-aspartate (NMDA)-type glutamate receptor antagonists. Among them, efficacy is best documented for the NMDA receptor antagonist ketamine.

Overview of the Nociceptive System

The nociceptive system is a sensory component of the peripheral and central nervous systems devoted to signal input that is potentially harmful. The system controls involuntary defensive and adaptive responses to injurious stimuli and mediates the perception

of pain. Nociception typically starts by activation of peripheral nerves tuned to respond to potentially harmful thermal, mechanical, or chemical stimuli. Physical or chemical input is transduced into transmembrane potential changes that can trigger action potentials (see Chapter 8). Primary sensory afferents consisting of nonmyelinated slow-conducting C-fibers and thinly myelinated faster-conducting Aδ fibers propagate action potentials to the dorsal horn of the spinal cord, where they synapse with spinal neurons. The neuronal architecture of the dorsal horn is complex and consists largely of interneurons that either amplify or inhibit transmission of incoming signals. Processed nociceptive input is relayed to supraspinal sites by projection neurons ascending in the spinothalamic and spinomedullary tracts, but the input is also transmitted to spinal sites serving autonomic and motor functions. Integration of nociceptive information in supraspinal brain regions results in complex somatic, emotional, autonomic, and endocrine responses. Finally, descending fibers emerge from supraspinal sites, including the cerebral cortex, hypothalamus, and brainstem, and project to the spinal cord where they facilitate or inhibit transmission of nociceptive signals and regulate behavior.

Peripheral Nociception

Nociceptor Classification

Nociceptors are a specific set of primary afferent nerve fibers that conduct noxious signals from peripheral somatic and visceral tissue to the spinal cord. They are pseudo-unipolar in architecture with distal and proximal projections arising from their cell bodies located in dorsal root and other sensory (e.g., trigeminal) ganglia. The peripheral nerve endings of nociceptors exhibit significant arborization and cover receptive fields from a few square millimeters to a few square centimeters, contingent on body location and fiber type. At the unmyelinated nerve endings, membrane ion channels and receptors convert nociceptive input into changes in transmembrane potential, ultimately triggering the propagation of action potentials if nociceptive input is of sufficient magnitude.

An important characteristic of nociceptors is their ability to become sensitized in injured tissue, requiring less input to initiate action potentials. Nociceptor sensitization is the neurophysiologic correlate of primary hyperalgesia, the increased sensitivity to nociceptive stimuli in injured and inflamed tissue. The term *primary* indicates that hyperalgesia is due to local events at the site of injury rather than central processes that can also amplify nociceptive input (secondary hyperalgesia is discussed later in this chapter).

Pain signals are conducted to the dorsal horn of the spinal cord via two distinct populations of peripheral nociceptors that are characterized by their fast and slow conduction velocities: small myelinated Aδ fibers (5–25 m/sec) and unmyelinated C-fibers (<2 m/sec). Aδ fibers transmit "fast" pain that is typically well localized and causes a rapid withdrawal of the affected body region, whereas C-fibers transmit "slow-onset" pain that is diffuse in character, intensifies over time, and often elicits a guarding response. These divergent responses are partially due to the difference in conduction velocities but also reflect differential neuronal integration of Aδ and C- fiber signals in the central nervous system (CNS).

Aδ fibers can be further subdivided into *type I high-threshold mechanical (HTM) nociceptors* that are activated by mechanical and chemical stimuli but exhibit a high threshold for activation by noxious heat (>50°C), and *type II* Aδ fibers that conversely exhibit low thresholds for activation by noxious heat (~43°C) but high thresholds for mechanical stimuli. *Type I* fibers are generally thought to conduct "fast" pain triggered by mechanical input (e.g., pinprick), whereas *type II* fibers conduct "fast" pain triggered to noxious heat.[11]

C-fibers are classified as peptidergic or nonpeptidergic. Peptidergic fibers constitute the largest group of nociceptors and contain the neuropeptides substance P (SP) and/or calcitonin gene-related peptide (CGRP). Upon their release after tissue injury, SP and CGRP activate receptors on capillaries and terminal arterioles, causing vasodilation (CGRP) or plasma extravasation (SP). They also trigger the release of inflammatory and nociceptive mediators by neighboring cells, which amplifies inflammation and pain. Clinically, this phenomenon is known as neurogenic inflammation, which is thought to underlie chronic pain states with prominent vasomotor components such as fibromyalgia and complex regional pain syndrome.[12,13]

Peptidergic C-fibers also express tropomyosin receptor kinase A (TrkA), the high-affinity receptor for nerve growth factor (NGF). The critical importance of peptidergic C-fibers, TrkA, and NGF in normal neuronal development is highlighted by the rare autosomal recessive disease *congenital insensitivity to pain with anhidrosis,* which is caused by loss of TrkA receptor function.[14] Patients with this disorder retain touch perception and proprioception but lack any sensory response to heat, cold, and nociceptive input (including visceral input). TrkA loss of function has wide-ranging clinical consequences, including self-mutilation and bone fractures owing to lack of nociception, frequent fevers owing to lack of adequate thermoregulation (anhidrosis), autonomic abnormalities, and cognitive impairment.

Nonpeptidergic C-fibers are stimulated by glial cell line–derived neurotrophic factors (GDNFs, neurterin, artemin, and persephin) and can be identified by the expression of the target for GDNF, the c-RET tyrosine kinase receptor. Nonpeptidergic fibers also frequently express the purinergic $P2X_3$ receptor, which is thought to mediate signals initiated by ATP released from damaged tissues, ultimately causing pain and itch.

Although fiber size and molecular markers provide some basis to differentiate nociceptive neurons, mapping specific pain modalities (heat, chemical, and mechanical) onto specific nociceptors is a challenge because of the significant heterogeneity among nociceptive neurons. Some nociceptors respond to multiple noxious modalities, whereas others are modality-specific or remain silent until activated by tissue injury or inflammation. Examples of well-characterized nociceptors are "polymodal" mechanical and heat-sensitive C-fibers *(CMH)*, and mechano-insensitive afferent *(MIA)* C-fibers, which respond only to heat and chemical stimuli. MIA C-fibers constitute up to 20% of nociceptors in human skin. They may play a particularly important role in the development and maintenance of hyperalgesia, as these mechanically silent nociceptors become responsive to mechanical stimulation in inflamed tissue.

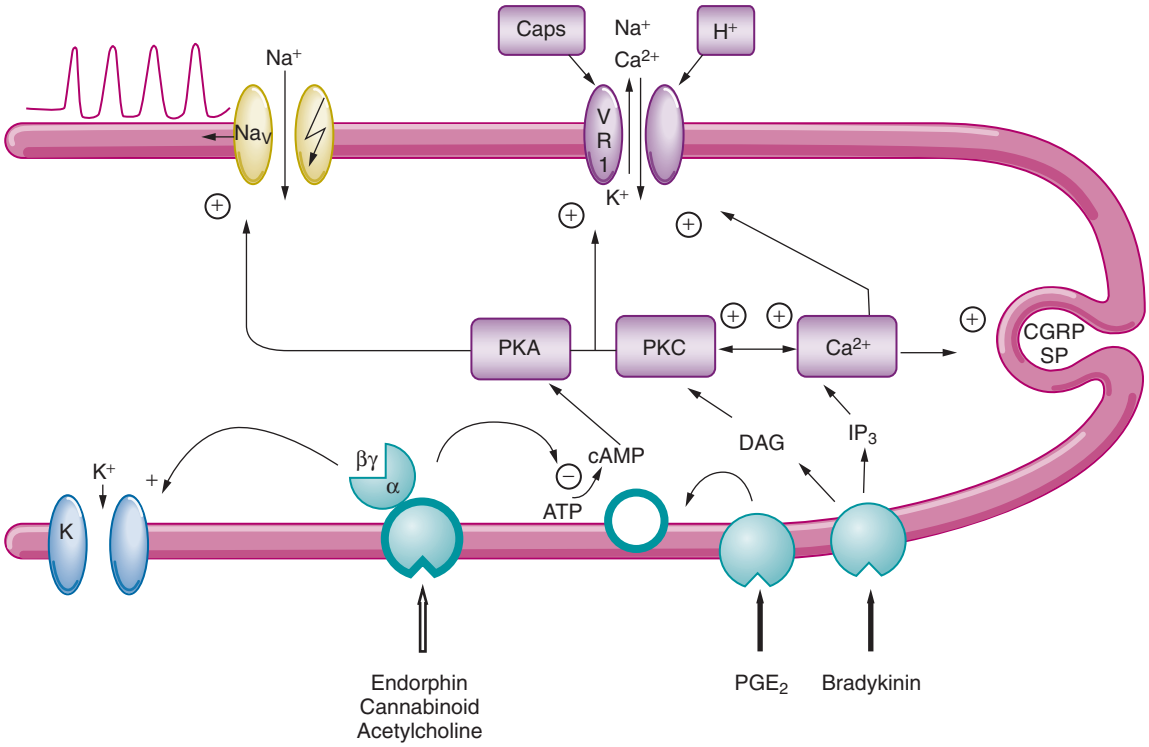
Identification of ion channels and receptors responding to specific nociceptive modalities has provided further means to group nociceptors into subpopulations that roughly correlate with their functional roles. For example, the transient receptor potential vanilloid 1 (TRPV1) receptor is the predominant sensor of noxious heat. Although genetic deletion studies in mice suggest that TRPV1 is not the sole channel responsible for transmission of nociceptive heat, chemical ablation of TRPV1-expressing neurons eliminates the response to nociceptive heat without altering responses to other nociceptive modalities. This finding implicates TRPV1 as an excellent molecular marker for nociceptors responsive to noxious heat.[15] Similar approaches targeting nociceptors that express the Mas-related G-protein–coupled (MRG) receptor demonstrate that

MRG is a specific marker for nociceptors that transmit noxious mechanical input.[16]

Nociceptor Activation

The peripheral terminals of nociceptive neurons contain a mosaic of receptors responsive to both endogenous ligands and exogenous physical or chemical stimuli. A complex set of excitatory and inhibitory signals originating from these receptors ultimately governs the degree to which a nociceptive stimulus is transduced from the periphery to the CNS. This is illustrated schematically in Fig. 16.1 for a TRPV1-expressing nociceptor.[17] TRPV1 is directly activated by exogenous input, including noxious heat, acidosis, and the pungent agent capsaicin derived from "hot" chili peppers,[18] whereas endogenous ligands, including bradykinin 2, prostaglandin E_2, and 5-hydroxytryptamine, modulate TRPV1 indirectly via second-messenger systems. Endogenous ligands are derived from nonneuronal neighboring cells, including resident cells (e.g., keratinocytes and mast cells) and migrating immune cells (e.g., neutrophils and lymphocytes). Nociceptive signaling thus involves a complex integration of exogenous cues acting directly on the nociceptor and endogenous modulators that communicate the state of the surrounding nonneuronal tissue.

The cell surface proteins responsible for encoding nociceptive signals fall into three general classes: ion channels, metabotropic G-protein–coupled receptors (GPCRs), and receptors for neurotrophins or cytokines.[19] Although significant progress has been made in elucidating the basic biophysical properties of individual channels and receptors involved in nociception, it is the complex integration of multiple channels and receptors in vivo that results in nociceptive signaling. The scale of this complexity is further amplified by variations in channel expression and activity in different tissue types (e.g., skin vs. viscera) and contexts (e.g., type and time course of injury). Processing of specific noxious inputs can also



• **Fig. 16.1** Nociceptive signal transduction. Nociceptive signal transduction involves interactions between excitatory and inhibitory molecular mechanisms at the peripheral nerve terminal. Some relevant interactions are illustrated for the transient receptor potential vanilloid 1 receptor *(VR1),* which plays a critical role in the transduction of noxious heat and directly responds to ligands such as capsaicin and hydrogen ions. Bradykinin and prostaglandin E_2 *(PGE_2)* lead to phosphorylation of VR1 by protein kinase C *(PKC)* or protein kinase A *(PKA)* via second-messenger systems, including inositol trisphosphate *(IP_3),* diacylglycerol *(DAG),* and cyclic adenosine monophosphate *(cAMP).* Receptor phosphorylation leads to increased permeability of VR1 and voltage-gated channels such as the sodium ion *(Na^+)* channel Na_V 1.8 *(Na_V).* Voltage-gated channels play an important role for the transduction of sensor potentials into spike sequences in the conductile part of the nerve. Increased concentration of intracellular calcium ions *(Ca^{2+}),* which act as a second messenger, is critical in the secretion of neuropeptides from the peripheral terminal. Calcitonin gene-related peptide *(CGRP)* and substance P *(SP)* are sentinel mediators triggering peripheral neurogenic inflammatory events. Endogenous inhibitory ligands, including endorphins, endocannabinoids, and acetylcholine, modulate the transduction process through activation of their respective G-protein–coupled receptors. Cannabinoid and opioid receptors oppose depolarization by activation of potassium ion *(K^+)* channels via the β-subunit of the G protein, while inhibition of adenylyl cyclase via the α-subunit reduces production of cAMP from adenosine triphosphate *(ATP).* cAMP is required for activating protein kinase A. (Modified from Handwerker HO. Nociceptors: neurogenic inflammation. *Handb Clin Neurol.* 2006;81:23–33.)

often involve multiple redundant channels, receptors, and second-messenger systems, further complicating our ability to *a priori* predict the efficacy of promising drug candidates acting at novel targets. Recent attempts to attenuate the activity of peptidergic C-fibers illustrate this well. Although TrkA receptor and CGRP antagonists are both promising novel analgesic agents (discussed in later text), neurokinin-1 (SP) receptor antagonists exhibit a surprising lack of analgesic efficacy for treatment of acute pain.[20]

Ion Channels

Table 16.1 lists representative ionotropic receptors that regulate nociceptive signaling. Particularly relevant examples of ion channels, including members of the TRP-family, isoforms of the voltage-gated sodium ion (Na^+) channel, and two-pore potassium (K_{2P}) leak K^+ channels, are discussed in more detail.

The family of transient receptor potential (TRP) ion channels is characterized by a conserved structural architecture consisting of a tetrameric assembly of six transmembrane-domain subunits that form a nonselective cation channels with high calcium ion (Ca^{2+}) permeability. The early discovery of the key role of TRPV1 receptors in encoding nociceptive heat and the burning pain sensation triggered by the vanilloid compound capsaicin from hot chili peppers laid the groundwork for the effective use of natural chemical compounds to probe the nociceptive sensory system.[18] Subsequent

TABLE 16.1 Ionotropic Nociceptive Transducers[a]

Abbreviation	Name	Stimulus Transduction	Activation	Sensitization
ASIC 1-4	Acid-sensing ion channels, subtypes 1-4	Chemical	Protons	Ischemia-induced pain, muscle hypersensitivity
TRPV1	Transient receptor potential vanilloid 1 receptor (URI)	Thermal Chemical	Heat, protons, vanilloids, fatty acids, arachidonic acid derivatives	Heat hyperalgesia
TRPV4	Transient receptor potential vanilloid 4 receptor	Mechanical	Osmotic challenge, stretching	Visceral and cutaneous hypersensitivity in inflammation and nerve injury
TRPA1	Transient receptor potential subfamily A1 receptor	Chemical Mechanical	Mustard oil, cinnamaldehyde, acrolein, formalin	Chemically induced hyperalgesia Mechanical hyperalgesia
TRPM8	Transient receptor potential subfamily M8 receptor	Thermal	Cold	Cold hyperalgesia
P2X3	P2X purinoceptor 3	Mechanical (indirect)	Adenosine triphosphate	Visceral and somatic pain in inflammation and nerve injury
P2X1-6	P2X purinoceptor 1-6	Chemical	Adenosine triphosphate	Pain and hypersensitivity associated with injury in various tissues
TREK 1	TWIK-related potassium channel 1	Mechanical Thermal Chemical	Stretching Heat Protons, arachidonic acid	Inflammatory hyperalgesia, mechanical hyperalgesia
TRAAK	TWIK-activated arachidonic acid potassium channel	Mechanical Thermal Chemical	Stretching Heat Protons arachidonic acid	Mechanical hyperalgesia
TMEM16A	Anoctamin calcium-activated chloride channel	Chemical Thermal	Heat Bradykinin	Roles in thermal, mechanical, and inflammatory hyperalgesia
5-HT3	5-Hydroxytryptamine receptor	Chemical	Serotonin	Most prominent role in visceral pain
nACh (multiple subunits)	Nicotinic acetylcholine receptor	Chemical	Acetylcholine	May be pronociceptive at peripheral terminals, antinociceptive at central terminals
Glutamate (GluR1-5 and NR1-2)	Ampakine (GluR1-4), kainate (GluR5), and NMDA (NR1-2) receptors	Chemical	Glutamate and subtype specific agonists	Evidence for peripheral role in pain, but most compelling evidence for role at central terminals
GABA (multiple subunits)	Gamma-aminobutyric acid receptor	Chemical	GABA and subunit specific agonists	May be inhibitory or excitatory

NMDA, *N*-methyl-D-aspartate.

[a]Metabotropic receptors exist in large numbers on nociceptive neurons and are not included in this table.

Modified from Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. *Nat. Med.* 2010;16:1248–1257.

work has elucidated the role of the TRPM8 receptors, activated by the natural "cooling" compound menthol, as a critical target for transducing noxious cold stimuli.[21] TRPA1 receptors transduce the effects of numerous pungent natural agents, including the isothiocyanate compounds found in mustard, horseradish, and wasabi, and thiosulfinate found in garlic. TRPA1 is also potently activated by proalgesic agents including bradykinin and formalin, suggesting that TRPA1 is important in nociceptive signaling associated with inflammation including a wide range of exogenous and endogenous irritant compounds.[22]

Voltage-gated Na^+ channels (Na_v) play an essential role in initiating and propagating action potentials. They are large, multimeric complexes that consist of an α subunit and one or more auxiliary β subunits (see Chapter 20). The α subunit contains the ion-conducting aqueous pore that is the essential element of Na^+ channel function. The β subunits modify kinetics and voltage dependence and are involved in channel localization via interaction with cell adhesion molecules, extracellular matrix, and the intracellular cytoskeleton.[23] Nine isoforms of Na_v α subunits have been identified ($Na_v1.1$ through $Na_v1.9$), each with specific physiologic and pharmacologic functions. Numerous Na^+ channels have been found to play a role in inflammatory and neuropathic pain, including $Na_v1.1$, $Na_v1.3$., $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$.[24] Three isoforms, $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$, are expressed nearly exclusively in the peripheral nervous system, with $Na_v1.7$ expressed in sensory, sympathetic, and myenteric neurons, $Na_v1.9$ expressed in sensory and myenteric neuron, and $Na_v1.8$ expression solely in sensory neurons. The importance of $Na_v1.7$ in nociception has been highlighted by the discovery of multiple inherited pain syndromes that derive from mutations in the *SCN9A* gene encoding $Na_v1.7$, including a dominant gain-of-function mutation that causes inherited erythromyalgia, and a recessive loss-of-function mutations that causes congenital insensitivity to pain.[25,26] Gain-of-function mutations in the $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ channels underlie various forms of painful small fiber neuropathy, further highlighting the importance of these sodium channels in human pain processing.[27] Upregulation of $Na_v1.3$ expression on peripheral axons after nerve damage or in dorsal horn neurons after spinal cord injury leads to increased neuronal excitability and likely contributes to the genesis of neuropathic pain after nerve injury.[28] While $Na_v1.1$ has not historically been considered a contributor to nociception, a recent study demonstrated that $Na_v1.1$ plays an important role regulating activity of HTM Aδ fibers.[29]

The inhibitory function of K^+ channels in nociceptive signal transduction is well established. Many GPCR ligands, including opioids and endocannabinoids, exert their antinociceptive effects by activating K^+ channels via their respective second-messenger systems. Of particular recent interest are members of the K_{2P} channel family, as these channels can be directly activated by nociceptive input, including mechanical, thermal, and chemical stimuli.[30,31] The numbing and tingling sensation produced by ingestion of Chinese peppercorns has been attributed to inhibitory effects on TASK K_{2P} channels in peripheral nociceptive fibers, whereas volatile anesthetic agents activate TASK and TREK K_{2P} channels.[32,33] A human pain syndrome, familial migraine with aura, has been linked to a dominant negative mutation in the TRESK K_{2P} channel, further emphasizing the role of these channels in pain signaling.[34] Although K_{2P} channels represent potential novel analgesic targets, expression of the K_{2P} family is not limited to the sensory nervous system. The wide distribution and functional importance of these channels throughout the body may complicate efforts to target these channels for the treatment of pain.

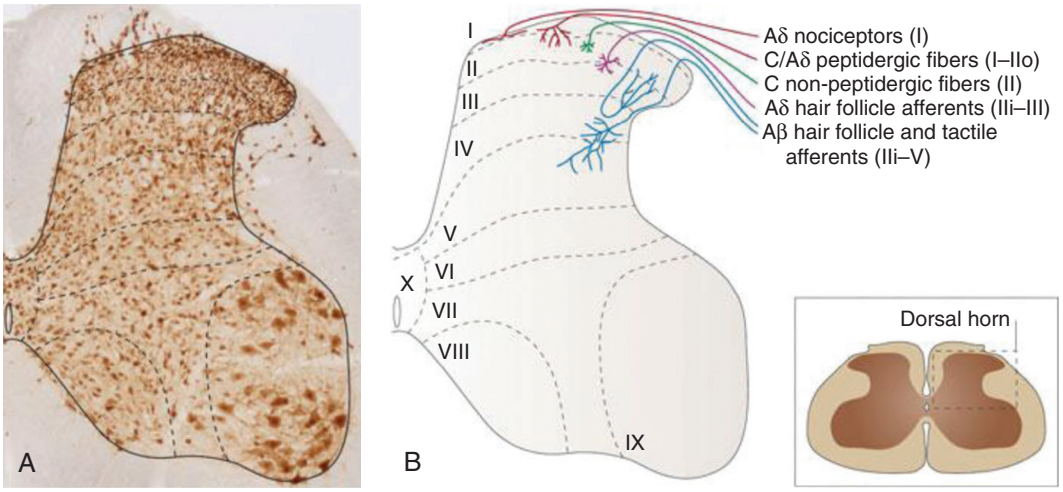
Metabotropic G-Protein–Coupled Receptors

Many excitatory and inhibitory GPCRs modulate nociceptor excitability by activating or inhibiting ion channels via second-messenger systems. Examples of *excitatory* receptors include the receptors for CGRP, bradykinin (B1 and B2), endothelin A (ET_A), protease (PAR 1-4), and prostaglandin (EP1, EP3C, and EP4). Although these GPCRs would appear to be suitable targets for novel analgesic compounds, their relative abundance and heterogeneity within nociceptors seems to account for the fact that specific receptor antagonists mostly lack efficacy.[19] CGRP antagonists and antibodies are a notable exception as they are effective for the treatment of migraine headache.[35] By contrast to the pronociceptive receptors, several *inhibitory* GPCRs are effective drug targets, including opioid receptors (μ, δ, κ), cannabinoid receptors (CB1, CB2), and serotonin receptors (5HT-1B and -D). While opioids exert broad analgesic effects, the efficacy of serotonergic antagonists is limited to migraine. Cannabinoids have been used extensively for their anxiolytic, antiemetic, and antinociceptive properties. The development of nonpsychogenic cannabinoid derivative for use in clinical pain management is an area of active study.

Receptors for Neurotrophins

Nociceptors express one of two distinct classes of neurotrophic factor receptors that are infrequently coexpressed in a specific nociceptor. Neurotrophins belong either to the NGF family expressed (NGF, brain-derived neurotrophic factor [BDNF], and neurotrophin 3 and 4) mainly in C-peptidergic fibers or the GDNF family (neurturin, artemin, and persephin) expressed in nonpeptidergic nociceptors. Neurotrophins promote the survival, growth, and maintenance of discrete populations of neurons by altering transcriptional and translational regulation of neuronal proteins, including key ion channels and GPCRs relevant for nociceptive signaling. Considering that neurotrophic factors are derived from nonneuronal tissues, they critically link tissue inflammation and nociception. Inflammation-induced surges of neurotrophic factors during tissue injury can profoundly affect nociceptor excitability and result in hyperalgesia.[36]

NGF is the most widely studied neurotrophic factor with regard to pain physiology. It is released from a host of inflammatory and resident cells upon tissue injury and binds to its high-affinity receptor TrkA on nociceptors. TrkA is a receptor tyrosine kinase able to activate multiple downstream second-messenger signaling cascades and promote nociceptor excitability via sensitization of several ion channels, including TRPV1, ASIC3, P2X3, and Na_V. The TrkA/NGF complex is also internalized within the nociceptor and transported in retrograde fashion to the cell body, where is exerts transcriptional control on numerous nociceptive pathways over the course of hours or even days. This longer-lasting action triggers the release of the neuroinflammatory peptides CGRP and SP. It also induces central sensitization via the synthesis of the centrally released neurotrophic factor BDNF.[37] In contrast to inflammatory states with elevated NGF levels, the loss of basal NGF or GDNF signaling after peripheral nerve or spinal cord injury appears to play a prominent role in the upregulation of $Na_v1.3$ that drives neuropathic pain after neuronal injury.[38] Based on the role of NGF in regulating key components of the nociceptive pathway, it has become an important drug target. Approaches sequestering NGF or antagonizing TrkA receptors are in



• **Fig. 16.2** Laminar organization of the spinal dorsal horn. The grey matter of the dorsal horn has been subdivided into 10 layers based on variations in size and neuron packing density. A, Neurons in a transverse section of the rat spinal cord have been immunostained. *Dashed lines* indicate the laminar boundaries. B, Primary afferents arborize in an orderly manner. The central terminations of the major primary afferents are shown (except proprioceptors). Aβ tactile and hair follicle afferents mainly end in laminae III-V. Aδ hair follicle afferents arborize on the border of laminae II and III. Aδ nociceptors predominantly terminate in lamina I and give some branches to laminae V and X. Peptidergic primary afferents consisting of C and Aδ nociceptors end in lamina I and the outer portion of lamina II, while nonpeptidergic C nociceptors form a band in the central part of lamina II. Inset, Illustration of the spinal cord grey matter showing the location of the dorsal horn (dashed box). (Modified from Todd AJ. Neuronal circuitry for pain processing in the dorsal horn. *Nat Rev Neurosci.* 2010;11:823–836.)

development to target chronic pain in patients with osteoarthritis, diabetic neuropathy, cancer, or back pain.[39]

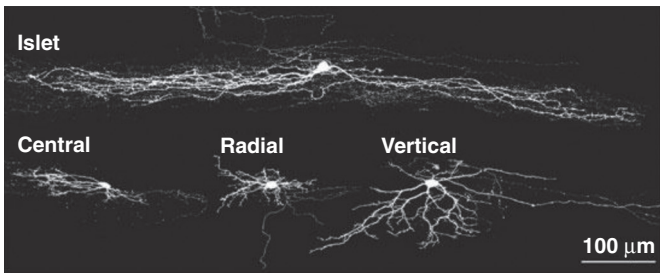
Signal Processing in the Dorsal Horn

Nociceptors transmit pain signals from the periphery to the dorsal horn of the spinal cord. The dorsal horn should not be considered a simple relay station but rather a region of complex signal processing. Incoming nociceptive signals are processed through a neuronal network built by primary nociceptive and nonnociceptive afferents, inhibitory and excitatory interneurons, and descending neurons originating in the brainstem. These neuronal circuits are ultimately linked to projection neurons, which relay nociceptive output from the dorsal horn to various supraspinal structures, including nuclei of the brainstem and the thalamus. Some processed nociceptive signals are also distributed locally within the spinal cord and underlie spinally mediated autonomic and motor responses to painful stimuli. Knowledge regarding the synaptic circuitry and function of dorsal horn neuronal structures is still quite incomplete, although some basic circuitry has been defined.

Structural Components

The spinal cord gray matter has historically been defined by 10 cyto-architecturally distinct layers (Fig. 16.2). The majority of nociceptive fibers terminate in the most superficial lamina I (the marginal layer) and lamina II (the substantia gelatinosa). The peptidergic C-fiber population that expresses TRPV1 and underlies noxious thermal responses projects to the most superficial layers of the dorsal horn (lamina I and the outer region of lamina II), whereas MRG-expressing nonpeptidergic C-fibers that mediate mechanical pain project to a deeper region within inner lamina II. This spatially distinct mapping of nociceptive modalities and specific nociceptive fibers within the dorsal horn is important to discriminate among different nociceptive modalities. Although many nociceptive Aδ fibers also terminate within lamina I, a subset project to lamina V, where they overlap with the projections of nonnociceptive low-threshold mechanosensitive Aβ and Aδ fibers within the deeper lamina (III-V). This allows for the integration of nociceptive and nonnociceptive sensory inputs.[40]

In the simplest arrangements, primary nociceptive afferents form simple axosomatic or axodendritic synapses with projection neurons, which then carry nociceptive signals forward to the brain. However, these arrangements represent only a small fraction of the neuronal network in the dorsal horn. More commonly, incoming nociceptive primary afferent fibers terminate at various excitatory and inhibitory interneurons, allowing for the complex modulation of incoming sensory information. The major neurotransmitter of excitatory interneurons is glutamate, while gamma-aminobutyric acid (GABA) and glycine are the main transmitters of inhibitory interneurons. Lamina II is enriched with interneurons, which have been studied in great detail and are classified based on morphologic criteria, as islet, central, vertical, and radial cells (Fig. 16.3). Islet and central cells tend to arborize solely within the lamina that contains their cell body. Vertical cells exhibit dendritic trees that extend over multiple laminae and thus are able to integrate multiple incoming afferent signals. Vertical cells receive afferent input from C, Aδ, and Aβ fibers, whereas islet and central cells tend to receive input only from C-fibers. Islet cells are virtually all inhibitory and invariably release GABA or glycine, whereas radial and most vertical cells are excitatory and release glutamate. Central cells can be either excitatory or inhibitory. It should be noted that the relationship between morphology and neurochemical function is not strict. Nearly 30% of interneurons do not fall into a strict morphologic category.



• **Fig. 16.3** Classification of lamina II interneurons. Confocal images of four lamina II interneurons labeled with the cell indicator neurobiotin are shown. Somatodendritic morphologic criteria allow characterizing these neurons as islet, central, radial, or vertical cells. Islet cells are inhibitory and are characterized by elongated dendritic trees, mainly spreading along the rostrocaudal axis. Central cells are similar in configuration but have much shorter dendritic trees and are either inhibitory or excitatory. Radial cells have compact dendritic trees that spread in multiple directions. Vertical cells have dendritic trees that fan out ventrally in conical shape. Radial and most vertical cells are excitatory. (Modified from Todd AJ. Neuronal circuitry for pain processing in the dorsal horn. *Nat Rev Neurosci*. 2010;11:823–836.)

Projection neurons carry nociceptive output from the dorsal horn to higher CNS structures. These efferent neurons are most densely present in lamina I, are virtually absent in interneuron-rich lamina II, and are scattered throughout the remaining laminae. Projection neurons belong to two general classes, nociceptive-specific projection neurons that exclusively transmit noxious signals, and wide-dynamic-range (WDR) projections neurons able to code for both noxious and nonnoxious signals. Nociceptive-specific projection neurons are concentrated within lamina I and are marked by the expression of the neurokinin-1 receptor (NK1R), the receptor targeted by the neuropeptide SP. SP-rich C-peptidergic nociceptors known to terminate within lamina I project to NK1R-expressing efferent neurons. While lamina III is not a significant target for nociceptive afferent fiber projections, a population of lamina III efferent neurons also expresses the NK1 receptor and receive nociceptive input by extending dendritic projections into the nociceptor-rich regions of laminae I and II. WDR projection neurons are concentrated within the deeper dorsal lamina V, where they receive inputs from nonnociceptive touch-coding Aβ fibers, nociceptive Aδ fibers, and interneurons originating in more superficial laminae. WDR neurons are unique in that they receive simultaneous input from somatic and visceral structures, allowing for the convergence of viscera-somatic signal, the neuronal substrate underlying the perception of referred pain (e.g., myocardial ischemia causing shoulder pain). Projection neurons ascend to numerous supraspinal structures, including nuclei in the brainstem and the thalamus, to mediate behavioral and emotional responses to pain.

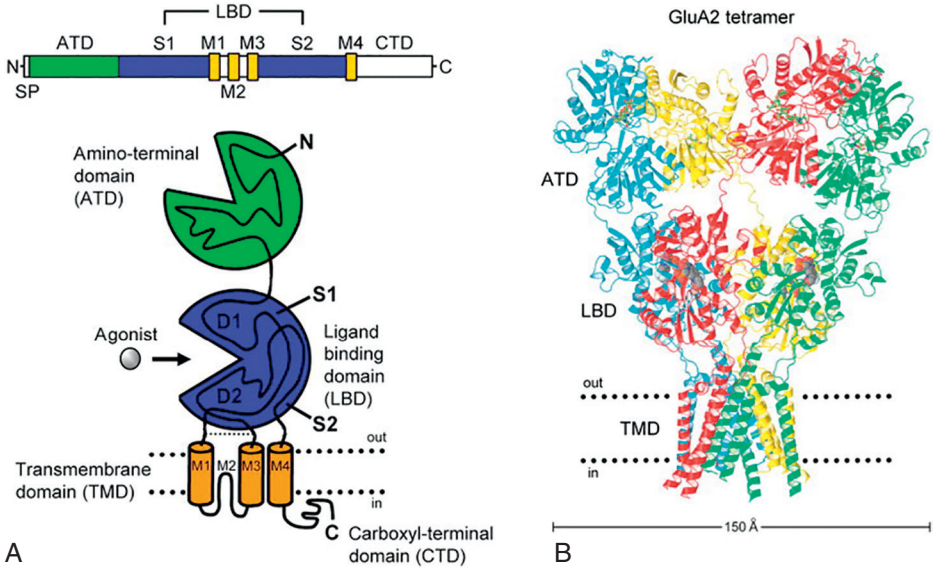
Neurochemistry

Virtually all nociceptive afferents are excitatory and signal to postsynaptic structures through the release of glutamate. Fast transmission of excitatory signals within the dorsal horn is mediated by the binding of glutamate to postsynaptic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate receptors. The AMPA and kainate receptors are glutamatergic cation-permeable ion channels that exhibit fast activation and inactivation kinetics underlying the rapid depolarization of the postsynaptic membrane. Glutamate also activates NMDA receptors, but these glutamatergic channels are activated more slowly as they are potently blocked by magnesium ions at resting hyperpolarized membrane potentials. In the setting of high-strength synaptic input, activation of AMPA and kainate receptors produces sufficient membrane depolarization to relieve the voltage-dependent magnesium ion (Mg^{2+}) block of NMDA receptors, which results in activation of these channels. NMDA receptors are permeable for calcium. The influx of calcium through NMDA receptors in the setting of high-strength synaptic signaling is a hallmark of long-term potentiation (LTP), the long-lasting use-dependent enhancement of synaptic signal transmission. LTP in the dorsal horn is one of a number of mechanisms underlying spinally mediated hyperalgesia (discussed later in this chapter) and the importance of NMDA receptors to this process is the rationale for the use of NMDA receptor antagonists like ketamine to prevent persistent pain after surgery. NMDA receptors exhibit complex pharmacologic regulation and varied subunit distributions, as further detailed in Fig. 16.4.[41]

Metabotropic glutamate receptors (mGluRs) are also present within the dorsal horn, at both presynaptic and postsynaptic terminals. Although all mGluRs are GPCRs activated by glutamate, they can be divided into subclasses based on their pharmacology and the second-messenger systems they engage. mGluR I channels are linked to the $G\alpha_q$ protein family responsible for phospholipase C activation and increased neuronal excitability. mGluR II and mGluR III channels are linked to inhibitory $G\alpha_{i/o}$ proteins and decrease neuronal excitability through inhibition of adenylyl cyclase. Consistent with these properties, mGluR I antagonists and mGluR II and III agonists produce antinociceptive effects in animal models, demonstrating a role for these channels in modulating pain.[42]

The release of glutamate from the central terminals of peripheral afferent fibers in the dorsal horn is tightly regulated as shown in Fig. 16.5. Primary afferents are able to autoregulate their activity via AMPA, kainate, and NMDA receptors expressed at their central termini. Released glutamate binds to these presynaptic receptors and inhibits further glutamate release.[43] Inhibitory interneurons act to decrease excitability through release of GABA and glycine, which bind to their receptor targets on presynaptic and postsynaptic terminals. Other modulatory receptors expressed at primary afferent central terminals include α_2-adrenergic and purinergic P2X3 receptors. Purinergic input to the central presynaptic terminal is largely the result of local adenosine triphosphate released by spinal glial cells, a means by which astrocytes and microglia increase neuronal excitability and nociceptive signaling. Presynaptic α_2-adrenergic receptors are activated by norepinephrine released from descending projection neurons, one of many targets of descending monoaminergic agents (adrenergic, dopaminergic, and serotonergic) that inhibit nociceptive signaling (discussed later in this chapter). The CB1 cannabinoid receptor and all three opioid receptor classes (μ, δ, and κ) are present at central termini of afferent fibers and oppose excitatory neurotransmitter release. Intrathecal or epidural delivery of opioids or α_2-adrenergic agonists (e.g., clonidine) is common in clinical anesthetic practice, which highlights the importance of central presynaptic receptors as analgesic targets. Intrathecal delivery of ziconotide, a synthetic peptide derivative of cone snail ω-conotoxin, selectively blocks central terminal N-type voltage-gated calcium channels, thereby inhibiting glutamate release. Ziconotide is highly efficacious but its clinical use requires intrathecal delivery. It is therefore reserved for treatment of severe refractory chronic pain conditions.[44]

The discovery of molecular markers that differentiate subclasses of interneurons in the dorsal horn has been crucial to understanding the complex neuronal network that regulates nociceptive signaling.



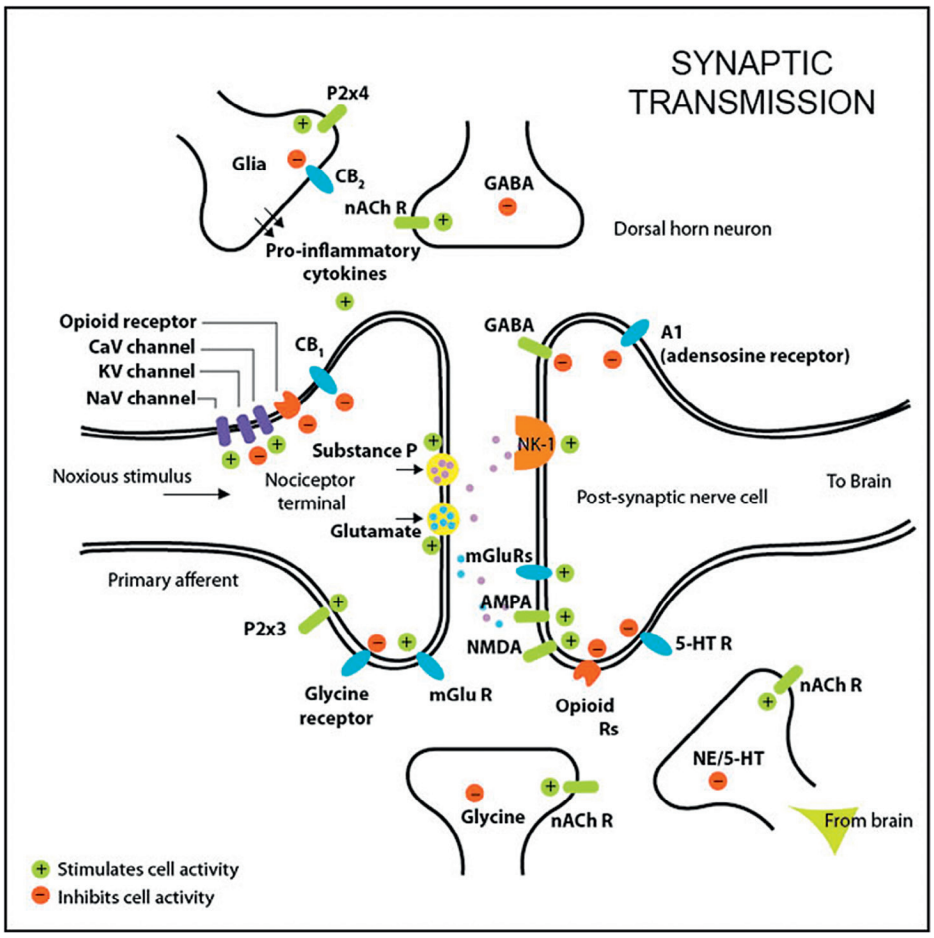
• **Fig. 16.4** Glutamate receptor structure. Glutamate receptors are formed by a tetrameric assembly of subunits. Each individual subunit contains three modular domains (A), the regulatory amino terminal domain *(ATD),* the ligand binding domain *(LBD)* responsible for binding glutamate (or glycine), and the transmembrane domain *(TMD)* that forms the ionic pore. The four subunits form a cationic channel (B) that is highly permeable to cations, including sodium ion (Na^+) and potassium (K^+) (α-amino acid-3-hydroxy-5-methyl-4-isoxazole [AMPA], kainate, and N-methyl-D-aspartate [NMDA]) and Ca^{2+} (only NMDA and some AMPA subtypes). The ATD is the binding site for numerous endogenous and exogenous channel regulators. including zinc and polyamines. In NMDA channels, two GluN1 subunits capable of binding glycine combine with two glutamate binding GluN2 subunits to form a functional channel. Although glycine does not directly open NMDA channels, it is a coagonist required for NMDA receptor activation (Modified from Traynelis SF, Wollmuth LP, McBain CJ, et al. Glutamate receptor ion channels: structure, regulation, and function. *Pharmacol Rev.* 2010;62:405–496.)

As a general rule, excitatory interneurons express the neuropeptide somatostatin, whereas inhibitory interneurons express the somatostatin receptor type 2A (SST_{2A}). The restricted distribution of somatastatin and its receptor provide a means for crosstalk between excitatory and inhibitory interneurons, an ultimately pro-nociceptive pathway due to the hyperpolarizing effect of somatastatin on SST2A expressing inhibitory interneurons. Numerous other neuropeptides exhibit functionally important and nonoverlapping expression patterns, thereby defining subclasses of interneurons. For example, neurotensin, neurokinin B, and gastrin-releasing peptide define distinct subclasses of excitatory interneurons, whereas the calcium binding proteins calretinin and protein kinase C gamma (PKCγ) are expressed less distinctively in subclasses of excitatory interneurons.[45] Inhibitory interneurons are defined by four largely nonoverlapping populations that express either neuropeptide Y, parvalbumin, neuronal nitric oxide synthase, or galanin/dynorphin.[46]

Armed with molecular markers to identify specific subpopulations of primary afferents and their targets on interneurons, attempts to map basic spinal pain circuitry are becoming increasingly informative. This is particularly true for the dorsally directed pain circuit that ultimately activates lamina I NK1R-expressing projection neurons, as shown in Fig. 16.6. Of particular interest is the recent elucidation of a circuit that underlies mechanical allodynia, the experience of pain in response to a typically nonnoxious mechanical stimulus.[47] Low-threshold mechanosensitive Aβ or Aδ fibers responsive to light touch but not to nociceptive mechanical stimuli can gain access to the nociceptive circuit through a population of excitatory interneurons that transiently express the vesicular glutamate transporter 3 (vGLUT3) during postnatal development. Under normal circumstances, inhibitory interneurons expressing parvalbumin and dynorphin prevent propagation of low-threshold A-fiber signals through the dorsally directed pain pathway. However, in the context of inflammation or nerve injury, the inhibition by parvalbumin and dynorphin inhibitory interneurons is reduced, allowing vGLUT3 excitatory interneurons to excite PKCγ, calretinin, and vertical excitatory interneurons, which ultimately drives signaling of NK1R-expressing neurons projecting to supraspinal sites. Loss of inhibitory signaling in the dorsal horn is just one mechanism underlying hyperalgesia or allodynia. Further elucidation of the complex neuronal circuits engaged in physiologic and pathologic pain conditions is an area of active investigation.

Spinal Mechanisms of Hyperalgesia and Allodynia

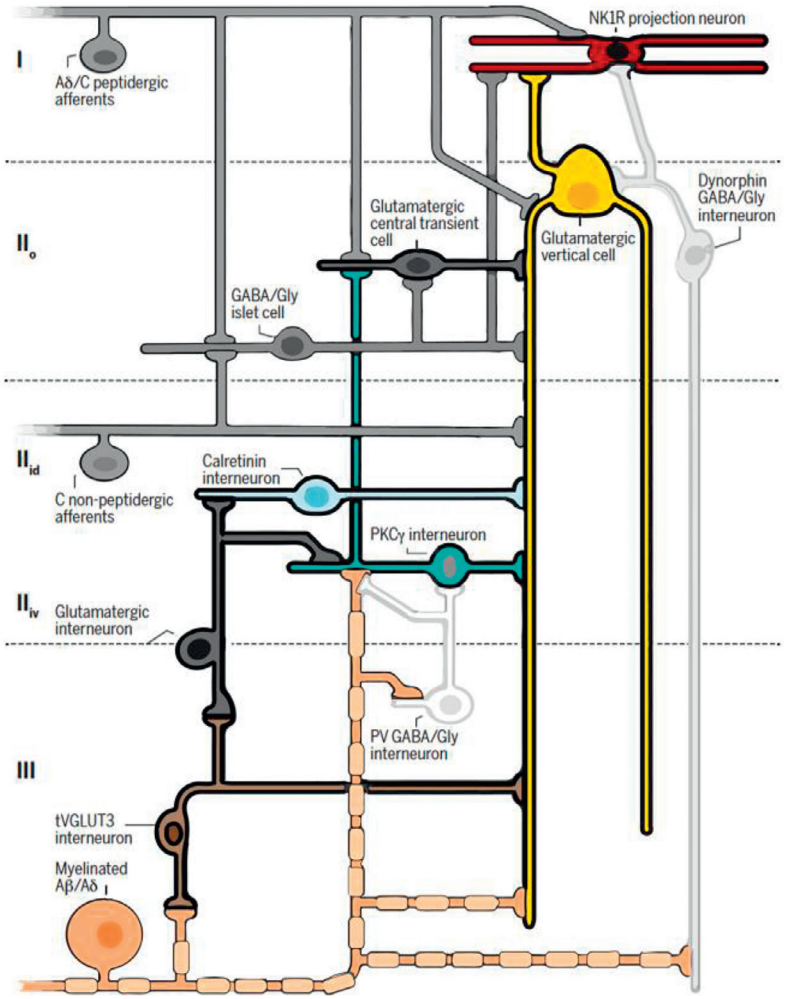
Tissue and nerve injuries are associated with the development of spontaneous pain, hyperalgesia, and allodynia. Hyperalgesia describes the occurrence of amplified pain in response to stimuli that are normally noxious. It can be visualized as a left shift of the stimulus intensity versus pain response relationship (Fig. 16.7). Allodynia describes the occurrence of pain in response to stimuli that are normally nonnoxious (e.g., light touch). These phenomena can be explained by several spinal mechanisms, including LTP, loss of inhibitory control, gain in excitatory function, and alterations in the properties of low-threshold mechanoreceptive Aβ fibers.[48,49]



• **Fig. 16.5** Dorsal horn synaptic transmission. Arrangement of a dorsal horn synapse between a primary afferent and a projection neuron are shown. The central terminal of the primary afferent contains glutamate and substance P. Release of glutamate results in activation of *AMPA* (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate (KA) receptors and depolarization of the postsynaptic membrane via fast sodium ion (Na^+) influx. Release of substance P acts synergistically via metabotropic neurokinin 1 receptors (NK1) that on activation, upregulate second-messenger systems, including cyclic adenosine monophosphate and protein kinase A. Sustained synaptic input can depolarize the postsynaptic membrane sufficiently to activate the voltage-gated N-methyl-D-aspartate (NMDA) receptor. Activation of NMDA receptors is associated with long-term enhancement of synaptic transmission (long-term potentiation), which might underlie hyperalgesic states. Released glutamate also binds to metabotropic glutamate receptors *(mGluRs)* to modulate postsynaptic responsiveness. The synapse is also under control of other neuronal structures, including inhibitory interneurons and descending projection neurons. Release of *GABA* (gamma-aminobutyric acid) or glycine from interneurons enhances influx of chloride ion *(Cl^-),* which hyperpolarizes presynaptic or postsynaptic membranes and inhibits activity. Descending projection neurons modulate activity via release of serotonin and norepinephrine *(NE)* to bind to 5-hydroxytryptamine *(5-HT)* or α-adrenergic receptors. *A1,* Adenosine Receptor; CB_1, CB_2, cannabanoid receptor 1 and 2; Ca_V channel, Ca_V: Voltage gated calcium channel; *nAChR,* nicotinic acetylcholine receptors; K_V channel, Voltage gated potassium channel; Na_V channel, Voltage gated sodium channel; *R,* receptor. (Modified from Kennedy J.D. Neuropathic pain: molecular complexity underlies continuing unmet medical need. *J Med Chem.* 2007;50:2547–2556.)

LTP is triggered by high-strength synaptic input and can be described as the long-term enhancement of synaptic signal transmission (synaptic plasticity). In the dorsal horn, induction of LTP at synapses between C-fibers and NK1R projection neurons is an important driver of hyperalgesia.[50] Elevated postsynaptic intracellular calcium is the signal that ultimately causes LTP. A diverse set of postsynaptic channels and receptors contributes to this process. Postsynaptic ion channels, including NMDA receptors, T-type voltage-gated calcium channels, and calcium-permeable AMPA receptor subtypes (lacking the GluR2 subunit) facilitate cellular calcium influx when activated. By contrast, activated mGluRs and neurokinin-1 receptors facilitate release of calcium from intracellular stores via second-messenger signals. Ultimately, increased postsynaptic intracellular calcium levels activate multiple Ca^{2+}-dependent signaling pathways, which amplifies nociceptive signal transmission.

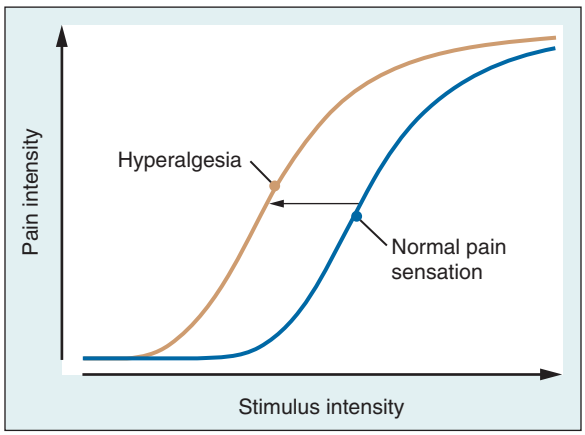
As described previously, loss of inhibitory signaling can contribute to the miscoding of tactile input as pain (allodynia). This is due to loss of regular inhibitory control over excitatory interneurons that link low-threshold mechanoreceptive Aβ afferents to lamina



• **Fig. 16.6** Chronic pain and the dorsal horn neuronal circuit. Peripheral Aδ and substance P–positive C nociceptors enter lamina I and synapse with excitatory vertical and central interneurons and NK1R projection neurons. Mechanosensitive C fibers expressing MRG enter the dorsal horn in lamina II and project to excitatory vertical cells. Incoming peripheral nociceptors also make synaptic connections with inhibitory islet interneurons to modulate circuit activity. Innocuous Aβ and Aδ fibers *(orange)* project to lamina III and are not normally integrated into the pain circuitry. In chronic pain with mechanical allodynia, loss of PV and dynorphin inhibitory interneuron activity *(shaded)* allows normally innocuous Aβ and Aδ fiber input to activate neurokinin-1 receptor *(NK1R)* projection neurons *(red)*, through a key synaptic connection with transient vesicular glutamate transporter 3 *(tVGLUT3)*-expressing interneurons *(brown)*. vGLUT3 interneurons synapse with glutamatergic vertical cells and also activate a network of protein kinase C gamma *(PKCγ)* and calretinin excitatory interneurons to link innocuous touch with NK1R pain signaling and produce mechanical allodynia. *GABA*, gamma-aminobutyric acid; *Gly*, glycine; *MRG*, Mas-related G-protein coupled receptor. (Modified from Peirs C, Seal RP. Neural circuits for pain: recent advances and current views. *Science*. 2016;354:578–584.)

I NK1R projection neurons. Tissue injury–induced release of BDNF at the central termini of primary afferents is another mechanism resulting in disruption of regular inhibitory control. BDNF binds to interneurons that express the TrkB receptor, which decreases the activity of the potassium-chloride exchanger 2 (KCC2) expressed in TrkB$^+$ interneurons. Reduced KCC2 activity leads to increased intracellular chloride concentrations, decreasing the driving force for chloride through inhibitory GABAergic and glycinergic chloride channels. This leads to dampening of inhibitory control over spinal nociceptive circuits.[47] Recent animal studies have demonstrated that viral transfer of the *KCC2* gene into the dorsal horn of animals with experimentally induced neuropathic pain eliminates hyperalgesia, raising the possibility of KCC2 as a gene therapy target for treatment in intractable neuropathic pain.[51]

Similar to loss of inhibitory function, gain in excitatory function can also facilitate nociceptive signal transmission. In experimental models of neuropathic pain, the expression or activity of a number of potassium channels, including voltage-gated (K_v),



• **Fig. 16.7** Hyperalgesia. Sensitization of peripheral nociceptors results in hyperalgesia that is characterized by a left shift of the nociceptive stimulus versus pain response relationship. This is reflected clinically by an increased sensitivity to painful stimuli.

calcium-activated (BK), and K_{2P} channels is decreased. K^+ channels are critical for hyperpolarizing cell membranes and loss of activity allows for more pronounced neuronal depolarization and excitation.[52]

Finally, aberrant connectivity of low-threshold mechanoreceptive Aβ afferents to nociceptive pathways can contribute to tactile allodynia. Sprouting of Aβ fibers from terminals in the deeper dorsal horn to superficial laminae I and II has been observed after nerve injury.[53] Aβ-fibers can also undergo a phenotypic switch in response to injury and start synthesizing SP, which then can activate NRK1 receptors of nociceptive lamina I projection neurons.[54]

Supraspinal Structures

To reach the brain, nociceptive projection fibers exiting the spinal dorsal horn form two major ascending tracts, the spinothalamic tract (STT) and the spinomedullary tract (SMT), defined by their terminations in either the thalamus or brainstem. Thalamic or medullary subcortical waypoints serve important functions in the autonomic and descending modulation of nociceptive information and also route the ascending signals to appropriate limbic and cortical brain regions. An overview of the major supraspinal pathways underlying the nociceptive system is provided in Fig. 16.8.

There are multiple interconnected cortical and subcortical brain regions that contribute to the cognitive experience of pain. In a landmark study, Melzack asked patients to describe their experience of pain and grouped the descriptive responses into sensory, affective, and cognitive categories.[55] The sensory component refers to the ability to discriminate stimuli according to their intensity, location, and temporal relationship. The affective component relates to typically negative hedonic aspects of pain, and the cognitive component represents the evaluation of pain in terms of past experiences, environmental context, and overall significance. These three basic domains of pain remain extremely useful conventions to functionally group the supraspinal processing of nociception and synthesis of the pain experience. In this section, we identify the brain regions that process and modulate these distinct domains of pain and examine their connectivity.

Thalamus

The thalamus is the key neuroanatomical structure linking ascending nociceptive input from the STT to several cortical areas that serve distinct functions. The importance of the thalamus in nociceptive signaling is clinically highlighted by the Dejerine-Roussy syndrome that can develop in patients who sustain a thalamic stroke. The syndrome is initially characterized by the development of contralateral paresthesia and numbness that progress to intractable centrally mediated allodynia or dysesthesia.[56] The lateral thalamic nuclei play an important role in the sensory and discriminative coding of pain, while the medial thalamus exerts control over affective and motivational aspects of pain.

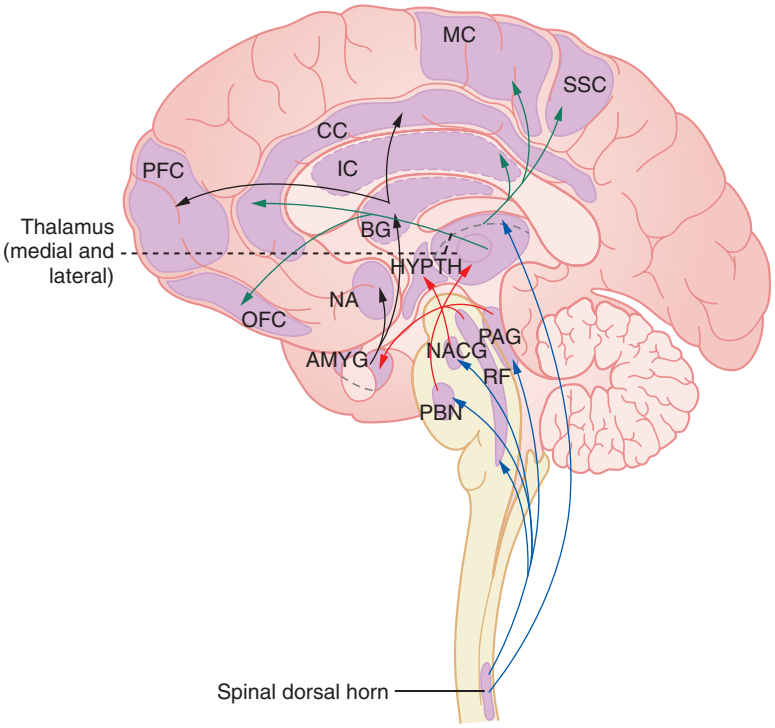
The ventral posterior nuclei (VPN) of the lateral thalamus are the target of nearly all afferent fibers carrying somatosensory information through the dorsal column via the STT, including pain, innocuous touch and proprioception. The VPN play a key role in linking ascending nociceptive input to the somatosensory cortex (SI and SII), which encodes sensory and discriminative components of pain. Afferent signals relayed via the VPN to cortical structures remain somatotopically organized to facilitate the precise topographic mapping of both innocuous and noxious sensory input from various body locations. The ventral posterior medial (VPM) nucleus receives input from the trigeminal nerve, while the most lateral portions of the ventral posterior lateral (VPL) nucleus encodes input from the feet. VPN neurons receive input from densely innervated, "high-resolution" receptive fields and encode a wide range of afferent load (signal strength) to precisely gauge sensory discriminative information. The majority of VP neurons that process nociceptive signals, which constitute about 10% of VP neurons, receive input from WDR projection neurons originating in lamina V of the dorsal horn.

A subset of spinal lamina I nociceptive projection neurons also target the lateral thalamus but innervate an alternate region, namely the posterior ventral medial nucleus (VMpo). Unlike VP nuclei, the VMpo is targeted exclusively by nociceptive fibers and projects to an alternative cortical structure, the insula. The insular cortex plays a critical role in interception, which is the awareness of the physiologic state of one's own body. The insula projects to the prefrontal cortex, anterior cingulate cortex, amygdala, hippocampus, and SII somatosensory cortex, a neuronal network merging nociceptive input with attention, memory, and emotion. Finally, the ventral lateral nucleus also receives input from STT fibers and projects to the motor cortex, likely contributing to integration of nociceptive sensory signals with the motor system.

Unlike the nuclei of the lateral thalamus, the nuclei of the medial thalamus process nociceptive input relevant for affective and motivational aspects of pain. The medial dorsal nucleus receives input from nociceptive neurons located in lamina 1 of the spinal dorsal horn and projects to the anterior cingulate cortex, a key structure regulating affective and behavioral aspects of pain. The nucleus submedius also receives input from lamina I but projects to the ventral lateral orbital cortex, a structure regulating descending antinociceptive control via the periaqueductal gray (PAG).[57]

Brainstem

Neurons in laminae I, V, and VII of the spinal dorsal horn and the trigeminal nucleus build the SMT that runs in parallel with the STT. These paired neuronal projections enable differential supraspinal modulation of spinal nociceptive input.[58] The SMT terminates at three major brainstem sites—namely, the reticular formation, the



• **Fig. 16.8** Major components of the nociceptive system. An overview of the major anatomic components that process nociceptive information from the periphery to cortical structures. Myelinated and nonmyelinated primary afferent fibers provide nociceptive input to the spinal cord. Major nociceptive projections target the brainstem (spinomedullary tract) and the thalamus (spinothalamic tract). Projections from the brainstem reach the medial thalamus, hypothalamus, and amygdala; these structures play a predominant role in regulating autonomic, neuroendocrine, and emotional states. The lateral thalamus projects to the somatosensory cortex, which decodes sensory-discriminative aspects of pain. The amygdala pairs noxious input with affective content. Its critical integrative function is underlined by connections to various cortical and subcortical structures modulating emotional and behavioral processes. *AMYG,* amygdala; *BG,* Basal Ganglia; *CC,* Cingulate Cortex; *HYPTH,* hypothalamus; *IC,* Insular Cortex; *MC,* Motor Cortex; *NA,* Nucleus Accumbens; *NACG,* Noradrenergic Cell Group; *OFC,* Olfactory Cortex; *PAG,* Periaqueductal Grey; *PBN,* Parabrachial Nucleus; *PFC,* Prefrontal Cortex; *RF,* Reticular Formation; *SSC,* Somatosensory Cortex.

noradrenergic cell group, including the locus coeruleus and the parabrachial nucleus (PBN), and the PAG.[57] Unlike STT fibers that project contralaterally, neurons of the SMT can terminate bilaterally, which is compatible with the predominant homeostatic role of the brainstem, including the modulation of autonomic, neuroendocrine, and emotional responses to nociceptive input. More specifically, the noradrenergic cell group projects to the hypothalamus and modulates the neuroendocrine and autonomic response to pain, while the PBN projects to the amygdala and modulates the affective response to pain. The PBN also projects to the VMpo of the thalamus, which allows for the integration of SMT and STT signals at the insular cortex, the ultimate projection target of the VMpo.

A significant fraction of SMT projection neurons from spinal lamina I express NK1R and receive input from peripheral afferent peptidergic C-fibers.[59] SMT input to the reticular formation, locus coeruleus, and PAG trigger reciprocal input back to the spinal dorsal horn, a key neuronal network by which SMT signals exert descending nociceptive control.

Basal Ganglia

The basal ganglia (BG) are interconnected nuclei located in the white matter of both hemispheres. They include the caudate nucleus, the putamen, the nucleus accumbens, the globus pallidus, the substantia nigra, and the subthalamic nucleus. The primary role of the BG involves coordination of motor function, but they are also thought to be involved in the processing of pain. This is exemplified by clinical disorders that feature both movement disturbance and chronic pain. For example, patients with Parkinson disease, caused by loss of the dopaminergic neurons in the substantia nigra of the BG, exhibit a high incidence of chronic pain, which improves after deep brain stimulation of the globus pallidus or pallidotomy. Complex regional pain syndrome, a disorder often caused by a relatively minor traumatic insult to a peripheral nerve, frequently manifests with movement disorders including dystonia or tremor, which suggests recruitment of the BG in nociceptive signaling associated with complex regional pain syndrome. These clinical observations are bolstered by functional imaging studies documenting nociceptive signaling activity in the BG in acute and chronic pain states.[60]

The BG provide reciprocal efferent output to several brain structures, including the anterior cingulate cortex, the prefrontal cortex, the amygdala, and the thalamus. This reciprocal neuronal network likely modulates affective and cognitive components of pain. Unlike the somatotopically organized signals arising from the thalamus, the BG do not encode detailed sensory discriminative

information. However, the BG provide graded encoding of noxious inputs to mount appropriate behavioral and emotional responses.

Pharmacologic evidence further suggests a role of the BG in nociceptive processing. Microinjections of opioids, dopamine, or GABA into BG regions, including the substantia nigra, the putamen, and the globus pallidus, alter nociceptive signaling. Similarly, reward circuitries in the nucleus accumbens are an experimental target for exploiting antinociceptive effects of opioids, dopamine, and cholinergic receptor agonists. Despite these experimental findings, the overall significance of the BG for mediating antinociceptive effects by commonly used pain therapeutics remains unknown.[61]

Amygdala

The amygdala is part of the limbic system and plays a sentinel role in pairing sensory input with emotional significance. In the domain of pain, the amygdala matches nociceptive signals with affective content and serves as the neuronal interface for the reciprocal relationship between pain and an affective state or an affective disorder.[62] The amygdala receives nociceptive information from the spinal cord, brainstem, thalamus, and several cortical regions (insular, anterior cingulate, and association areas). The lateral (LA) nucleus of the amygdala serves as the initial site of signal convergence and connects with the basolateral (BLA) nucleus, forming a LA/BLA network that attaches emotional significance to sensory input. Most signals within the LA/BLA network are transmitted to the central nucleus, the major center from which efferent signals exit the amygdala. Nociceptive signaling converges in the laterocapsular portion of the central nucleus (CeLC), a region labeled the "nociceptive amygdala" because of its high content of nociceptive neurons. Although much of the neuronal input to the CeLC arrives from the LA/BLA network, the previously described SMT neurons that traverse the parabrachial nucleus also terminate in the CeLC. From the central nucleus, efferent projections build widespread connections with the forebrain, thalamus, hypothalamus, and brainstem areas (e.g., the PAG), thereby regulating autonomic, neuroendocrine, and somatosensory functions related to emotional experiences. Although most of the output from the amygdala arises from the central nuclei, the BLA nucleus provides important projections to the medial prefrontal cortex, a brain region important for value-based decision making, including risk assessment and strategic planning. This neuronal connection has been implicated in the impaired decision-making skills of patients with persistent pain.[63]

Qualitatively negative *and* positive emotions are known to modify neuronal activity in the amygdala, such that affect can play a dual role in either amplifying or mollifying the perception of pain.[61] The biochemistry underlying nociceptive processing in the amygdala features a large number of signaling molecules and receptor subtypes, and remains incompletely understood. The most prominent receptor systems include ionotropic (NMDA and AMPA) and metabotropic glutamate receptors, $GABA_A$ receptors, and neuropeptides, including CGRP, corticotropin-releasing factor, and neuropeptide S (NPS).[64]

Cortical Structures

Interconnected and functionally distinct cortical areas process nociceptive signals to build a complex neuronal network underlying the experience of pain (Fig. 16.9). Cortical areas can be organized according to their relative contribution to the sensory, affective, and cognitive components of pain.[55] The primary sensory cortex (SI) is the major neuroanatomic region underlying the sensory component of pain, responsible for encoding the location, time course, and intensity of pain stimuli. The secondary somatosensory cortex (SII) also receives sensory discriminative input but plays a complementary role to the SI by integrating sensory discriminative information with nociceptive information processed by the limbic system. This is accomplished through reciprocal connections between SII and its neuroanatomic neighbor, the insular cortex. The insula receives limbic cortical input from brain regions that modulate affective components of pain (e.g., anterior cingulate and entorhinal cortex) and thus the SII and insular cortex act as a neuronal interface between sensory and affective components of pain. Functional magnetic resonance imaging studies documenting concurrent activation of the posterior insula and SII regions in individuals experiencing distress from acute social rejection (a recent unwanted breakup) further highlight the importance of this neuronal interface.[65]

The anterior insula appears to play a role in modulating early aspects of pain including its anticipation. Connections between the anterior insula and memory centers in the entorhinal cortex of the temporal lobe facilitate this process, as anticipation relies on recall of past experiences.[66] The entorhinal cortex and hippocampus are part of the cortical network that stores and retrieves sensory information and participates in elaborating the experience of pain based on emotional state, expectations, and past experiences.

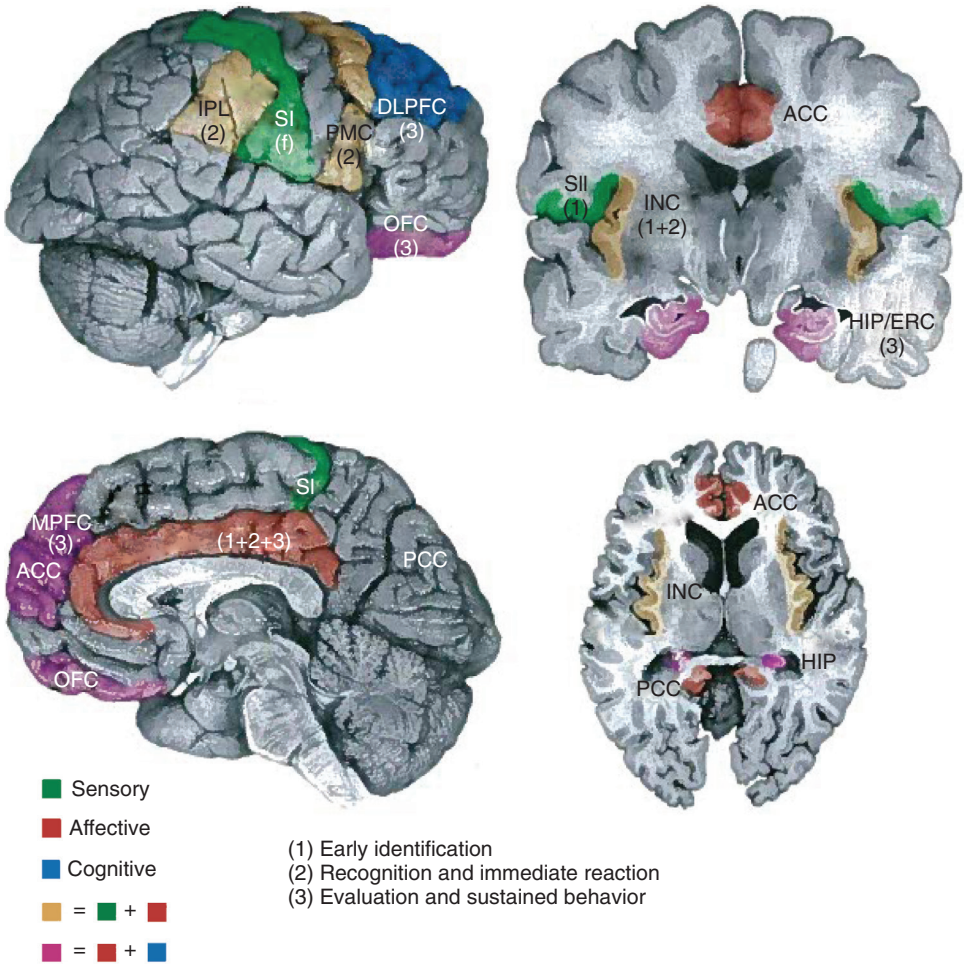
The cognitive component of pain derives from a number of neuroanatomic regions that are heavily interconnected. The dorsolateral prefrontal cortex (DLPFC) is involved in shifting attention between tasks and can thereby modulate attention to pain. This brain region has been implicated in mediating the placebo effect, as subjects given placebo treatments during noxious stimulation show functional magnetic resonance imaging activity in the dorsolateral prefrontal cortex that correlates with the magnitude of the placebo response.[67] The orbitofrontal cortex plays a critical role in the integration of emotional and sensory inputs to produce reward-seeking and punishment-aversive behaviors. Along similar lines, the medial prefrontal cortex engages in longer-term evaluation of pain and the development of cognitive adaptive strategies.

The anterior cingulate cortex (ACC) is a key relay linking brain pathways responsible for processing affective and cognitive components of pain. Whereas the ventral ACC is strongly interconnected with the amygdala and the insular cortex, the dorsal ACC forms connections with neighboring regions of the prefrontal cortex (see Fig. 16.9). The ACC exerts central modulatory control of interconnected brain regions to mediate goal-directed and reward-based cognitive behaviors. The ACC also interacts with the premotor cortex to assist in the orchestration of motor responses to pain.

Descending Pathways

The significance of descending control mechanisms in modulating pain was first recognized and incorporated into a neurophysiologic model called the "gate theory" by Melzack and Wall in 1965.[68] According to their theory, a gate built by primary afferent fibers, interneurons, and neurons descending from supraspinal sites controls and modulates nociceptive traffic. Although many of the neurophysiologic details turned out to be incorrect, the model was a conceptual breakthrough.

As proposed by Melzack and Wall, spinal synaptic transmission is modulated by descending inhibitory and excitatory pathways



• **Fig. 16.9** Cortical network regulating nociceptive processes. An anatomic and functional overview of the interconnected cortical areas of the pain processing network is shown. Areas are coded numerically and by color to indicate their temporal and functional role. For more details see text. *ACC*, Anterior cingulate cortex; *DLPFC*, dorsolateral prefrontal cortex; *ERC*, entorhinal cortex; *HIP*, hippocampus; *INC*, insular cortex; *IPL*, inferior parietal lobule; *MPFC,* medial prefrontal cortex; *OFC*; orbitofrontal cortex; *PCC*, posterior cingulate cortex; *PMC*, premotor cortex; *SI*, primary sensory cortex; *SII*, secondary somatosensory cortex. (Modified from Casey KL, Tran TD. Cortical mechanisms mediating acute and chronic pain in humans. *Handb Clin Neurol*. 2006;81:159–177.)

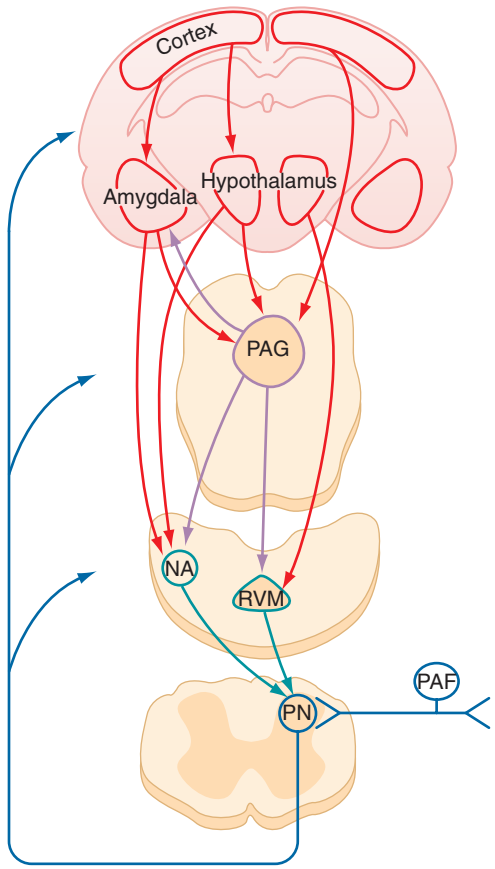
that originate in the brainstem. Descending control mechanisms either attenuate or augment nociceptive and nonnociceptive signaling contingent on overall biologic needs. For example, if a fight-or-flight response is most meaningful in the context of an injury, descending control mechanisms typically dampen spinal nociceptive processes. Alternatively, if a "guarding-and-heeling" behavior is most beneficial, descending facilitatory pathways can enhance spinal nociceptive processes (e.g., central sensitization and hyperalgesia associated with tissue injury).[69] Accordingly, the balance between inhibitory and facilitatory descending influences is highly dynamic and changes over the course of acute and chronic injuries.[70] Supraspinal modulation of nociception is integrated with related alterations in autonomic and motor responses elicited by painful stimuli, allowing for meaningful and teleologically useful responses to injury and pain.[71]

In the absence of a painful stimulus, descending inhibitory control mechanisms are dominant and dampen spinal nociceptive signaling. Upon initiation of an acute nociceptive input, inhibitory control is enhanced at all heterotopic body regions distant from the site of injury to direct attention toward the affected body site. This neuronal regulation is called *diffuse noxious inhibitory control,* which equates with the observation that pain at one body site ameliorates pain at another distant site.

The neuroanatomic architecture of the descending control system reflects its multidimensional role (Fig. 16.10). Central to the system is the rostral ventral medulla (RVM), which integrates input from several supraspinal structures and acts as the major relay between supraspinal and spinal sites. In accordance with the dynamic demands on descending inhibitory and facilitating circuits, many neuroanatomic sites exerting such control are capable of mounting both inhibitory and excitatory responses.

Structural Components

The best studied components of descending control pathways include the PAG and the RVM, regions rich in opioid receptors



• **Fig. 16.10** Major structural components exerting descending nociceptive control. The interrelationship of major neuroanatomical components exerting descending nociceptive control is shown. The periaqueductal gray *(PAG)* and rostral ventral medulla *(RVM)* are strategically located to integrate input from cerebral structures and relay processed information to the spinal dorsal horn. Noradrenergic pontine and medullary nuclei *(NA)* constitute a second important structure directly projecting to the dorsal horn. Presynaptic and postsynaptic mechanisms modulate nociceptive information that is transmitted from primary afferents *(PAF)* to spinal projection neurons *(PN)*. Alternatively, indirect actions are exerted via inhibition or excitation of spinal interneurons. Cortical areas, the amygdala, and the hypothalamus are among the cerebral structures exerting top-down control. These structures are relevant for the modulation of pain by stress, emotion, and cognition. (Modified from Millan MJ. Descending control of pain. *Prog Neurobiol*. 2002;66:355–474.)

and critical for mediating endogenous analgesia.[72,73] Numerous supraspinal regions help tune descending control signals and most act via the PAG-RVM axis. However, some descending signals are transmitted via a second important descending modulatory complex built by pontine and medullary noradrenergic nuclei including the locus coeruleus. Additionally, certain brain regions (including the parabrachial nucleus and dorsal reticular nucleus) bypass these centers and project directly to the dorsal horn.

The PAG receives input from multiple supraspinal structures, including the prefrontal cortex, hypothalamus, and amygdala. This top-down control of the PAG-RVM axis is important for the modulation of pain by cognitive influences, emotional factors, and stress. For example, projections from the amygdala and hypothalamus are relevant for hypoalgesia associated with intense fear or stress. Similarly, projections from the prefrontal cortex that are relayed via the cingulate cortex have been implicated in placebo-mediated analgesia.[74] The PAG projects to the RVM, which in turn projects profusely via the dorsolateral funiculus to superficial and deep laminae in the dorsal horn. Flow of information is bidirectional, with the PAG and RVM both receiving direct input from the spinal dorsal horn.

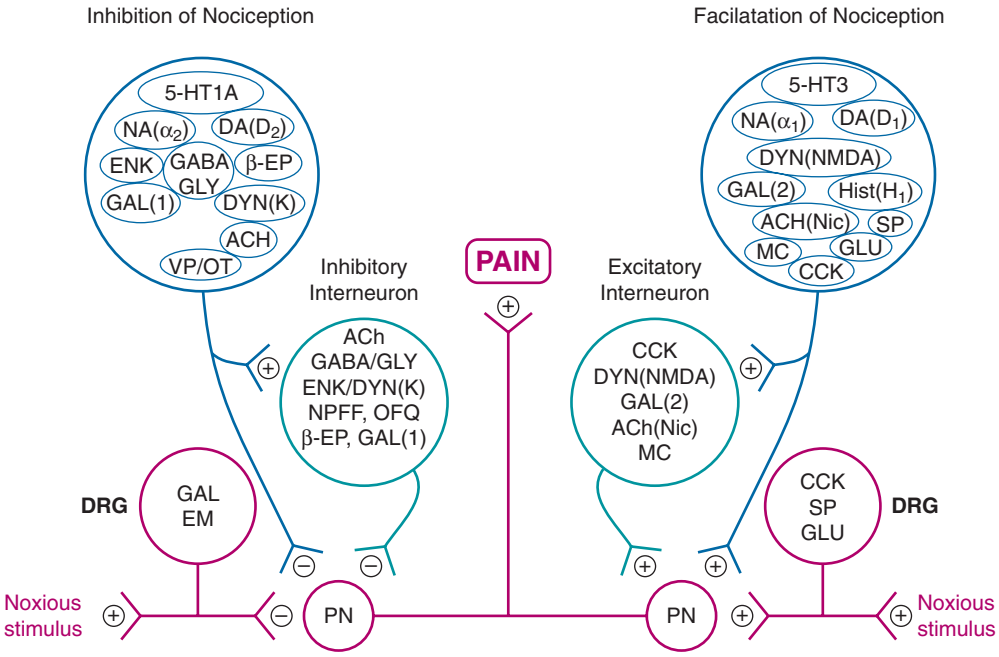
The RVM includes the nucleus raphe magnus and the adjacent nucleus reticularis gigantocellularis and paragigantocellularis lateralis. It is functionally defined as the pontomedullary area in which electrical stimulation and microinjection of opioids produce behavioral analgesia, and is a central site of action for many analgesic drug classes, including opioids, cyclooxygenase inhibitors, and cannabinoids. However, the RVM is not solely an analgesic center as it is able to exert both inhibitory and facilitating influences on spinal nociceptive processes. This is exemplified by the finding that injection of the neuropeptides cholecystokinin or neurotensin into the RVM leads to exaggerated pain responses. The dual role of the RVM in descending control is enabled by distinct neurons called ON and OFF cells. OFF cells exert inhibitory nociceptive control, whereas ON cells exert facilitating effects.[75] The PAG-RVM axis is tonically active and the balance between ON- and OFF-cell activity determines the *nociceptive response threshold* of the spinal dorsal horn.

Output from the PAG-RVM axis exerts spinal control via numerous mechanisms, including presynaptic inhibition of primary afferents, postsynaptic inhibition of spinal projection neurons, inhibition or activation of dorsal horn interneurons, or nonsynaptic release of mediators that diffuse within the dorsal horn (volume transmission). Chronically increased RVM ON-cell activity is one mechanism implicated in the pronociceptive states associated with inflammation or nerve injury.

In addition to the PAG-RVM axis, pontine and medullary noradrenergic nuclei also send projections to the dorsal horn (via the ventrolateral funiculus) and are the primary source of spinal noradrenaline.[76] Pontine and medullary centers receive input from the amygdala, hypothalamus, and the parabrachial nucleus and are also a target for some PAG output fibers, providing integration between the two descending systems. The noradrenergic system exhibits low tonic activity, which becomes significantly enhanced with tissue or nerve injury. This might explain why spinally administered α-adrenergic agonists are particularly efficacious for attenuating pain associated with significant inflammation or nerve injury. The noradrenergic pathway also plays an important role in mediating stress-induced analgesia.

Neurochemistry

The biochemistry of descending control mechanisms is complex, involving numerous neurochemical mediators, multiple sites of action, and a variety of receptor target subtypes. Fig. 16.11 provides an overview of relevant neurotransmitters and their predominant action on spinal nociceptive processes. In accordance with the dual inhibitory or facilitating role of descending control mechanisms, many neurotransmitters can exert either pronociceptive or antinociceptive effects, depending on their site of release within the descending control circuitry and the expressed receptor subtypes. For example, histamine elicits pronociceptive effects when administered spinally but exerts antinociceptive effects at supraspinal sites by enhancing descending inhibitory control. In this section, we focus on the major signaling systems involved in descending modulation, which include the monoaminergic (serotonin, norepinephrine, and dopamine) and opioidergic systems. The reader should note that many additional transmitters participate in



• **Fig. 16.11** Major biochemical components exerting descending nociceptive control. Descending control of spinal nociceptive processes is exerted by multiple neurotransmitters. Transmitters contributing to inhibition of nociceptive signaling are depicted on the left, whereas transmitters enhancing nociceptive signaling are depicted on the right. This physical separation serves didactic reasons and has no anatomic foundation. Transmitters are contained in descending pathways, in inhibitory or excitatory interneurons, and in primary afferent terminals. Only principal transmitter locations are shown (subtypes are indicated in parentheses). *ACH*, Acetylcholine; *β-EP*, β-endorphin; *CCK*, cholecystokinin; *DA*, dopamine; *DRG*, dorsal root ganglion; *DYN*, dynorphin; *EM*, endomorphin; *ENK*, enkephalin; *GABA*, gamma-hydroxybutyric acid; *GAL*, galanin; *GLU*, glutamate; *GLY*, glycine; *Hist*, histamine; *5-HT*, serotonin; *MC*, melanocortin; *NA*, noradrenaline; *NMDA*, *N*-methyl-D-aspartate; *NPFF*, neuropeptide FF; *OFQ*, orphanin FQ; *OT*, oxytocin; *PN*, projection neuron; *SP*, substance P; *VP*, vasopressin. (Modified from Millan MJ. Descending control of pain. *Prog Neurobiol*. 2002;66:355–474.)

descending control mechanisms, including glutamate, glycine, GABA, histamine, vasopressin, oxytocin, cholecystokinin, neurotensin, galanin, SP, and cannabinoids.[71]

Descending monoaminergic projection neurons are the only source of spinally released serotonin, norepinephrine, and dopamine. Serotonin has long been implicated as an important mediator in the PAG-RVM axis by studies demonstrating that electrical stimulation of either the PAG or the RVM triggers serotonin release in the spinal cord. Interestingly, serotonin plays a role in both descending inhibition and facilitation by its differential effects on 5-HT receptor subtypes. Studies with 5-HT antagonists demonstrate that 5-HT_{2A} and 5-HT_3 facilitate nociception, whereas 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, and 5-HT_7 exert inhibitory effects. Despite the importance of serotoninergic mechanisms in the PAG-RVM axis, serotonergic neurons in the RVM (approximately 20% of all neurons) are not part of the ON- or OFF-cell population relevant for opioidergic descending inhibitory control. The interplay between ON and OFF cells and serotonergic RVM neurons remains incompletely understood.

Descending projection neurons from pontine and medullary noradrenergic nuclei provide another important modulatory input to the spinal dorsal horn via the release of norepinephrine. As is the case with serotonin, norepinephrine can exert pronociceptive or antinociceptive effects depending on expressed adrenergic receptor subtype. Activation of spinal α_1-adrenergic receptors augment pronociceptive signaling, whereas activation of spinal α_2-adrenergic receptors produces antinociceptive effects. Numerous drug classes used for the treatment of neuropathic pain, including tricyclic antidepressants (amitriptyline), gabapentanoids (neurontin), and serotonin and norepinephrine reuptake inhibitors (duloxetine), may exert their clinical efficacy by enhancing spinal noradrenergic signaling.[77] Spinal release of dopamine is another mechanisms either facilitating or inhibiting nociceptive signaling via activation of dopamine D1 or D2 receptors.

The μ-, δ-, and κ-opioid receptors are differentially stimulated by exogenous agents and their endogenous ligands β-endorphin (μ), endomorphin (μ), enkephalin (μ, δ), and dynorphin (κ). Endomorphin and enkephalin elicit antinociceptive effects at both spinal and supraspinal sites. By contrast, dynorphin exerts dual actions. Activation of spinal κ receptors attenuates nociceptive signaling, whereas supraspinal activation of κ receptors exhibit both pronociceptive and antinociceptive influences on descending control mechanisms. In addition, dynorphin activates non-opioidergic spinal receptors, including NMDA glutamate receptors, which produces a pronociceptive effect.

Emerging Developments

Biased μ-Opioid Receptor Agonists

Although opioids are the cornerstone therapeutics for the treatment of moderate to severe pain, their clinical utility is hampered by

side effects, including nausea, constipation, sedation, and respiratory depression, as well as physical dependence and addiction. The use of partial opioid agonists such as buprenorphine has mitigated some of these concerns in the treatment of chronic pain. However, partial opioid agonists are by definition suboptimal analgesics. Similarly, the use of peripherally restricted opioid antagonists like alvimopan have been helpful in blocking some systemic adverse effects of opioids (most notably constipation), they do not counteract centrally mediated respiratory depression, the most detrimental opioid-related side effect. An ideal opioid agonist would be a highly efficacious analgesic agent devoid of serious adverse effects. Recent advances in our understanding of the signaling pathways downstream of the μ-opioid receptor have laid the groundwork for the design of such an agent.

While the analgesic effects of μ-opioid receptor agonists are mediated by $G\alpha_i$ G-protein signaling pathways that include activation of the G-protein–gated potassium channel (GIRK) and inhibition of adenylyl cyclase many adverse effects are mediated by an alternative pathway involving the molecule β-arrestin 2. Activation of the μ-opioid receptor by classical agonists leads to receptor phosphorylation, a signal that triggers binding of β-arrestin 2 to the μ-opioid receptor and the resultant activation of downstream signaling pathways mediating adverse effects such as constipation and respiratory depression. In an important experiment, increased analgesic efficacy was demonstrated in β-arrestin 2 knockout mice treated with morphine, while constipation and respiratory depression were diminished and antinociceptive tolerance was absent after prolonged exposure.[78,79] These findings provided the impetus for the subsequent development of a novel class of opioid agonists called biased agonists. Biased agonists activate the $G\alpha_i$ cascade but do not promote receptor phosphorylation and subsequent binding of β-arrestin 2. An example of a biased agonist is oliceridine (TRV130), developed by Trevena Inc. In a double-blind, placebo-controlled study in healthy human male volunteers, oliceridine was more efficacious in alleviating experimental pain than morphine and caused less nausea and respiratory depression.[80] Oliceridine is now in phase III clinical trials for the treatment of moderate to severe pain after abdominoplasty.

Recent structural-based docking of candidate molecules to the μ-opioid receptor crystal structure has identified PZM21, an agonist that exhibits a greater degree of bias for the $G\alpha_i$ cascade over β-arrestin 2 recruitment compared with TRV130. In preclinical studies in mice, PMZ21 outperformed both TRV130 and morphine with respect to its analgesic efficacy and the severity of observable adverse effects including respiratory depression and constipation.[81] While biased opioid agonists hold significant potential to outperform traditional opioids, they do not eliminate all relevant opioid adverse effects. Most notably, biased opioid agonists exert similar sedative effects as traditional agonists. This underscores the need for alternative, non-opiate–based strategies for the treatment of pain.

$Na_V1.7$, a Novel Drug Target at the Peripheral Nociceptor

Since the discovery that $Na_V1.7$ sodium channel mutations underlie the inherited disease congenital insensitivity to pain, attempts to develop selective $Na_V1.7$ antagonists for the treatment of acute and chronic pain have been a major focus in analgesic drug development. Individuals with congenital insensitivity to pain lack any pain sensation, while they perfectly sense touch, temperature, and pressure.[25] This remarkable clinical presentation and the restricted expression of $Na_V1.7$ on sensory neurons raised the possibility that selective blockade of $Na_V1.7$ could produce complete analgesia while preserving sensory and motor function. Such prospect is exciting as traditional nonselective sodium channel blockers including currently available local anesthetics block all sensory and motor fibers, which limits their utility as analgesic agents.

Efforts to develop clinically useful $Na_V1.7$ antagonists have proven difficult because of a number of technical challenges. One example relates to the early development of the peptide toxin ProTx-II, isolated from the Peruvian green velvet tarantula.[82] ProTx-II binds with picomolar affinity and approximately 100-fold higher specificity to $Na_V1.7$ compared with other Na_V channels. Despite these promising properties, intravenous or intrathecal administration of ProTx-II did not alleviate acute or chronic inflammatory pain in rodent models, which was due to its poor penetrance into the perineural sheath. Overcoming poor penetrance required such high doses of ProTx-II that sodium channels expressed in cardiac ($Na_v1.5$) and skeletal muscle ($Na_v1.4$ and $Na_v1.6$) were concomitantly blocked. This resulted in significant toxicity. Although diligent studies have demonstrated some analgesic efficacy of ProTx-II, the therapeutic window of this novel compound is quite small.

A second technical challenge concerns the specificity of novel $Na_V1.7$ blocking agents. An example is vixotrigine, a drug that only poorly discriminates between Na_V subtypes, currently in phase II/III clinical trials for the treatment of lumbosacral radiculopathy. Similarly, a group of aryl-sulfonamide–based agents under development by several pharmaceutical companies show only modest selectivity for $Na_V1.7$ (about 10-fold).[83,84]

A number of recent advances in the realm of $Na_v1.7$-specific antagonist development have been encouraging. A structure/activity optimization study generated a ProTX-II toxin (JNJ63955918) with increased binding specificity at $Na_V1.7$ and a promising antinociceptive profile in animal models.[85] An alternative naturally derived $Na_V1.7$ blocking toxin (Ssm6a) retrieved from the venom of the Chinese redheaded centipede exhibits greater than 600-fold specificity for $Na_V1.7$ over other Nav subtypes. Intraperitoneal injection of Ssm6a was nontoxic and produced antinociceptive effects similar to morphine in a rodent model of thermal and chemically induced pain.[86] Another promising strategy is the development of a state-specific monoclonal antibody (SVmab1) that preferentially binds to the closed $Na_V1.7$ channel and prevents its opening and activation. SVmab1 binding to $Na_V1.7$ is highly specific. Intrathecal injection of SVmAb1 exerts relevant antinociceptive effects in animal models.[87]

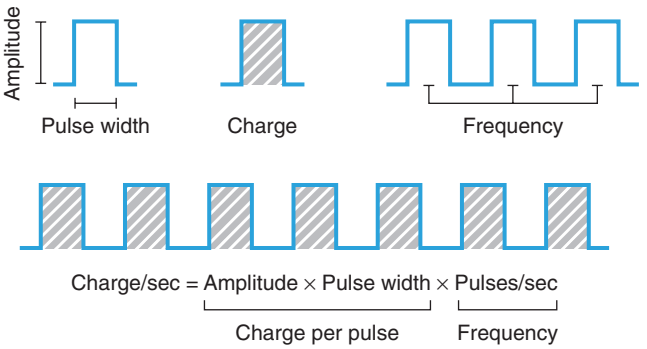
Neuromodulation

The analgesic effects of electrical neuromodulation of the dorsal spinal cord was first demonstrated in 1967.[88] Since that time, the use of spinal cord stimulators for the treatment of refractory chronic pain has become increasingly popular. Indications for the use of spinal cord stimulators include a wide range of chronic pain conditions, including failed back surgery, radiculopathies, complex regional pain syndrome, angina pectoris, and pancreatitis. In traditional systems, stimulating electrodes delivering impulses to the spinal cord at 40 to 60 Hz are placed into the epidural space to align with the somatic distributions of a patient's pain. The basic concept is to generate a paresthesia that alters the processing of nociceptive inputs and masks the perception of pain. An example supporting the efficacy of this approach for select chronic pain conditions is a study in patients with neuropathic radicular pain after failed back surgery. Spinal cord stimulation was superior to conventional medical management and decreased pain by more

than 50% in about half of studied patients along with their improved satisfaction and physical function.[89] However, 25% to 50% of patients experience complications, including lead migration or fracture, pulse generator failure, loss of paresthesia, and infection, resulting in efficacy loss and the need for corrective procedures. Additionally, some patients find the paresthesias produced by traditional spinal cord stimulators uncomfortable with positional changes, limiting their utility or necessitating discontinuation of use.

Recent advances, including high-frequency (10,000 Hz) and selective dorsal root ganglion stimulation protocols, have overcome some of the traditional limitations, shown improved efficacy, and expanded the applicability of spinal cord stimulators.[90,91] A major breakthrough in the field enabling the development of high-frequency stimulators was the realization that analgesic efficacy was not dependent on evoking paresthesias but on delivering an adequate electrical charge to the spinal cord. As shown in Fig. 16.12, the electrical charge delivered per second is defined by pulse width × amplitude × frequency.[92] In contrasting to traditional spinal cord stimulators, high-frequency/low-amplitude protocols deliver electrical impulses that do not trigger action potentials and consequently, do not evoke paresthesias. Additional advantages of high-frequency stimulation protocols include simplified lead placement (as high-frequency stimulating electrodes do not need to overlap with the somatic region in which the patient experiences pain) and reduced risk of device failure resulting from lead migration.

Historically, clinical studies examining the efficacy of spinal cord stimulation were hampered by an inability to properly blind study participants because of evoked paresthesias. However, proper blinding is more readily achieved in studies examining the efficacy of high-frequency spinal cord stimulators as paresthesias are absent. Such studies are ongoing to better understand how to configure pulse width, amplitude, frequency, and burst pattern to maximize analgesic efficacy. Pairing advanced algorithms with mechanistic studies shedding light on the poorly understood molecular and neuronal processes affected by spinal cord stimulation hold significant promise to further advance the utility of this neuromodulatory strategy.



• **Fig. 16.12** Neuromodulatory stimulation parameters. Pulse width and pulse height (amplitude) contribute to the energy (charge) per pulse. By altering either the charge per pulse or the frequency of pulses, the total delivered charge per second can be controlled. (Modified from Miller JP, Eldabe S, Buchser E, et al. Parameters of spinal cord stimulation and their role in electrical charge delivery: a review. *Neuromodulation* 2016;19:373–384.

Key Points

- The transduction of pain signals in peripheral nociceptors is a complex process involving a mosaic of receptors and ion channels that are directly or indirectly activated by multiple ligands.
- Nociception-related signal transduction is highly interactive, redundant, tissue-specific, time-dependent, and contingent on the type of injury. This complexity poses significant challenges—and opportunities—for identifying novel and broadly effective analgesic compounds.
- Most effective might be compounds targeting structures conveying information from multiple nociceptive processes, such as certain ion channels. Analgesic strategies might also be tailored toward specific indications such as pain conditions arising from certain types of tissue or injury.
- Anatomic and neurochemical details of dorsal horn neurocircuits processing nociceptive signals are still quite limited. Recent studies shed light on the synaptic connections between primary afferents, interneurons, and projection neurons, as well as on the receptors and ion channels involved.
- Comprehensive functional characterization of neuronal networks in the dorsal horn explains available analgesic therapies and should facilitate identification of novel analgesic drug targets.
- Descending control mechanisms regulating nociceptive traffic at the level of the dorsal horn involve both pronociceptive and antinociceptive effects of some neurotransmitters contingent on release site and available receptor subtypes. Interactions and redundancies of different neurotransmitter systems are subject to dynamic modulation by tissue or nerve injury.
- Descending control mechanisms are not restricted to nociception but also involve projections to spinal sites exerting autonomic and motor control. The simultaneous actions on nociceptive, autonomic, and motor processes raise the possibility that compounds targeting this system might cause significant adverse effects.
- Multitarget strategies, including agonist and antagonist approaches simultaneously exploiting mechanisms of descending inhibition and facilitation, are promising for achieving clinically effective analgesia without exerting unacceptable side effects.
- The top-down control of spinal and supraspinal nociceptive processes also provides a rational for nonpharmacologic approaches, including behavioral therapies or brain stimulation techniques (e.g., magnetic or electrical).
- A complex network of cortical and subcortical structures is required to process and integrate pain at the conscious and subconscious level. Pain elicits integrated autonomic, endocrine, and motor responses at the subconscious level, as well as sensory, affective, and cognitive responses at the conscious level that are normally tailored to protection of the body, but can be pathologically activated in chronic pain states.
- Appreciation of the multifaceted nature of pain is critical to providing the multidimensional approaches required for its successful alleviation.

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Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain*. 1975;1:277–299. Melzack systematically analyzed the language used by patients to describe their pain, established the multidimensional character of pain, and built the basis for the definition of pain along the three experiential axes of sensation, affect, and cognition. An important consequence of this work was the insight that the multifaceted nature of pain requires a multidimensional approach for treatment including pharmacologic, behavioral, and cognitive strategies. (Ref. 55).

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17

Intravenous Opioid Agonists and Antagonists

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CHAPTER OUTLINE

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- Mechanism

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- Pharmacodynamics
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- Special Populations
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  - *Morphine*
  - *Methadone*
  - *Fentanyl*
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Historical Perspective

The white "latex" juice of the poppy plant is the source of more than 20 opiate alkaloids. *Opium,* a word derived from the Greek word for juice, is the brownish residue observed after the poppy's juice is desiccated. *Opiate* is the older term classically used in pharmacology to mean a drug derived from opium. *Opioid,* a more modern term, is used to designate all substances, both natural and synthetic, that bind to opioid receptors (including antagonists).

Opium and its derivatives have been known for millennia to relieve pain. Laudanum, or tincture of opium (a mixture of opium and alcohol), was used as early as the 1600s as an analgesic. Sir Christopher Wren, the acclaimed Englishman of arts and letters, was the first to inject opium into a living organism using a hollow feather quill as the delivery system in 1659. Sertürner, a German pharmacist, isolated morphine from opium in 1805. Having initially called morphine "somniferum" (after the Latin botanical name *Papaver somniferum*— the poppy that brings sleep), the name was later changed to *morphine,* alluding to Morpheus, the Greek god of dreams.

Opium and its derivatives have sometimes been the basis of international conflict. The Opium Wars of the 1800s were fought between China and the Western powers in large part in response to Western importation of opium into China. The opium houses of 19th century China, where opium was freely available for sale and consumption, illustrated the frightening societal consequences of large-scale drug abuse. Recognition of these problems in the United States eventually culminated in the Harrison Narcotics Tax Act of 1914 that criminalized narcotic possession. The prevalence of addiction clinics and drug-related violence and crime in modern society emphasizes the chronicity of the societal difficulties that stem from this drug class and others. The ongoing opioid abuse epidemic in the United States is a recent reflection of the complexity and recalcitrance of the problems associated with opioid addiction despite nearly a century of research devoted to the conundrum.

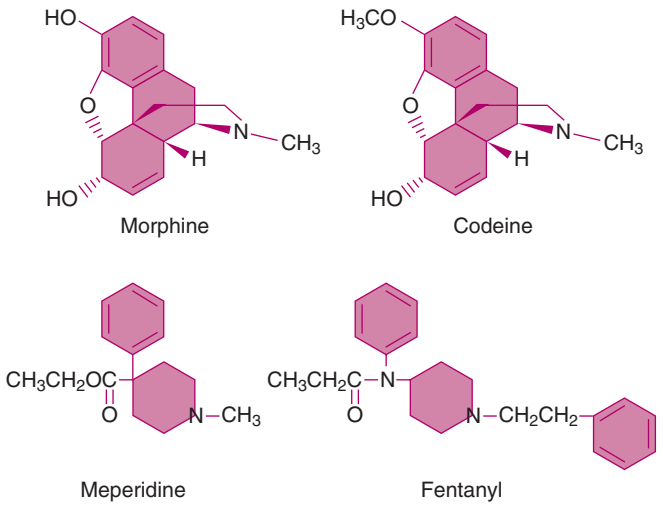
Despite their abuse potential, opioids play an indispensable role in the practice of medicine, especially anesthesiology, critical care, and pain management. A sound understanding of opioid pharmacology, including both basic science and clinical aspects, is critical for the safe and effective use of these important drugs. This chapter focuses almost exclusively on intravenous opioids used perioperatively.

Abstract

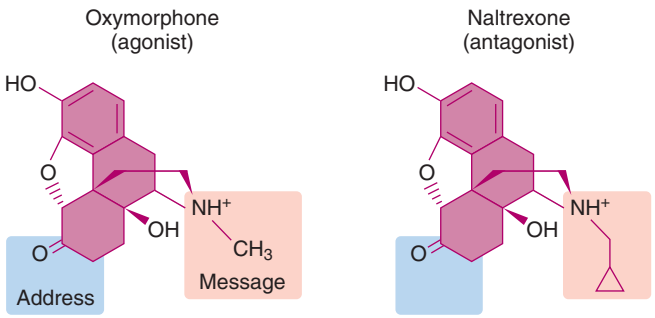
This chapter reviews the basic and clinical pharmacology of intravenous opioids in the context of anesthesiology and perioperative medicine. Unique features of commonly used opioids are discussed and the principles underlying rational drug selection and administration are outlined. Emerging developments of contermporary interest are briefly examined.

Keywords

Opioids
morphine
fentanyl
remifentanil
codeine
naloxone
naltrexone
biased opioids
opioid epidemic



• **Fig. 17.1** The molecular structures of morphine, codeine, meperidine and fentanyl. Note that codeine is a simple modification of morphine (as are many other opiates); fentanyl and its congeners are more complex modifications of meperidine, a phenylpeperidine derivative.



• **Fig. 17.2** Structures of prototypical opioid ligands (i.e., oxymorphone and naltrexone) highlighting regions involved in conferring selectivity (i.e., addressing) shaded in *blue*, and efficacy (i.e., messaging) shaded in *pink*. (Adapted with permission from Huang W, Manglik A, Venkatakrishnan AJ, et al. Structural insights into micro-opioid receptor activation. *Nature* 2015;524:315–321.)

Basic Pharmacology

Structure-Activity

The opioids of clinical interest in anesthesiology share many structural features. Morphine, the principal active compound derived from opium, is a benzylisoquinoline alkaloid; the benzylisoquinoline structural backbone is present in many important naturally occurring drugs including papaverine, tubocurarine, and morphine. Morphine's benzylisoquinoline based structure is shown in Fig. 17.1. Many commonly used semisynthetic opioids are created by simple modification of the morphine molecule. Codeine, for example, is the 3-methyl derivative of morphine. Similarly, hydromorphone, hydrocodone, and oxycodone are also synthesized by relatively simple modifications of morphine. More complex alteration of the morphine molecular skeleton results in mixed agonist-antagonists such as nalbuphine and even pure competitive antagonists such as naloxone.

Some of the morphine derivatives have chiral centers and thus are typically synthesized as racemic mixtures of two enantiomers; only the levorotatory enantiomer is significantly active at the opioid receptor. The naturally occurring, stereospecific enzymatic machinery in the poppy plant produces morphine only in the levorotatory form.

The fentanyl series of opioids are chemically related to meperidine. Meperidine is the first completely synthetic opioid and can be regarded as the prototype clinical phenylpiperidine. As shown in Fig. 17.1, fentanyl is a simple modification of the basic phenylpiperidine structure found within meperidine; the other commonly used fentanyl congeners such as alfentanil and sufentanil are somewhat more complex versions of the same phenylpiperidine skeleton. As these drugs have no chiral center and therefore exist in a single form, the pharmacologic complexities of stereochemistry do not apply.[1]

As shown in Fig. 17.2, evidence from x-ray crystallography investigations and other techniques suggests that distinct parts of the opioid agonist or antagonist molecule confer specificity (i.e., addressing) and efficacy (i.e., messaging).[2] Agonists and antagonists have similar addressing segments in their structures; their action at the receptor is determined by the messaging portion of the molecule (see Chapter 1).

As outlined in Table 17.1, opioids share many physicochemical features in common, although some individual drugs have unique features. In general, opioids are highly lipid soluble, weak bases that are highly protein bound and largely ionized (protonated) at physiologic pH. Opioid physicochemical properties are thought to have important implications on their clinical behavior. For example, highly lipid soluble, relatively unbound, un-ionized molecules such as alfentanil and remifentanil have a shorter latency to peak effect after bolus injection presumably because of their more rapid transfer across cellular membranes.

Mechanism

Opioids produce their main pharmacologic effects by interacting with opioid receptors. Investigation of opioid receptor genetics, structure, and function over the past several decades has greatly enhanced understanding of opioid pharmacology.

Cloning of the opioid receptors, first accomplished in rodents and subsequently in humans, was an important first step in eventually elucidating opioid receptor structure and function. Using the rat μ-opioid receptor complementary DNA sequence as a guide, investigators were able to identify its human homolog, describing the amino acid sequence, strong binding affinity for an endogenous opioid ligand (i.e., enkephalin) and chromosomal assignment (i.e., chromosome 6).[3]

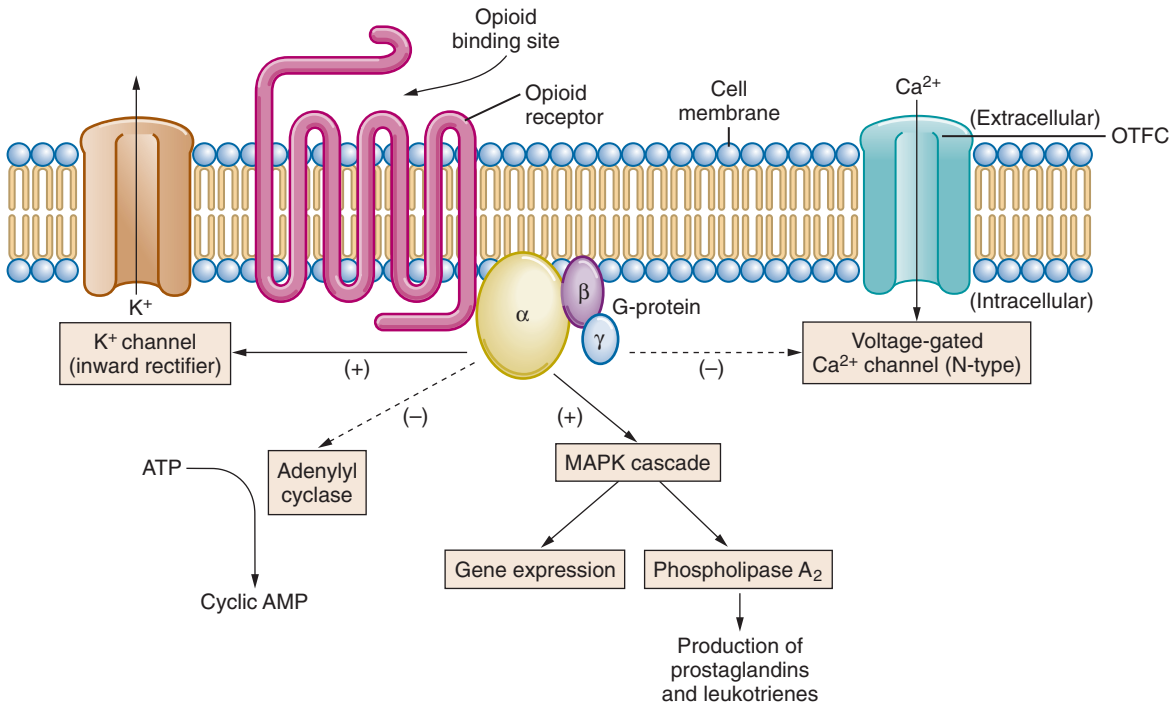
Opioid receptors are typical of the G-protein–coupled family of receptors widely found in biology (e.g., β-adrenergic, dopaminergic, among others). Like other G-protein–coupled receptors, opioid receptors have seven transmembrane portions, intracellular and extracellular loops, an extracellular N-terminus, and an intracellular C-terminus. There is considerable amino acid sequence homology among the various opioid receptor subtypes; most of the nonhomologous sequences occur in the extracellular portions of the protein. The extracellular domains are thought to be important in discriminating between the various receptor ligands.

Expression of cloned opioid receptors in cultured cells has facilitated analysis of the intracellular signal transduction mechanisms activated by opioid receptors.[4] As shown in Fig. 17.3, binding

TABLE 17.1 Selected Opioid Physicochemical and Pharmacokinetic Parameters

Parameter	Morphine	Fentanyl	Sufentanil	Alfentanil	Remifentanil
pKa	8.0	8.4	8.0	6.5	7.1
% Un-ionized at pH 7.4	23	<10	20	90	67?
Octanol-H_2O partition coefficient	1.4	813	1778	145	17.9
% Bound to plasma protein	20-40	84	93	92	80
Diffusible fraction (%)	16.8	1.5	1.6	8.0	13.3
Vdc (L/kg)	0.1-0.4	0.4-1.0	0.2	1.1-0.3	0.06-0.08
Vdss (L/kg)	3-5	3-5	2.5-3.0	0.4-1.0	0.2-0.3
Clearance (mL/min per kilogram)	15-30	10	10-15	4-9	30-40
Hepatic extraction ratio	0.6-0.8	0.8-1.0	0.7-0.9	0.3-0.5	NA

NA, Not applicable; *pKa,* acid dissociation constant; *Vdc,* volume of distribution of central compartment; *Vdss,* volume of distribution at steady state.
From Bailey PL. Egan TD. Stanley TH. Intravenous opioid anesthetics. In: Miller RD, ed. *Anesthesia.* 5th ed. New York: Churchill Livingstone; 2000:312.



• **Fig. 17.3** Opioid mechanisms of action. The endogenous ligand or drug binds to the opioid receptor and activates the G protein (three distinct protein subunits), resulting in multiple effects that are primarily inhibitory. The activities of adenylate cyclase and the voltage-dependent calcium ion *(Ca^{2+})* channels are depressed. The inwardly rectifying potassium ion *(K^+)* channels and mitogen-activated protein kinase *(MAPK)* cascade are activated. *AMP,* Adenosine monophosphate; *ATP,* adenosine triphosphate.

of opioid agonists with the receptors leads to activation of the G-protein (actually three distinct G-protein subunits), producing effects that are primarily inhibitory (decreased cyclic adenosine monophosphate production, decreased calcium ion influx, increased potassium ion efflux); these effects ultimately culminate in membrane hyperpolarization of the cell and reduction of neuronal excitability.

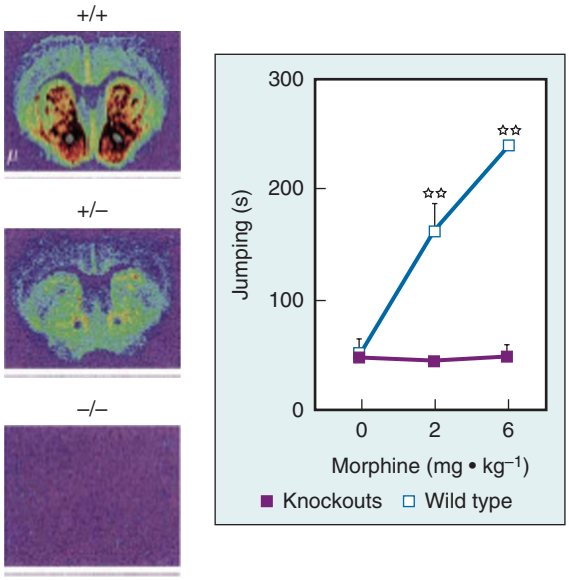
Three classical opioid receptors have been identified using molecular biology techniques: μ, κ, and δ receptors. These receptors are also described by an international nomenclature scheme as MOP, KOP, and DOP (mu, kappa, or delta opioid peptide). The μ-opioid receptor is commonly abbreviated in the scientific literature as MOR. More recently, a fourth opioid receptor, ORL1 (also known as NOP), has also been identified, although its function

TABLE 17.2 Summary of Selected Features of Opioid Receptors

	TYPE OF RECEPTOR		
	Mu (μ)	**Delta (δ)**	**Kappa (K)**
Tissue bioassay[a]	Guinea pig ileum	Mouse vas deferens	Rabbit vas deferens
Endogenous ligand	β-Endorphin Endomorphin	Leu-enkephalin Met-enkephalin	Dynorphin
Agonist prototype	Morphine Fentanyl	Deltorphin	Buprenorphine Pentazocine
Antagonist prototype	Naloxone	Naloxone	Naloxone
Supraspinal analgesia	Yes	Yes	Yes
Spinal anagesia	Yes	Yes	Yes
Respiratory depression	Yes	No	No
Gastrointestinal effects	Yes	No	Yes
Sedation	Yes	No	Yes

[a]Traditional experimental method to assess opioid receptor activity in vivo.

From Bailey PL, Egan TD, Stanley TH. Intravenous opioid anesthetics. In: Miller RD, ed. *Anesthesia.* 5th ed. New York: Churchill Livingstone; 2000:312.



• **Fig. 17.4** Receptor distribution and response to morphine in μ-opioid receptor knockout mice. On the left side are computer-enhanced color autoradiograms of coronal sections of mice brain demonstrating diminished μ-opioid receptors in the heterozygotes (+/–) and complete absence of μ-opioid receptors in the homozygotes (–/–) compared with wild-type littermates (+/+). The right panel shows the antinociceptive responses to morphine administration during the "hot-plate" test in μ-opioid receptor knockouts (–/–) and their wild-type littermates. The knockouts are represented by the *solid squares*; the wild-type are the *open squares*. The two *stars* indicate a highly significant difference between groups ($P < 0.01$). The knockouts exhibit no analgesic response to morphine. (Adapted with permission from Matthes HW, Maldonado R, Simonin F, et al. Loss of morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the mu-opioid-receptor gene. *Nature.* 1996;383:819–823.)

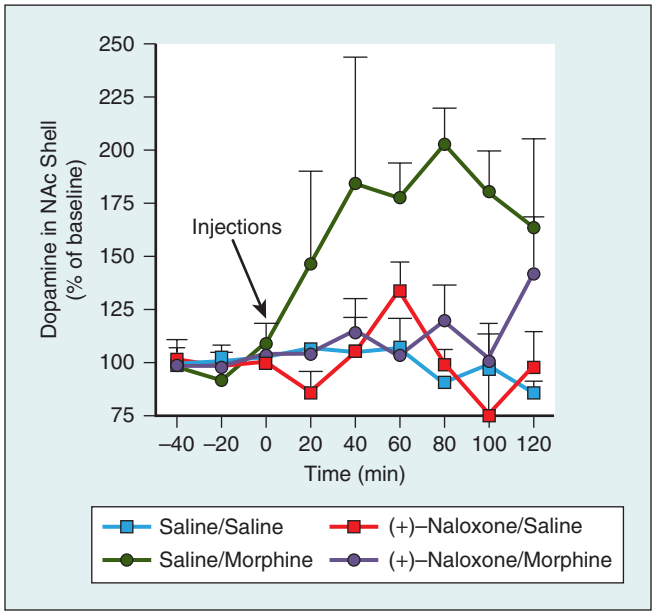
appears to be quite different from the classical opioid receptors. As shown in Table 17.2, each of these opioid receptors has a commonly used experimental bioassay, associated endogenous ligand(s), a set of agonists and antagonists, and a spectrum of physiologic effects when the receptor is activated. Although the existence of opioid receptor subtypes (e.g., μ-1, μ-2, and so on) has been proposed, it is not clear from molecular biology techniques that distinct genes code for them. Posttranscriptional and post-translational modification of opioid receptors certainly occurs and could be responsible for conflicting data regarding opioid receptor subtypes. It is well known, for example, that the messenger RNA coding for the human μ-receptor undergoes alternative splicing, resulting in subtle differences in the final receptor.[5]

As confirmed by autoradiographic and binding techniques, opioid receptors are widely expressed in the central nervous system (CNS). In the spinal cord, they are mainly localized to the substantia gelatinosa of the dorsal horn. In the brain, they are especially concentrated in the periaqueductal gray region, the limbic system, area postrema, thalamus, and cerebral cortex. Opioid receptors are also found outside the CNS in gastrointestinal, biliary, and other tissues. Action by agonists at these peripheral receptors accounts for some of the adverse effects of opioids such as constipation.

In accordance with the wide distribution of opioid receptors in the CNS, opioids appear to exert their therapeutic effects at multiple sites. Opioid agonism at the level of the spinal cord inhibits the release of substance P from primary sensory neurons in the dorsal horn, mitigating the transfer of painful sensations to the brain. Opioid actions in the brainstem modulate nociceptive transmission in the dorsal horn of the spinal cord through descending inhibitory pathways. Opioids are also thought to change the affective response to pain through actions in the forebrain; decerebration prevents opioid analgesic efficacy in rats.[6] Furthermore, functional magnetic resonance imaging studies in humans have demonstrated that morphine induces signal activity in reward structures in the brain.[7]

Studies in genetically altered mice have yielded important information about opioid receptor function. In μ-opioid receptor knockout mice, morphine induced analgesia, reward effect, and withdrawal effect are absent.[8,9] Fig. 17.4 demonstrates the simple power of these site-directed mutagenesis techniques, confirming how MOR knockout mice exhibit no analgesic effect to morphine as assessed by measuring the time to jumping off a hot plate. Importantly, MOR knockout mice also fail to exhibit respiratory depression in response to morphine.[10] Confirming the importance of opioid receptor ligands in the biology of "endogenous" analgesia systems, β-endorphin knockout mice fail to show naloxone-reversible, stress-induced analgesia but maintain a normal analgesic response to morphine.[11]

Opioid addiction, as with many addictive drugs and practices, involves dopamine-related reward mechanisms. As shown in Fig. 17.5, microdialysis techniques in a rodent model demonstrate an opioid-induced, naloxone-reversible increase in dopamine levels in the nucleus accumbens region, a brain area known to be important in addiction (see Chapter 12).[12] Toll-like receptors (i.e., TLR4), a receptor system involved in the identification of foreign molecules and the inflammatory response in the CNS, may play a role in the



• **Fig. 17.5** Rodent model evidence of opioid-induced, naloxone-reversible increases in dopamine in the nucleus accumbens region. (+)-Naloxone suppresses morphine-induced dopamine release in the nucleus accumbens shell. In vivo microdialysis was used to test the effect of (+)-naloxone (1 mg/kg subcutaneous) on morphine (6 mg/kg subcutaneous)-induced increases in extracellular dopamine in the nucleus accumbens shell. After three baseline samples, rats received saline solution plus saline solution, saline solution plus morphine, (+)-naloxone plus saline solution, or (+)-naloxone plus morphine. Repeated-measures analysis of variance revealed a significant effect of treatment condition ($P < 0.01$). Data are means per group ± standard error of the mean; $n = 4$/group. (Adapted with permission from Hutchinson MR, Northcutt AL, Hiranita T, et al. Opioid activation of toll-like receptor 4 contributes to drug reinforcement. *J Neurosci.* 2012;32:11187–11200.)

Main metabolic pathway
Minor metabolic pathway
! Metabolic pathway leading to active metabolite formation

Opioid	CYP2B6	CYP2C19	CYP2D6	CYP3A4	UGT	Sulfotransferase	Esterases
Codeine			!	■	■		
Tramadol	■		!	■	□		
Tapentadol		□			■	□	
Oxycodone			!	■			
Morphine					!		
Hydromorphone					■		
Meperidine				!			■
Methadone	■	□	□	■			
Buprenorphine				□	□		
Fentanyl				■			
Sufentanil				■			
Alfentanil				■			
Remifentanil							■

• **Fig. 17.6** Major enzymes involved in opioid drug metabolism. *CYP,* Cytochrome P450; *UGT,* uridine 50-diphosphate glucuronosyltransferase. (Adapted with permission from Bosilkovska M, Walder B, Besson M, et al. Analgesics in patients with hepatic impairment: pharmacology and clinical implications. *Drugs*. 2012;72:1645–1669.)

biology of opioid addiction; in silico evidence confirms that opioids such as remifentanil can interact with this receptor complex.[12]

Metabolism

The intravenous opioids in common perioperative clinical use are transformed and excreted by a wide variety of metabolic pathways. In general, opioids are metabolized by the hepatic microsomal cytochrome P450 (CYP) system, although hepatic conjugation and subsequent excretion by the kidney are important for some drugs. The major and minor metabolic enzymes involved in the metabolism of a number of commonly used opioids are shown in Fig. 17.6.[13] For certain opioids, the specific metabolic pathway involved has important clinical implications in terms of active or toxic metabolites (e.g., morphine, meperidine) or an ultrashort duration of action (e.g., remifentanil). For others opioids, genetic variation in the metabolic pathway can drastically alter the clinical effects (e.g., codeine). These nuances are addressed in a subsequent section focused on individual drugs.

Clinical Pharmacology

Pharmacokinetics

Because in most respects opioids are pharmacodynamically similar, pharmacokinetic differences form the scientific foundation for the rational selection and administration of opioids in anesthesia practice. Key pharmacokinetic behaviors to consider are the latency-to-peak effect after bolus injection (i.e., bolus front-end kinetics), the time to offset of effect after bolus injection (i.e., bolus back-end kinetics), the time to steady-state after starting a continuous infusion (i.e., infusion front-end kinetics), and the time to offset of effect after stopping a continuous infusion (i.e., infusion back-end kinetics).

Applying opioid pharmacokinetic concepts to clinical anesthesiology requires recognition of several fundamental principles. First, a table of opioid pharmacokinetic parameters can rarely be instructive in terms of understanding how the pharmacokinetic behavior of the individual drugs compares (see Chapter 2). Understanding pharmacokinetic behavior is best achieved through computer simulation. Second, because opioid clinical behavior differs depending on whether the drugs are administered by bolus injection or continuous infusion, these two clinical conditions must be considered separately.[14] Third, the time course of drug levels predicted through pharmacokinetic simulation cannot be considered in a vacuum; pharmacokinetic information must be integrated with knowledge about the concentration-effect relationship and drug interactions (pharmacodynamics) to be clinically useful.

The latency-to-peak effect and the offset of effect after bolus injection of various opioids can be explored by predicting the time course of effect site concentrations after a bolus is administered. Because the opioids differ in terms of potency (and thus the required dosages), for comparison purposes the effect site concentrations must be normalized to the percent of peak concentration for each

drug. Considering morphine, hydromorphone, fentanyl, sufentanil, alfentanil, and remifentanil as among the most commonly used intravenous opioids intraoperatively, the top panel of Fig. 17.7 illustrates how these opioids differ in terms of latency-to-peak effect (i.e., bolus front-end kinetics); the simulations are based on pharmacokinetic-dynamic parameters from the literature.[15-21]

The simulation of a bolus injection (Fig. 17.7A) has obvious clinical implications. For example, when a rapid onset of opioid effect is desirable, morphine may not be a good choice. Similarly, when the clinical goal is a brief pulse of opioid effect followed by a rapid dissipation of effect, remifentanil or alfentanil is preferred. Note how remifentanil's concentration has declined substantially before fentanyl's peak concentration has been achieved (bolus back-end kinetics). The simulation illustrates why the front-end kinetics of fentanyl make it a drug well suited for patient-controlled analgesia (PCA). In contrast to morphine, the peak effect of a fentanyl bolus is manifest before a typical PCA lockout period has elapsed, thus mitigating a "dose stacking" problem.

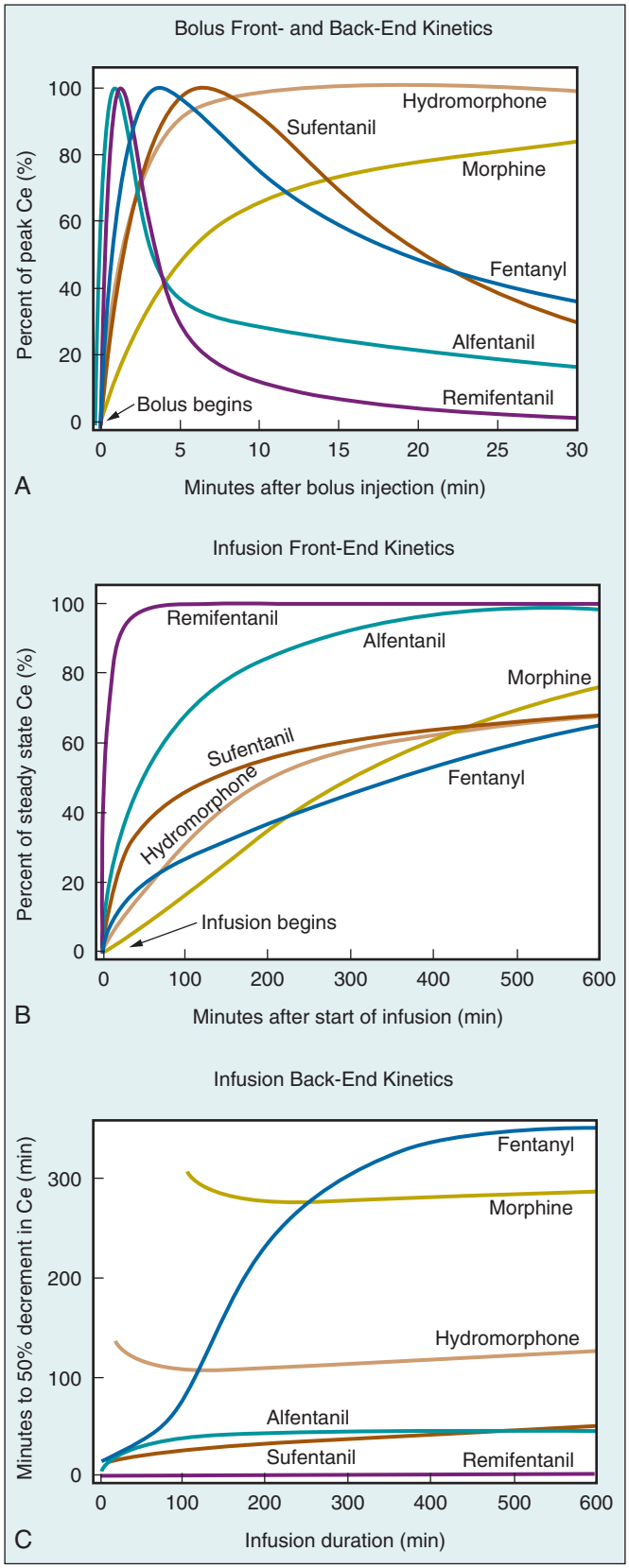
The latency-to-peak effect is governed by the speed with which the plasma and effect site come to equilibrium (the k_{eo} parameter). Drugs with a more rapid equilibration are thought to have a higher "diffusible" fraction (the proportion of drug that is un-ionized and unbound). It is important to emphasize that a substantial limitation of these latency-to-peak effect simulations is that a very large dose of any opioid can produce a rapid onset (because a supratherapeutic drug level in the effect site is reached even though the peak concentration comes later).

The time to steady-state after beginning a continuous infusion is also best explored through pharmacokinetic simulation. Again, because the potency of the various opioids differs, the predicted effect site concentrations must be normalized to the final steady-state concentrations to contrast the behavior of the drugs. Using the same prototypes, Fig. 17.7B shows the time required to achieve steady-state effect site concentration (infusion front-end kinetics).

The simulation of simple, constant rate infusions has obvious clinical implications. First, it is clear that for most commonly used intravenous opioids, the time required to reach a substantial fraction of the ultimate steady-state concentration is very long in the context of intraoperative use. To reach a near steady-state more quickly requires a bolus be administered before the infusion is commenced (or increased). Remifentanil perhaps represents a partial exception to this general rule. Another extremely important clinical application of this simulation is that concentrations will rise for many hours after an infusion is commenced (without a bolus); thus practitioners must be aware that concentrations are typically rising even though the infusion rate may have been the same for hours. That remifentanil achieves a near steady-state relatively quickly makes it an especially useful drug for total intravenous anesthesia because it is thus more "titratable."

The time to offset of effect after stopping a steady-state infusion is often explored through context-sensitive half-time simulation (CSHT).[22] Defined as the time required to achieve a 50% decrease in plasma concentration after stopping a continuous, steady-state infusion, the CSHT is a means of normalizing the pharmacokinetic behavior of drugs so that rational comparisons can be made regarding the predicted offset of drug effect. The CSHT is thus focused on infusion back-end kinetics.

Fig. 17.7C shows a CSHT simulation for commonly used opioids (strictly speaking, it is the 50% decrement time because the simulation is for effect site concentrations).[23] Several clinically important points are obvious. First, for most drugs, the time to a



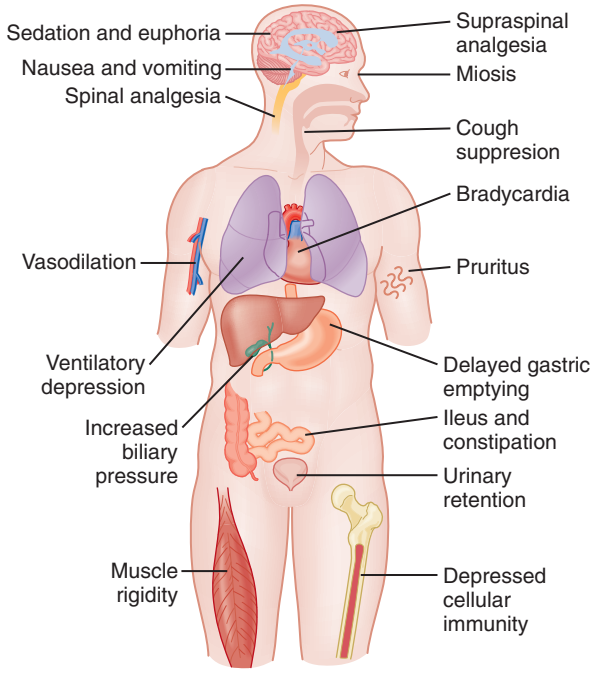
• **Fig. 17.7** Opioid pharmacokinetics. Simulations illustrating front-end and back-end pharmacokinetic behavior after administration by bolus injection or continuous infusions for morphine, hydromorhpone, fentanyl, alfentanil, sufentanil, and remifentanil using pharmacokinetic parameters from the literature (see text for details). *Ce,* Effect site concentration. (Data from references 15–21.)

50% decrease in concentration changes with the length of the infusion. Thus for very brief infusions, the predicted back-end kinetics for the various drugs do not differ much (remifentanil is a notable exception). As the infusion time lengthens, the CSHTs begin to differentiate, providing a rational basis for drug selection. Second, depending on the desired duration of opioid effect, the clinician can choose the shorter-acting drugs or the longer-acting ones. Finally, the shapes of these curves differ depending on the degree of concentration decline required; in other words, the curves representing the time required to achieve a 20% or an 80% decrease in concentration (e.g., the 20% or 80% decrement time simulations) are quite different.[14] Thus, depending on the anesthesia technique applied, the CSHT simulations (or 50% decrement time) are not necessarily the clinically relevant simulations. It is also important to recognize that the CSHT simulation for morphine does not account for its active metabolite (see the section on individual drugs in later text).

Pharmacodynamics

Given that μ-receptor agonists share a common mechanism of action, in most respects the commonly used MOR agonists can be considered pharmacodynamic equals with important pharmacokinetic differences. In other words, their effect profiles, both therapeutic and adverse, are very similar. Their efficacy as analgesics and their propensity to produce ventilatory depression are indistinguishable when one μ-agonists is compared with another at equipotent concentrations. Where pharmacodynamic differences exist, they are typically a function of non-opioid receptor mechanisms, such as histamine release, among others.

Clinically important μ-agonist pharmacodynamic effects are observed in many organ systems. Fig. 17.8 summarizes the major pharmacodynamic effects of the fentanyl congeners. Depending on the clinical circumstances and clinical goals of treatment, some of these widespread effects can be viewed as therapeutic or adverse.



• **Fig. 17.8** Opioid pharmacodynamics. A summary chart of selected effects of the fentanyl congeners (see text for details).

For example, in some clinical settings the sedation produced by μ-agonists might be viewed as a goal of therapy; in others, this would clearly be thought of as an adverse effect.

Therapeutic Effects

The relief of pain is the primary therapeutic effect of opioid analgesics. Acting at spinal and brain μ-receptors, opioids are thought to provide analgesia both by attenuating the nociceptive traffic from the periphery and also by altering the affective response to painful stimulation centrally. μ-agonists are most effective in treating "second pain" sensations carried by slowly conducting, unmyelinated C fibers; they are less effective in treating "first pain" sensations (carried by small, myelinated A-δ fibers) and neuropathic pain. A unique aspect of opioid-induced analgesia (in contrast to drugs like local anesthetics) is that other sensory modalities are not affected (e.g., touch, temperature, among others).

Perioperatively (certainly intraoperatively), the sedation produced by μ-agonists is also one of the targeted effects. The brain is the anatomic substrate for the sedative action of μ-agonists. With increasing doses, μ-agonists eventually produce drowsiness and sleep (the relief of pain no doubt contributes to the promotion of sleep in uncomfortable patients both preoperatively and postoperatively, independent of the intrinsic sedative effect). With sufficient doses (higher than typically used clinically), the μ-agonists produce pronounced δ wave activity on the electroencephalogram that resembles the pattern observed during natural sleep.

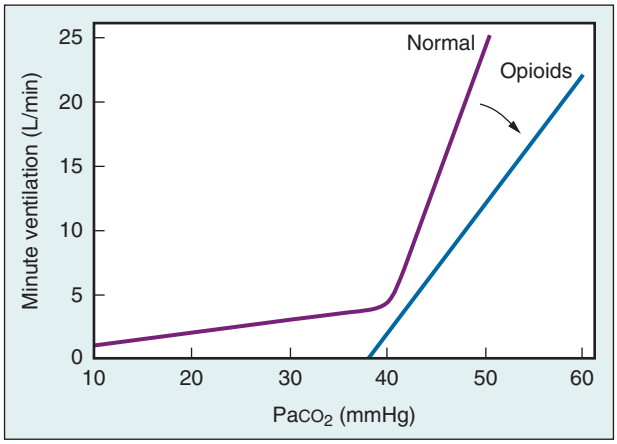
μ-agonists produce significant pain relief at doses that do not produce sleep; this is the basis of their clinical utility in the treatment of pain in ambulatory patients. On the other hand, the fact that increasing doses eventually produce drowsiness (and therefore the inability to request additional doses) is the essential scientific foundation for the safety of patient controlled analgesia devices. It is important to emphasize that μ-agonists, even when given in very high doses, do not reliably produce unresponsiveness and amnesia; thus they cannot be viewed as complete anesthetics when used alone.[24]

Suppression of the cough reflex is another important therapeutic effect of the μ-agonists in the practice of anesthesia. This antitussive effect is mediated through the cough centers in the medulla. Attenuation of the cough reflex presumably makes coughing and struggling against an indwelling endotracheal tube less likely. This effect is particularly important during fiberoptic intubation of the trachea in an awake patient as an approach to the difficult airway. Curiously, dextrorotatory isomers of opioids (e.g., dextromethorphan) produce this effect even though they do not have analgesic activity. Opioids can sometimes be associated with a paradoxical increase in coughing, typically after a bolus dose is administered. This poorly understood phenomenon is often briefly observed during induction of anesthesia when opioids are used as part of the induction regimen.

Adverse Effects

Depression of ventilation is the most significant adverse effect associated with μ-agonist drugs. Of course, when the airway is secured and ventilation is controlled intraoperatively, opioid-induced depression of ventilation is of little consequence. However, in the postoperative period, significant depression of ventilation associated with opioid analgesia can be a life-threatening complication and is a major source of morbidity and mortality, especially in high-risk populations such as patients with obstructive sleep apnea.

μ-agonists alter the ventilatory response to arterial carbon dioxide. That depression of ventilation is mediated by the MOR is supported



• **Fig. 17.9** Opioid-induced ventilatory depression study methodology. The method characterizes the relationship between the partial pressure of carbon dioxide in arterial blood *($Paco_2$)* and minute volume. The curve labeled *Normal* represents the expected response of minute volume to rising $Paco_2$ levels in an awake human. Note the dramatic increase in minute volume as carbon dioxide *(CO_2)* tension rises. The curve labeled *Opioid* represents the blunted response of minute volume to rising CO_2 levels following administration of an opioid. Note that the slope of the curve decreases and the curve no longer has a "hockey-stick" shape; this means that at physiologic $Paco_2$ levels, the patient receiving sufficient opioid may be apneic or severely hypoventilatory. (Adapted with permission from Gross JB: When you breathe IN you inspire, when you DON'T breathe, you…expire: new insights regarding opioid-induced ventilatory depression. *Anesthesiology.* 2003;99:767–770.)

TABLE 17.3 Factors Increasing the Magnitude or Duration of Opioid-Induced Ventilatory Depression

High dose
Sleep
Old age
Central nervous system depressants
Inhaled anesthetics, alcohol, barbiturates, benzodiazepines
Hyperventilation, hypocapnia
Respiratory acidosis
Decreased clearance
Reduction of hepatic blood flow
Renal insufficiency

by the observation that μ-receptor knockout mice do not exhibit the effect when they receive morphine.[25] Central pattern generators in the brainstem are the main anatomic substrate for depression of ventilation by the μ-agonists (see Chapter 29). Detailed studies of the brainstem anatomy involved in the control of ventilation reveal multiple, anatomically proximate collections of cells that are responsive to opioid agonists and antagonists, including the pre-Bötzinger complex in the rostral medulla, and the parabrachial nucleus and Kölliker-Fuse nucleus in the rostral pons.[26] An important nuance of these investigations is that these brainstem nuclei control not only the ventilatory pattern, but also influence the muscles that maintain airway patency.[27]

The depression of ventilation is studied by artificially increasing inspired carbon dioxide while maintaining normal oxygen tension.[28] As shown in Fig. 17.9, an increase in arterial carbon dioxide partial pressure dramatically increases the minute ventilation. Under the influence of opioid analgesics, the curve is flattened and shifted to the right such that at a given carbon dioxide partial pressure the minute ventilation is lower. More importantly, the "hockey-stick" shape of the normal curve is lost such that under the influence of μ-agonists there may be a partial pressure of carbon dioxide below which the patient does not breathe (this point can be thought of as the "apneic threshold"). μ-agonists also depress the hypoxic drive to breathe, although this effect is less important clinically than the effect on carbon dioxide–controlled ventilatory drive.[29]

The clinical signs of depressed ventilation are quite subtle with moderate opioid doses. Postoperative patients receiving opioid analgesic therapy can be awake and alert and yet sensitive testing will reveal significantly decreased minute ventilation. Moderate doses of μ-agonists produce a decrease in the ventilatory rate (often associated with a slightly increased tidal volume). As the opioid concentration is increased, both ventilatory rate and tidal volume progressively decrease, eventually culminating in an irregular ventilatory rhythm and then complete apnea.

A variety of factors can increase the risk of opioid-induced ventilatory depression (Table 17.3). Clear risk factors include high opioid dose, advanced age, concomitant use of other CNS depressants, and renal insufficiency (for morphine). Natural sleep also appears to increase the ventilatory depressant effect of μ-agonists.[30]

Opioids can alter cardiovascular physiology by a variety of mechanisms. Compared with many anesthetic drugs (e.g., propofol, volatile anesthetics), however, the cardiovascular effects of opioids, particularly the fentanyl congeners, are relatively mild (the unique cardiovascular effects of morphine and meperidine are discussed in the section on individual drugs). In fact, in some clinical circumstances, such as when anesthetizing patients with ischemic heart disease, the cardiovascular effects of the fentanyl congeners can be viewed as therapeutic.

The fentanyl congeners produce a slowing of heart rate by directly increasing vagal nerve tone in the brainstem. In experimental animals this effect can be blocked by microinjection of naloxone into the vagal nerve nucleus or by peripheral vagotomy.[31,32] If the bradycardia is considered undesirable in patients, it can be readily treated with antimuscarinic drugs.

Opioids also produce vasodilation by depressing vasomotor centers in the brainstem (i.e., by decreasing central vasomotor tone) and, to a lesser extent, by a direct effect on vessels. This action affects both the venous and arterial vasculature, thereby reducing both preload and afterload. The resulting decrease in blood pressure, while typically mild in healthy patients, is much more pronounced in patients with elevated sympathetic tone such as patients with congestive heart failure or hypertension. At typical clinical doses, opioids do not appreciably alter myocardial contractility.

Opioid-induced muscle rigidity is another potentially serious adverse effect of this drug class. Typically observed during the rapid administration of high bolus doses of the fentanyl congeners, opioid-induced muscle rigidity can make bag-mask ventilation during anesthesia induction impossible; the difficulty with bag-mask ventilation appears to be in large part a function of vocal cord rigidity and closure.[33] The rigidity tends to coincide with the onset of unresponsiveness.[34] Although the mechanism of opioid-induced muscle rigidity is unknown, it does not appear to be a direct action on muscle fibers because it can be prevented and treated with neuromuscular blockers.

In the perioperative setting, perhaps one of the most vexing (although not life-threatening) adverse effects associated with the μ-agonists is nausea and vomiting. Opioids stimulate the chemoreceptor trigger zone in the area postrema on the floor of the fourth ventricle (opioid receptors are expressed here) in the brain. This can lead to nausea and vomiting, an effect that is exacerbated by movement (this is perhaps why ambulatory surgery patients are more likely to be troubled by postoperative nausea and vomiting [PONV]). The use of postoperative opioids is a clear risk factor for the occurrence of PONV.[35] Numerous effective therapies exist for both the prophylaxis and treatment of PONV associated with opioids and other risk factors (see Chapter 28).[36]

Although it is of no clinical consequence in terms of patient safety or suffering, the pupillary constriction induced by μ-agonists can be a useful diagnostic sign indicating some ongoing opioid effect. Opioids stimulate the Edinger-Westphal nucleus of the oculomotor nerve to produce miosis. Even small doses of opioid elicit the response and very little tolerance to the effect develops. Thus miosis is a useful albeit nonspecific indicator of opioid exposure even in opioid-tolerant patients. Opioid-induced pupillary constriction is naloxone reversible.

The μ-agonists have important effects on gastrointestinal physiology. Opioid receptors are found throughout the enteric plexus of the bowel; their activation causes tonic contraction of gastrointestinal smooth muscle, thereby decreasing coordinated, peristaltic contractions. Clinically, this results in delayed gastric emptying and presumably higher gastric volumes in patients receiving opioid therapy preoperatively. Postoperatively, patients can develop opioid-induced ileus that can potentially delay the resumption of proper nutrition and discharge from the hospital. An extension of this acute problem is the chronic constipation associated with long-term opioid therapy.

Similar effects are observed in the biliary system, which also has an abundance of μ-receptors. The μ-agonists can produce contraction of the gallbladder smooth muscle and spasm of the sphincter of Oddi, potentially causing a falsely positive cholangiogram during gallbladder and bile duct surgery. These untoward effects are completely reversible by naloxone and can be partially reversed by glucagon treatment. The mixed agonist-antagonists (e.g., butorphanol) appear to produce less pronounced biliary effects.[37]

In contrast to the gastrointestinal system, the urologic effects of opioids are regarded as minimal. Opioids can cause urinary retention by decreasing bladder detrusor tone and by increasing the tone of the urinary sphincter. These effects are at least in part centrally mediated, although peripheral effects are also likely given the widespread presence of opioid receptors in the genitourinary tract.[38,39] Although the urinary retention associated with opioid therapy is not typically pronounced, it can be troublesome in males, particularly when the opioid is administered intrathecally or epidurally.

The euphoria produced by μ-agonists must be viewed as an adverse effect because it is the primary reason this drug class is so widely abused. Opioid addicts experience a euphoria that drives a drug-seeking lifestyle that often ends tragically in death or incarceration. The physical tolerance and dependence that inevitably develop in chronic users result in an increased dose requirement and a withdrawal syndrome upon cessation of drug intake. The withdrawal syndrome is characterized by intense drug craving, restlessness, body aches and pains, runny nose, lacrimation, and perspiration. An acute withdrawal syndrome can be precipitated by the administration of opioid antagonists (e.g., naloxone) during routine clinical care to patients who are not openly known to be opioid addicts.

Although perhaps not typically thought of as an acute effect that would be relevant to perioperative practice, opioids are known to depress cellular immunity. This effect is particularly well documented for morphine, although data exist for other μ-agonists as well. Morphine and the endogenous opioid β-endorphin, for example, inhibit the transcription of interleukin 2 in activated T cells, among other immunologic effects.[40] It appears that individual opioids (and perhaps classes of opioids) differ in terms of the exact nature and extent of their immunomodulatory effects. The clinical implications of opioid-induced impairment of cellular immunity are not well understood, but these effects might influence wound healing, perioperative infection risk, and cancer recurrence, among other outcomes. How this rapidly expanding knowledge will eventually impact clinical practice is evolving.

Drug Interactions

Drug interactions can be based on two mechanisms: pharmacokinetic (i.e., where one drug influences the concentration of the other) or pharmacodynamic (i.e., where one drug influences the effect of the other). In anesthesia practice, although unintended pharmacokinetic interactions sometimes occur, pharmacodynamic interactions occur with virtually every anesthetic and are produced by design.

The most common pharmacokinetic interaction in opioid clinical pharmacology is observed when intravenous opioids are combined with propofol. Perhaps because of the hemodynamic changes induced by propofol and their impact on pharmacokinetic processes, opioid concentrations are expected to be modestly higher when given in combination with a continuous propofol infusion.[41]

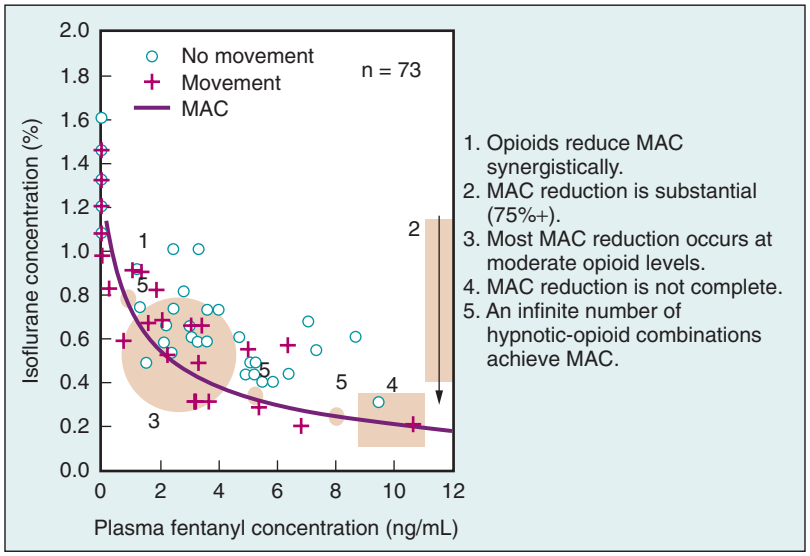
The most important pharmacodynamic drug interaction involving opioids is the synergistic interaction that occurs when opioids are combined with CNS depressants (see Chapter 5).[42] As illustrated in Fig. 17.10 for fentanyl and isoflurane, opioids dramatically reduce the minimum alveolar concentration (MAC) of a volatile anesthetic. Careful examination of "opioid-MAC reduction" data such as in Fig. 17.10 reveals several clinically critical concepts. First, opioids synergistically reduce MAC. Second, the MAC reduction is substantial (depending on the dose, as much as 75% or more). Third, most of the MAC reduction occurs at moderate opioid levels (i.e., even modest opioid doses substantially reduce MAC). Fourth, the MAC reduction is not complete; that is, opioids are not complete anesthetics. The addition of the opioid cannot completely eliminate the need for the other anesthetic. And fifth, there are an infinite number of hypnotic-opioid combinations that will achieve MAC (this implies that clinicians must choose the optimal combination based on the goals of the anesthetic and operation). As one might expect based on first principles, the synergistic interaction applies to both therapeutic and adverse effects such as depression of ventilation and hemodynamic variables.[43]

Because general anesthesia in the modern era is a least a two-drug process consisting of a sedative and an opioid, these MAC reduction concepts form an important part of the scientific foundation of anesthesia clinical pharmacology. All of these concepts also apply when opioids are used in combination with propofol for total intravenous anesthesia (TIVA).[44] Recent work has advanced the understanding of opioid-sedative pharmacodynamic interactions by applying response surface analysis methods.[45] This approach enables the investigator to identify optimal target concentrations of the sedative and the opioid through simulation (see Chapter 2).

Special Populations

Hepatic Failure

Perhaps surprisingly, even though the liver is the metabolic organ primarily responsible for the biotransformation of most opioids,



• **Fig. 17.10** Volatile anesthetic minimum alveolar concentration *(MAC)* reduction by opioids: the prototype example of isoflurane and fentanyl. The *solid curve* is MAC (see text for details). (Adapted with permission from McEwan AI, Smith C, Dyar O, et al. Isoflurane minimum alveolar concentration reduction by fentanyl. *Anesthesiology.* 1993;78:864–869.)

the degree of liver failure typically encountered in perioperative patients is usually not severe enough to have a major impact on the disposition of the fentanyl congeners.[13] The anhepatic phase of orthotopic liver transplantation is a notable exception to this general rule. With ongoing drug administration, concentrations of opioids that rely on hepatic metabolism are expected to rise significantly when the patient has no liver. Even after partial liver resection a decrease in the ratio of morphine glucuronides to morphine is observed, indicating a decrease in the rate of morphine metabolism.[46] Because remifentanil's metabolism is completely unrelated to hepatic clearance mechanisms, its disposition is not affected during liver transplantation.[47]

Of course, pharmacodynamic considerations can be important for opioid therapy in patients with severe liver disease. Patients with ongoing hepatic encephalopathy are thought to be particularly vulnerable to the sedative effects of opioids and thus this drug class must be used with caution in these patients.[13]

Kidney Failure

Renal failure has implications of major clinical importance with respect to morphine and meperidine (see the later section on individual drugs). For the fentanyl congeners, the clinical importance of kidney failure is much less marked, but nonetheless measurable. As with hepatic failure, remifentanil is also an exceptional case with respect to renal failure. Remifentanil's metabolism is not affected by kidney disease (although the inactive acid metabolite does accumulate in such patients).[48]

Morphine is principally metabolized by conjugation in the liver; the resulting water-soluble glucuronides (i.e., morphine 3-glucuronide and morphine 6-glucuronide [M3G and M6G] are excreted via the kidney. The kidney also plays a role in the conjugation of morphine and may account for as much as half of its conversion to M3G and M6G.

M3G is inactive, but M6G is an analgesic with a potency rivaling morphine. Very high levels of M6G and life-threatening respiratory depression can develop in patients with renal failure as illustrated in Fig. 17.11.[49] In view of these pharmacokinetic changes induced by renal failure, morphine may not be a good choice in patients with severely altered renal clearance mechanisms.

The clinical pharmacology of meperidine is also significantly altered by renal failure. Normeperidine, the main metabolite, has analgesic and excitatory CNS effects that range from anxiety and tremulousness to myoclonus and frank seizures. Because the active metabolites are subject to renal excretion, CNS toxicity secondary to accumulation of normeperidine is especially a concern in patients with renal failure. This shortcoming of meperidine has caused many hospital formularies to restrict its use or to remove it from the formulary altogether.

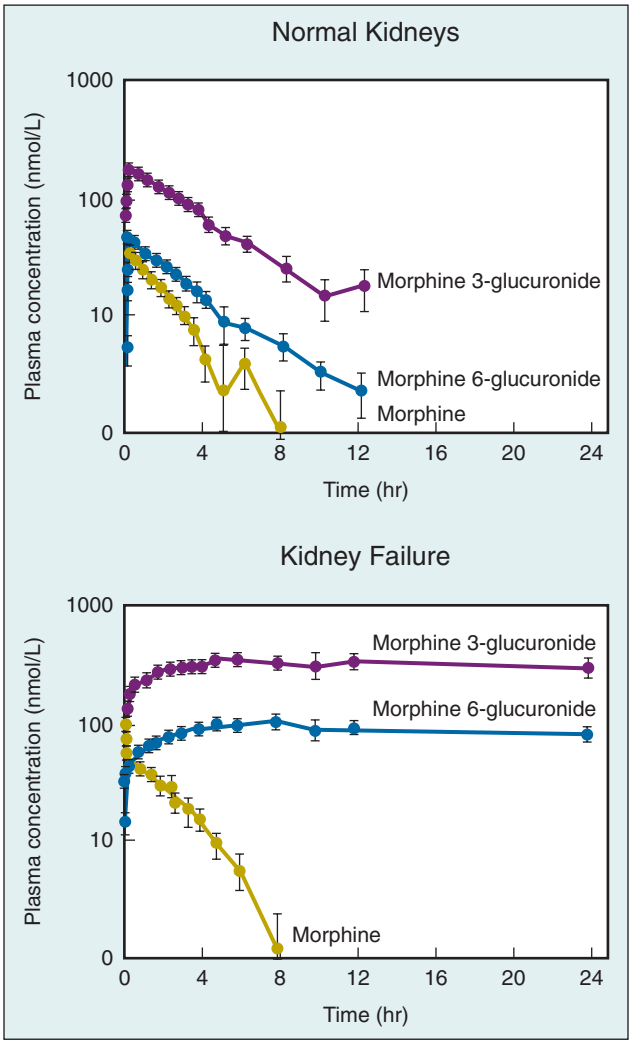
Gender

Recent data suggest that gender may have an important influence on opioid pharmacology. There is evidence, for example, that morphine is more potent in women than in men (i.e., that a lower concentration is required to produce comparable analgesia) and that it has a slower onset of action in women.[50] Although this information is clearly incomplete and emerging, some of these differences may be related to cyclic gonadal hormones.

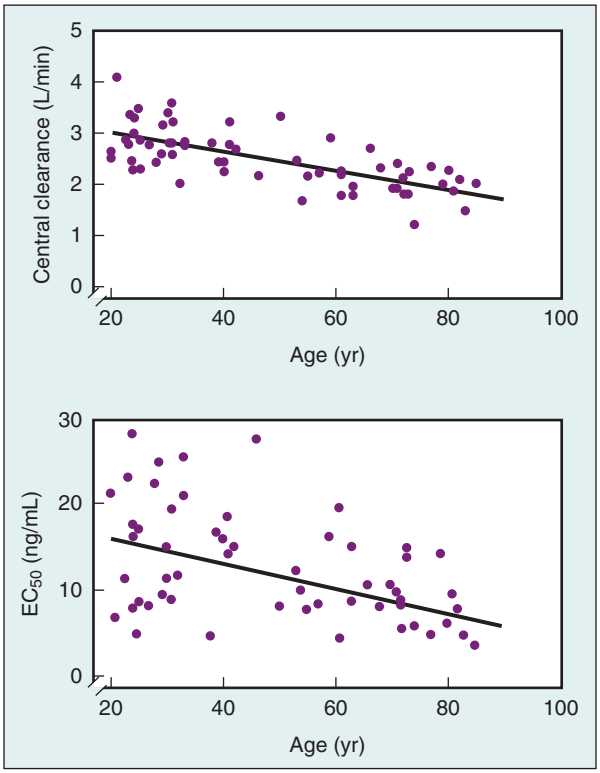
Age

Advancing age is undoubtedly an important factor influencing the clinical pharmacology of opioids. As shown in Fig. 17.12, kinetic-dynamic model-building studies in volunteers using the processed electroencephalogram as a surrogate measure of opioid effect have reproducibly shown that the fentanyl congeners are more potent in older patients.[19,21] Pharmacokinetic differences have also been described, including decreases in clearance and central distribution volume in older patients.

Although pharmacokinetic changes also play a role, pharmacodynamic differences are primarily responsible for the decreased dose requirement in older patients (e.g., >65 years of age). These combined pharmacokinetic and pharmacodynamic changes mandate



• **Fig. 17.11** The pharmacokinetics of morphine and its metabolites in normal volunteers versus kidney failure patients. Note the significant accumulation of the metabolites in renal failure. (Adapted with permission from Osborne R, Joel S, Grebenik K, et al. The pharmacokinetics of morphine and morphine glucuronides in kidney failure. *Clin Pharmacol Ther.* 1993;54: 158–167.)



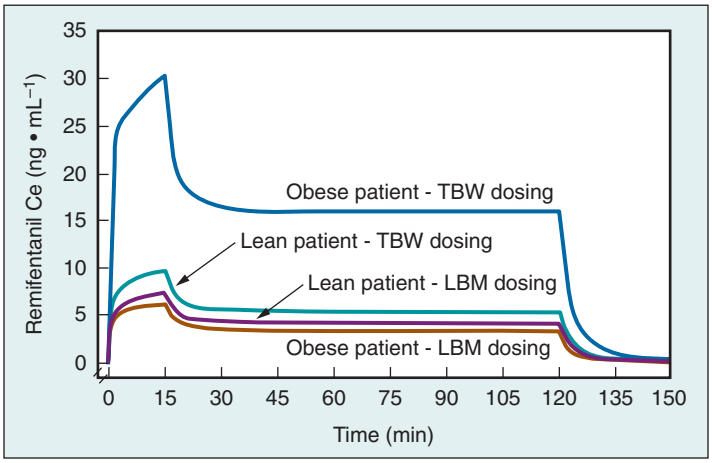
• **Fig. 17.12** The influence of age on the clinical pharmacology of remifentanil. Although there is considerable variability, in general, older subjects have a lower central clearance and a higher potency (lower EC_{50}). *EC_{50}*, Effective concentration for 50% of maximal effect. (Adapted with permission from Minto CF, Schnider TW, Egan TD, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology.* 1997;86:10–23.)

a reduction in remifentanil dosage by at least 50% or more in seniors. Similar dosage reductions are also prudent for other μ-agonists.

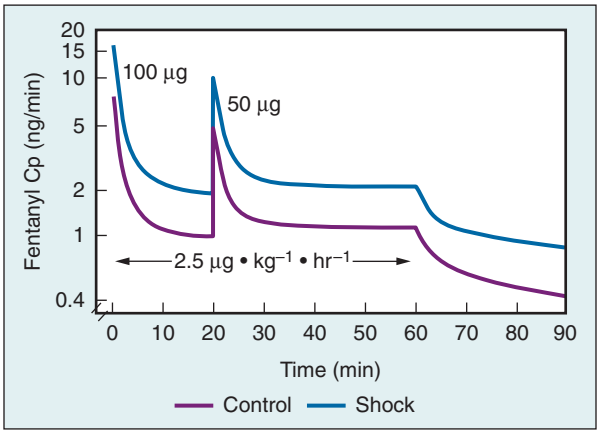
Obesity

Although detailed information is unavailable for many commonly used opioids, evidence from the study of drugs introduced more recently suggests that body weight is an important factor influencing the clinical pharmacology of opioids. Opioid pharmacokinetic parameters, especially clearance, are more closely related to lean body mass than to total body weight (TBW). In practical terms, this means that morbidly obese patients do indeed require a higher dosage than lean patients to achieve the same target concentration, but the very obese patients do not need nearly as much as would be suggested by their TBW.[51]

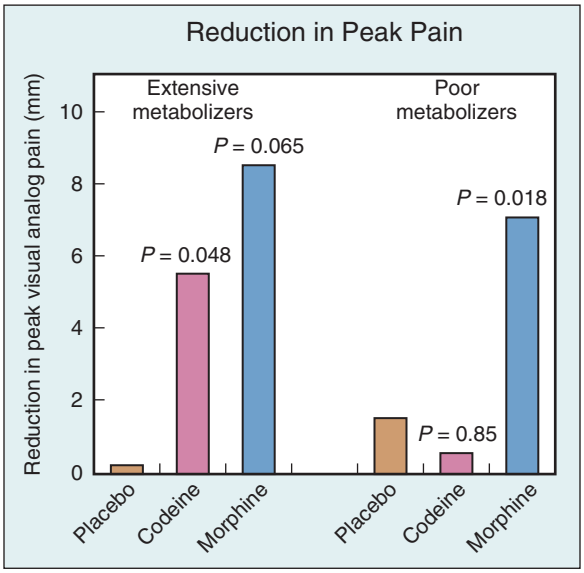
For example, as illustrated in the pharmacokinetic simulation shown in Fig. 17.13, a TBW- based dosing scheme in an obese patient results in excessive remifentanil effect site concentrations



• **Fig. 17.13** A pharmacokinetic simulation illustrating the consequences of calculating the remifentanil dosage based on total body weight *(TBW)* or lean body mass *(LBM)* in obese and lean patients (1-μg/kg bolus injection followed by an infusion of 0.5 μg/kg per minutes for 15 minutes and 0.25 μg/kg per minute for an additional 105 minutes). Note that TBW-based dosing in an obese patient results in dramatically higher concentrations. *Ce,* Effect site concentration. (Adapted with permission from Egan TD, Huizinga B, Gupta SK, et al. Remifentanil pharmacokinetics in obese versus lean patients. *Anesthesiology.* 1998;89:562–573.)



• **Fig. 17.14** A pharmacokinetic simulation illustrating the influence of severe hemorrhagic shock on the disposition of fentanyl. Animals in shock achieve substantially higher blood concentrations when receiving the same fentanyl dose. *Cp,* concentration in the plasma. (Adapted with permission from Egan TD, Kuramkote S, Gong G, et al. Fentanyl pharmacokinetics in hemorrhagic shock: a porcine model. Anesthesiology 1999;91:156–166.)



• **Fig. 17.15** A volunteer study demonstrating that codeine is no more effective than placebo in patients who cannot convert codeine to morphine (i.e., poor metabolizers). Morphine retains its normal analgesic efficacy in such patients. Both codeine and morphine are effective in normal subjects (i.e., extensive metabolizers). The *bars* represent the median of the maximal reduction in peak pain as assessed by the cold pressor test using a visual analog scale. (Adapted with permission from Poulsen L, Brosen K, Arendt-Nielsen L, et al. Codeine and morphine in extensive and poor metabolizers of sparteine: pharmacokinetics, analgesic effect and side effects. *Eur J Clin Pharmacol.* 1996;51:289–295.)

compared with dosing calculation based on lean body mass.[52] In contrast, for lean patients, the concentrations that result from TBW-based dosing regimens are not much greater than those based on lean body mass. Recent evidence based on a large pharmacokinetic modeling study has confirmed these general impressions regarding remifentanil dosing guidelines in obese patients.[53]

Hemorrhagic Shock

Although the data are from animal studies, it is clear that severe hemorrhage significantly alters the pharmacokinetic behavior of opioids. Both the clearance and distribution parameters are affected. As shown in the pharmacokinetic simulation presented in Fig. 17.14, subjects experiencing severe hemorrhage can be expected to achieve blood concentrations that are approximately double those observed in control subjects when they receive identical doses.[54] Even a drug that does not require delivery to a metabolic organ like remifentanil is affected, although the effect is not as dramatic.[55] There is clear evidence from case reports that these observations apply to human pharmacology as well.[56]

Unique Features of Individual Agents

Codeine

Codeine, while not commonly used intraoperatively, has special importance among opioids because of a well-characterized pharmacogenomic nuance associated with it. Codeine is actually a prodrug that is metabolized in part by O-demethylation into morphine, a metabolic process mediated by the liver P450 isoform CYP 2D6.[57] As demonstrated in Fig. 17.15, patients who lack CYP 2D6 because of deletion, frame shift or splice mutations (approximately 10% of the Caucasian population), or those whose CYP 2D6 is inhibited (e.g., patients taking quinidine) do not respond normally to codeine even though they exhibit a normal response to morphine.[58,59]

Interestingly, Asians have less CYP 2D6 activity and thus may be an ethnic group particularly resistant to codeine therapy.[60] Conversely, certain ethnic groups (e.g., Ethiopians) are thought to be particularly susceptible to the effects of codeine because they carry frequently duplicated, functional CYP 2D6 genes, resulting in the ultrarapid conversion of codeine to morphine.[61]

In addition to therapeutic failure, pharmacogenetic variants in codeine metabolism can result in tragic adverse drug reactions. Functional CYP 2D6 gene duplication has recently been implicated in fatalities among infants breastfed by mothers who are ultrarapid metabolizers.[62] Deaths in children who received codeine after tonsillectomy and who, upon postmortem genotyping, were confirmed to be ultrarapid metabolizers have been reported; morphine levels in these children at autopsy were well beyond the toxic threshold.[63] Ironically, codeine was presumably prescribed to these children to avoid the respiratory depression typically associated with more powerful opioids.

More than 80 different alleles for CYP 2D6 have now been identified, creating numerous possible phenotypes for codeine metabolism. Consensus guidelines for the interpretation of CYP 2D6 diplotypes enable the clinician to categorize patients into one of four categories, reflecting a range of codeine conversion to morphine, from none to extensive.[64] Unfortunately, for the vast majority of patients who are candidates for codeine therapy, their diplotype is unknown at the time of treatment. Until an era dawns when most patients have their entire genome sequenced so that the pharmacogenetic information is available to the clinician at the point of care as part of a "personalized medicine" approach to health care, codeine's decline in popularity among prescribers is likely to continue.

Morphine

Morphine is the prototype opioid against which all newcomers are evaluated. Despite a century of opioid research, there is no

evidence that any synthetic opioid is more effective in controlling pain than nature's morphine. Were it not for the histamine release–mediated hypotension observed intraoperatively with high doses of morphine, it is conceivable that fentanyl would not have replaced morphine as the most commonly used opioid in anesthesia practice.

An important detail relating to morphine's clinical pharmacology is its slow onset time. Morphine's pK_a renders it almost completely ionized at physiologic pH. This property, combined with its low lipid solubility, presumably accounts for morphine's prolonged latency to peak effect; morphine penetrates the CNS slowly. This feature has both advantages and disadvantages. The prolonged latency to peak effect (see Fig. 17.7A) means that morphine is less likely to cause acute respiratory depression after bolus injection of typical analgesic doses compared with the more rapid-acting drugs because the relationship between minute ventilation and the partial pressure of carbon dioxide changes more slowly (thus there is more time for carbon dioxide to rise and sustain ventilatory drive). On the other hand, the slow onset time means that clinicians are more likely to inappropriately "stack" multiple morphine doses in a patient experiencing severe pain, thus creating the potential for a toxic "overshoot."[65]

Morphine's active metabolite, M6G, also has very important clinical implications. Although conversion to M6G accounts for only 10% of morphine's metabolism, M6G contributes to morphine's analgesic effects even in patients with normal renal function, particularly with longer-term use. Because of morphine's high hepatic extraction ratio, the bioavailability of orally administered morphine is significantly lower than after parenteral injection. The hepatic first-pass effect on orally administered morphine results in high M6G levels; in fact, it appears that M6G may be the primary active compound when morphine is administered orally.[66] Accumulation of M6G to potentially toxic levels in dialysis patients is another important implication of this active metabolite.

Methadone

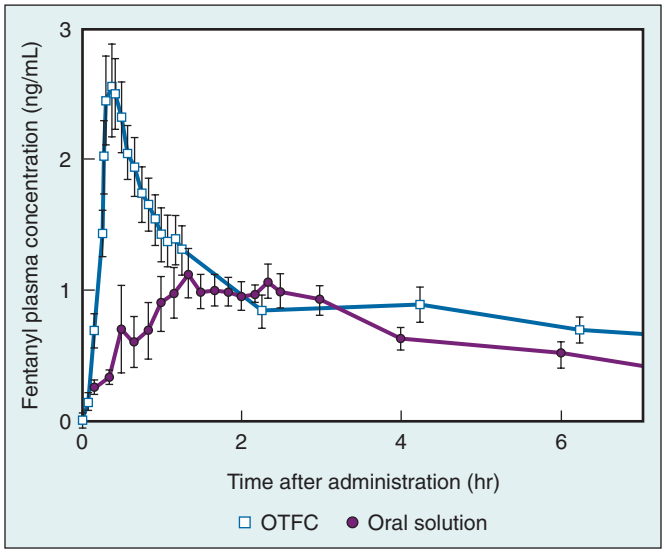
Available in both intravenous and oral forms, racemic methadone has long been a mainstay in the treatment of opioid addicts because its long-acting pharmacokinetic profile makes the development of an acute withdrawal syndrome less likely (i.e., methadone maintenance therapy). The N-methyl-D-aspartate (NMDA) receptor antagonism action of the dextrorotatory isomer of methadone may also serve to attenuate the effects of opioid tolerance and withdrawal syndrome.[67,68]

Methadone is also increasingly used in the treatment of patients with chronic pain, particularly cancer-related pain.[69] Methadone's propensity to prolong the QT interval of the electrocardiogram by blocking the delayed rectifier potassium ion channel may contribute to increased mortality in this patient population.[70]

Fentanyl

As the original fentanyl congener, its clinical application is well entrenched and highly diverse. Perhaps the most unique aspect of fentanyl's clinical application is the numerous ways in which fentanyl is delivered. In addition to the intravenous method, fentanyl has also been delivered by transdermal, transmucosal, transnasal, and transpulmonary routes.

Oral transmucosal delivery of fentanyl citrate results in the faster achievement of higher peak levels than when the same dose is swallowed as seen in Fig. 17.16.[71] It is the avoidance of the first-pass effect through transmucosal absorption that results in this significantly greater bioavailability. That oral transmucosal delivery of fentanyl citrate is noninvasive and rapid in onset has made it a successful therapy for breakthrough pain in opioid-tolerant cancer patients, often in combination with a transdermal fentanyl patch.



• **Fig. 17.16** A volunteer study contrasting the bioavailability and peak plasma concentrations of an identical dose (15 mcg/kg) of fentanyl delivered either orally or through the oral mucosa (i.e., oral transmucosal fentanyl *[OTFC]*). Note that the transmucosal approach yields higher peak concentrations earlier. (Adapted with permission from Streisand JB, Varvel JR, Stanski DR, et al. Absorption and bioavailability of oral transmucosal fentanyl citrate. *Anesthesiology.* 1991;75:223–229.)

Alfentanil

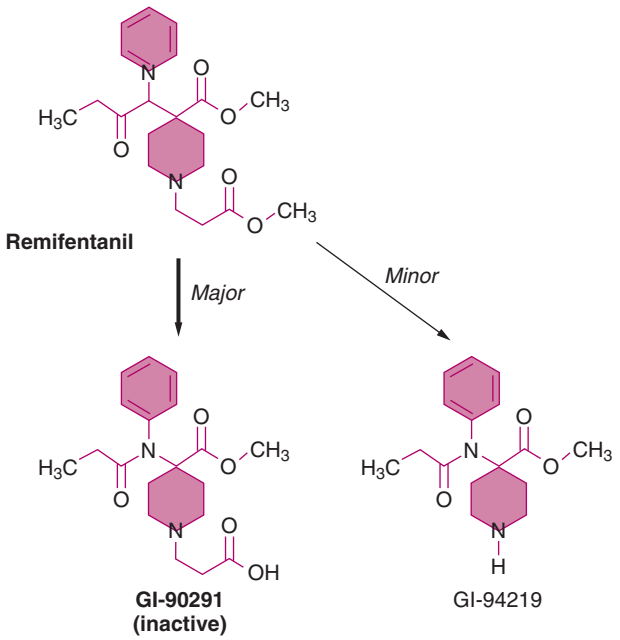
Alfentanil was the first opioid to be administered almost exclusively by continuous infusion. Because of its relatively short terminal half-life, alfentanil was originally thought to be an opioid with a rapid offset of effect after termination of a continuous infusion.[72] Subsequent advances in pharmacokinetic theory (i.e., the CSHT) proved this assertion to be false.[14] However, alfentanil is in fact a short-acting drug after a single bolus injection because of its high diffusible fraction; it reaches peak effect site concentrations quickly and then begins to decline (see earlier "Pharmacokinetics" and Fig. 17.7). Alfentanil illustrates how a drug can exhibit different pharmacokinetic profiles depending on the method of administration (i.e., bolus vs. continuous infusion). Relative to fentanyl and sufentanil, hepatic metabolism of alfentanil is more unpredictable because of the significant interindividual variability of hepatic CYP3A4, the primary enzyme responsible for alfentanil biotransformation. Because alfentanil has a relatively low hepatic extraction ratio compared with fentanyl, it is more vulnerable to variations in CYP 3A4 activity.[73]

Sufentanil

Sufentanil's distinguishing feature is that it is the most potent opioid commonly used in anesthesia practice. Because it is more intrinsically efficacious at the opioid receptor, the absolute doses used are much smaller compared with other less potent drugs (e.g., 1000-fold less than morphine).

Remifentanil

Remifentanil is a prototype example of how specific clinical goals can be achieved by designing molecules with specialized



• **Fig. 17.17** Remifentanil metabolic pathway. De-esterification (i.e., ester hydrolysis) by nonspecific plasma and tissue esterases to an inactive acid metabolite *(GI-90291)* accounts for the vast majority of remifentanil's metabolism. (Adapted with permission from Egan TD, Lemmens HJ, Fiset P, et al. The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. *Anesthesiology.* 1993;79: 881–892.)

structure-activity (or structure-metabolism) relationships. As shown in Fig. 17.17, the medicinal chemists responsible for the development of remifentanil sought to produce a potent opioid that would lose its μ-receptor agonist activity upon ester hydrolysis, thereby creating an intravenous opioid with a very short-acting pharmacokinetic profile.[74] The perceived unmet need driving remifentanil's development was that the practice of anesthesia requires a degree of pharmacokinetic responsiveness unnecessary in most medical disciplines and that anesthetics (opioids included) therefore ought to be short-acting so that they can be titrated during the rapidly changing conditions of anesthesia and surgery.

Compared with the currently marketed fentanyl congeners, remifentanil's CSHT is short, on the order of about 5 minutes (Fig. 17.7C).[75] Pharmacodynamically, remifentanil exhibits a short latency-to-peak effect similar to alfentanil and a potency slightly less than fentanyl (Fig. 17.7A).[76]

Remifentanil's role in modern anesthesia practice is now relatively well established; its unique pharmacokinetic profile makes it possible to manipulate rapidly the degree of opioid effect in a way that could not be achieved with the previously marketed fentanyl congeners. Remifentanil is therefore perhaps best suited for cases where its responsive pharmacokinetic profile can be exploited to advantage (e.g., when rapid recovery is desirable, when the anesthetic requirement rapidly fluctuates, when opioid titration is unpredictable or difficult, when there is a substantial danger to opioid overdose, or when a "high-dose" opioid technique is advantageous but the patient is not going to be mechanically ventilated postoperatively).[77] Today, remifentanil's most common clinical application may be the provision of TIVA in combination with propofol. It is also commonly used by bolus injection when a brief pulse of opioid effect followed by rapid recovery is advantageous (e.g., in preparation for local anesthetic injection during Monitored Anesthesia Care).

Opioid Agonist-Antagonists and Pure Antagonists

Because they bind to opioid receptors, the "mixed" agonist-antagonists and the pure antagonists are also classified as opioids. Opioid agonist-antagonists, of which nalbuphine is perhaps the modern prototype, are structurally related to morphine but do not behave as full agonists. These drugs serve as analgesics with more limited ventilatory depression and a lower potential for dependence as they demonstrate a "ceiling effect," producing less analgesia compared with pure agonists. The lower abuse potential was the primary perceived unmet need underlying the development of these drugs. Drugs in this category are used for the treatment of chronic pain, as well as the treatment of opioid addiction. These drugs cause some degree of competitive antagonism (i.e., withdrawal symptoms) when administered in the presence of ongoing full agonist activity (e.g., when administered after morphine and other pure agonists).

Pure opioid antagonists, of which naloxone is the prototype, are complete competitive antagonists of the opioid receptor that are devoid of any intrinsic agonist activity. These pure antagonists are used in the management of acute opioid overdose and chronic abuse.

Nalbuphine and Others

This group of synthetic and semisynthetic opioids includes nalbuphine, pentazocine, and butorphanol; these drugs are partial agonists at the κ receptor and complete, competitive antagonists at the μ-receptor. Both the analgesic and ventilatory depressant effects of these drugs exhibit a ceiling effect when compared to morphine[78] and they do not reduce MAC as powerfully as morphine or fentanyl.[79]

As a class, these opioid agonist-antagonists (or "partial agonists") were developed with the hope that they would be effective analgesics but less subject to diversion and abuse. These drugs are indeed efficacious in the treatment of mild to moderate pain (and they do have less abuse potential), but the analgesic ceiling effect has limited their more widespread use. Perhaps their most common perioperative use is the reversal of excessive opioid-induced ventilatory depression (μ-antagonism) while maintaining some analgesic effect (partial κ agonism).[80] As μ-antagonists, these drugs will of course precipitate a withdrawal syndrome in opioid-dependent patients[81] and are thus sometimes used in the maintenance treatment of opioid addicts.

Buprenorphine is a related drug that is an antagonist at the κ receptor but a partial agonist at the μ-receptor.[82] Buprenorphine is increasingly used in the treatment of opioid addiction.

Naloxone and Naltrexone

Naloxone, a derivative of oxymorphone, is a competitive antagonist of all opioid receptor types, but its greatest affinity is for the μ-receptor.[83] When administered in typical doses in the absence of ongoing opioid therapy (or abuse), naloxone has no discernable pharmacodynamic effects. When opioid effects are present, naloxone given in sufficient doses can reverse all effects mediated by opioid receptors.[84]

The most common clinical use of naloxone perioperatively is the reversal of excessive opioid-induced ventilatory depression.[85] Its important role in this regard has merited naloxone's inclusion on the World Health Organization's List of Essential Medicines. Other uses include the emergency reversal of ventilatory depression in neonates whose mothers received opioids for labor analgesia,

and in cases of accidental or intended opioid overdose (e.g., heroin) in the emergency department. Naloxone is also sometimes used in much smaller doses during emergence from anesthesia to restore adequate ventilatory effort and thereby expedite extubation of the trachea. The treatment of opioid-induced pruritus using small doses is another common therapeutic application.

A few nuances of naloxone's clinical pharmacology are extremely important for safe use. Naloxone is rapidly metabolized in the liver and has a very high clearance; thus its duration of action is nearly always shorter than that of the opioid whose effects it is intended to reverse. Patients who receive naloxone for the emergency reversal of life-threatening ventilatory depression must be monitored for recurrence of the opioid effects. Repeated naloxone dosing may be necessary to sustain adequate ventilation. Also, rarely, naloxone administration has been complicated by severe adverse hemodynamic effects including pulmonary edema and even sudden death in previously healthy individuals (some tachycardia is to be expected).[86] Other adverse effects include acute withdrawal syndrome, nausea, vomiting, and seizures, among others.[84]

In response to the opioid abuse epidemic in the United States, new naloxone delivery systems have been developed that are intended for emergency use by lay persons in the event of opioid overdose; these include nasal spray and autoinjector preparations.[87,88]

Several drugs closely related to naloxone have been developed for other purposes. Naltrexone, a longer-acting μ-opioid antagonist available in oral, injectable, and implantable forms, is used in the long-term management of previously detoxified opioid addicts in combination with other nonpharmacologic therapies.[89] Methylnaltrexone and alvimopan, permanently charged opioid antagonists that do not easily enter the CNS, were developed for the prevention and treatment of opioid-induced bowel dysfunction (see later text).

Clinical Application

Opioids play a vital role in virtually every area of anesthesia practice. In the treatment of postoperative pain, opioids are the primary therapeutic agent, whereas in most other settings in perioperative medicine opioids are therapeutic adjuncts used in combination with other drugs.

Common Clinical Indications

Postoperative analgesia is the longest standing indication for opioid therapy in anesthesia practice and of course dates back to the earliest days of the specialty. In the modern era, opioid administration via PCA devices is perhaps the most common mode of delivery. In recent years, opioids are increasingly combined postoperatively with various other agents such as nonsteroidal antiinflammatory drugs to increase efficacy and safety (see Chapter 16).

Internationally, the most common clinical indication for opioids in anesthesia practice is their use as part of what came to be known as "balanced anesthesia." The term connotes the use of multiple agents (e.g., inhalation agents, volatiles, neuromuscular blockers, and opioids) in smaller doses to produce the state of anesthesia. With this technique, the opioids are primarily used for their MAC reduction effects. A basic assumption underlying this balanced anesthesia approach is that the drugs used in combination mitigate the disadvantages of the individual drugs (i.e., the inhaled agents) used in higher doses as monotherapy.

"High-dose opioid anesthesia," a technique originally described for morphine in the early days of open heart surgery[90] and later associated with the fentanyl congeners,[91] is another common application of opioids. The original scientific underpinning of this approach was that high doses of opioids enabled the clinician to reduce the volatile agent to a minimum, thereby avoiding the direct myocardial depression and other untoward hemodynamic effects associated with high concentrations of volatile anesthetics in patients whose cardiovascular systems were already compromised. That the fentanyl drugs often produce a relative bradycardia is also thought to be helpful in mitigating against myocardial ischemia. Although the general concept is still applied, the opioid doses used today are more moderate. In this setting opioids are also administered for their possible beneficial effects in terms of cardioprotection (i.e., preconditioning).

TIVA is a more recently developed and increasingly popular indication for opioids in anesthesia practice. As the name implies, this technique relies entirely on intravenous agents for the provision of general anesthesia. Most commonly, continuous infusions of remifentanil or alfentanil are combined with a propofol infusion. Both the opioid and the sedative are often delivered by target-controlled infusion (TCI)-enabled pumps. A clear advantage of this technique, perhaps among others, is the enhanced patient well-being in the early postoperative period, including less nausea and vomiting and often a feeling of euphoria.[92]

Rational Drug Selection and Administration

In articulating a scientific foundation for rational opioid selection, it is most important to recognize that pharmacokinetic considerations are paramount. Indeed, the μ-agonists can be considered pharmacodynamic equals with important pharmacokinetic differences.[93] In other words, for practical purposes all μ-agonists are essentially equally efficacious when equipotent concentrations are achieved, but they differ in terms of their pharmacokinetic behavior. Thus rational selection of one μ-agonist over another requires the clinician to identify the desired temporal profile of drug effect and then choose an opioid that best achieves it (within constraints such as pharmacoeconomic concerns).

In selecting the appropriate opioid, among the key questions to address are as follows: How quickly must the desired opioid effect be achieved? How long must the opioid effect be maintained? How critical is it that opioid-induced ventilatory depression or sedation dissipate quickly (e.g., will the patient be mechanically ventilated postoperatively)? Is the capability to raise and lower the level of opioid effect quickly during the anesthetic critical? Will there be significant pain postoperatively that will require opioid treatment? All of these questions relate to the optimal temporal profile of opioid effect. The answers to these questions are addressed through the application of pharmacokinetic concepts.

For example, when a brief pulse of opioid effect followed by rapid recovery is desired (e.g., to provide analgesia for a retrobulbar block), a bolus of remifentanil or alfentanil might be preferred. When long-lasting opioid effect is desired, such as when there will be significant postoperative pain or when the patient's trachea will remain intubated, a fentanyl infusion is a prudent choice. In cases where it is critical that the patient be awake and alert shortly after the procedure is finished (e.g., a craniotomy in which the surgeons hope to perform a neurologic exam in the operating room immediately postoperatively), a remifentanil infusion might be advantageous.

The formulation of a rational administration strategy also requires the proper application of pharmacokinetic principles. An important goal of any dosing scheme is to reach and maintain a steady-state

level of opioid effect. To achieve a steady-state concentration in the site of action, opioids are frequently administered by continuous infusion. This is increasingly accomplished through the use of TCI technology (see later text), which requires familiarity with the appropriate pharmacokinetic model for the opioid of interest. When these systems are not available, the clinician must remember that infusions must be preceded by a bolus to come to a near–steady state in a timely fashion.

Computerized Delivery Methods

Advances in pharmacologic modeling and infusion pump technology have now made it possible to administer injectable anesthetics via a computer-controlled infusion pump.[94] By coding a pharmacokinetic model into a computer program and linking it to an electronic pump modified to accept computerized commands, delivery according to a drug's specific pharmacokinetic parameters can be achieved. The physician operating a TCI system designates a target concentration to achieve rather than specifying an infusion rate. The TCI system then calculates the necessary infusion rates to achieve the targeted concentration. The system changes the infusion rates at frequent intervals (i.e., as often as every 10 seconds). Successful use of a TCI pump thus requires knowledge of the therapeutic concentrations appropriate for the specific clinical application.

Computer-controlled drug delivery in the operating room is an exciting area with well-established clinical utility, although it is admittedly difficult to demonstrate obvious outcome improvements compared to traditional delivery methods. TCI administration of opioids is common for all of the fentanyl congeners. Although TCI systems are widely used in North America for research purposes, they are not yet commercially available for routine clinical use (unlike much of the rest of the world).[95]

Emerging Developments

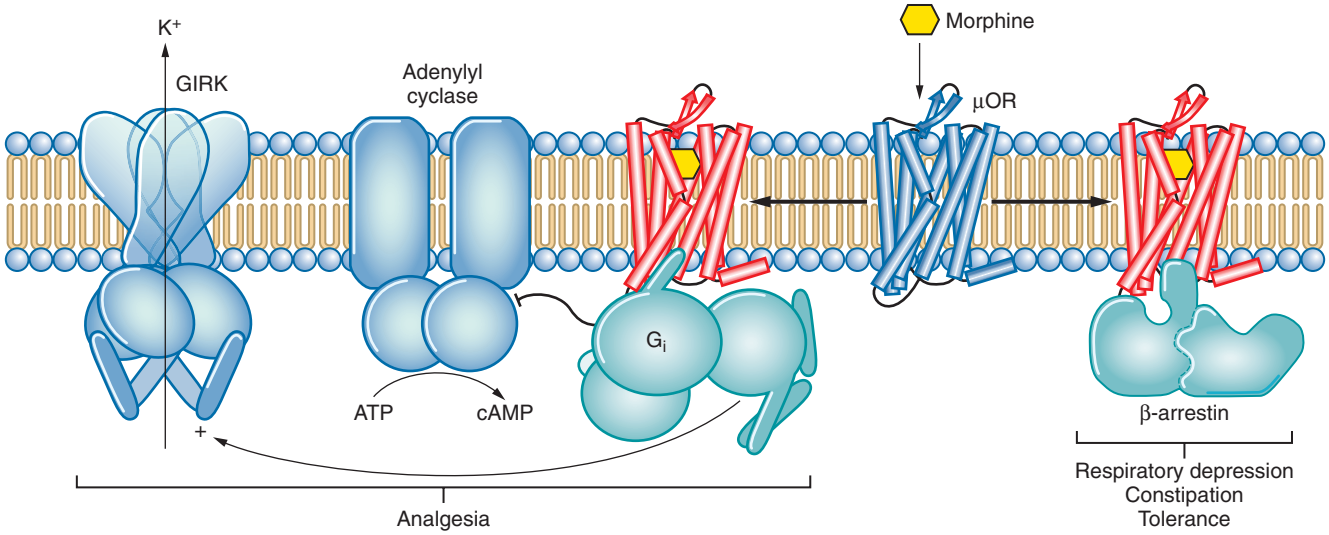
Opioids and Cancer Recurrence

Concerns have been raised recently that opioids administered as part of a general anesthetic for cancer surgery may have an adverse impact on cancer recurrence rates. This concern is supported by considerable in vitro and animal data demonstrating immunosuppressive and angiogenic effects of opioids (particularly morphine). Some early, retrospective data comparing prostate cancer recurrence rates in patients receiving standard postoperative opioid analgesia with those receiving alternative techniques (e.g., epidural pain management) generated the hypothesis that perioperative opioid use may promote cancer recurrence.[96] Some more recent, larger, retrospective studies focused on other types of cancer have failed to corroborate these earlier findings,[97,98] whereas other investigations have yielded supportive evidence.[99]

Confirmation of the hypothesis that perioperative opioid therapy promotes cancer recurrence would presumably have a major impact on the anesthesia techniques applied to cancer surgery patients, including a more prominent role for regional postoperative analgesia techniques to reduce the overall opioid load. At this stage, this hypothesis is unproven and the data must be interpreted with caution until more definitive information from ongoing controlled, randomized trials is available.[100,101] Ferreting out this dilemma is a major goal of contemporary anesthesiology research.

Biased μ-Opioid Agonists

There is evidence that the signaling pathways for opioid therapeutic and selected adverse effects may be distinct. As shown in Fig. 17.18, studies in animal models and in vitro techniques suggest



• **Fig. 17.18** The role of the β-arrestin pathway in μ-agonist adverse effects. Opiate-induced MOR signaling through Gi activates G-protein–gated inwardly rectifying potassium channels (GIRKs) and inhibits adenylyl cyclase, leading to analgesia. Conversely, recruitment of β-arrestin is implicated in tolerance, respiratory depression, and constipation. *ATP,* Adenosine triphosphate; *cAMP,* cyclic adenosine monophospate; *Gi,* G protein alpha subunit; *MOR,* μ-opioid receptor. (Adapted with permission from Manglik A, Lin H, Aryal DK, et al. Structure-based discovery of opioid analgesics with reduced side effects. *Nature.* 2016;537:185–190.)

that opioid-induced analgesia results from MOR signaling through G proteins, while many side effects, including respiratory depression, tolerance, and constipation, may be mediated by β-arrestin pathway signaling downstream of MOR agonism.[102-104] That separate pathways may mediate analgesic and adverse effects of μ-agonists presents an opportunity to create molecules that are "biased" toward the G-protein pathway, thereby minimizing respiratory depression while maintaining analgesic efficacy.

Using detailed knowledge of the crystal structures of the opioid receptors, medicinal chemists have taken a computational approach to identify potential candidate molecules that may have the desired biophysical properties in terms of how these molecules interact with the MOR (i.e., minimizing β-arrestin-2 signaling). In silico screening of millions of commercially available molecules resulted in identification of some candidate molecules structurally unlike currently available opioids that have intriguing clinical potential based on preclinical testing (e.g., PZM21).[105] Although this drug development effort is in its infancy, there are exciting basic science and clinical implications if this line of research can be carried forward.

Opioid Antagonists for Ileus and Constipation Therapy

An important development in the treatment of opioid-induced adverse effects is the use of μ-receptor antagonists to treat opioid-induced postoperative ileus and constipation.[106,107] Methylnaltrexone and alvimopan are μ-receptor antagonists whose physicochemical properties prevent them from crossing the blood-brain barrier in appreciable amounts. These drugs thus block the μ-receptors in the gut without antagonizing the therapeutic μ-agonist effects that are mediated in the CNS. Controlled, randomized trials have demonstrated their efficacy in the prevention and treatment of postoperative ileus and the constipation associated with chronic opioid use. A recent metaanalysis has confirmed their efficacy,[108] but treatment guidelines regarding patient selection are still evolving.[109]

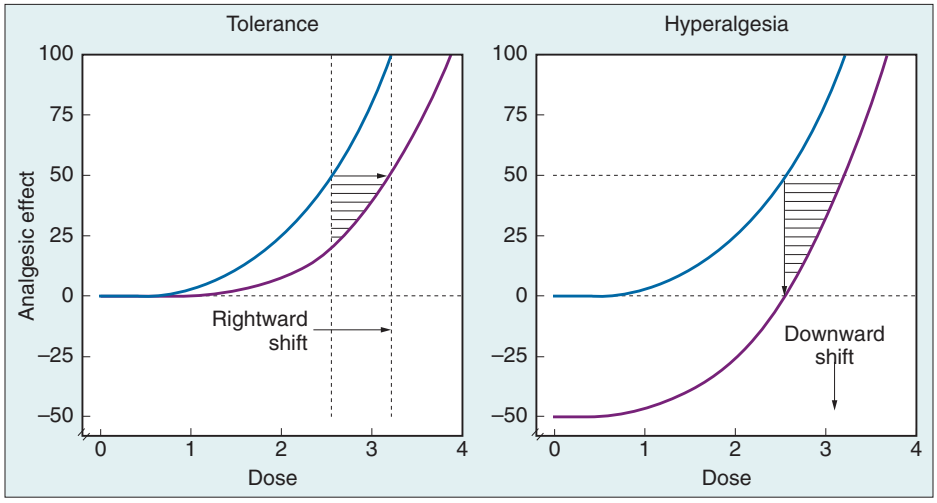
Opioid-Induced Hyperalgesia and Acute Tolerance

It is well known that long-term exposure to opioids produces tolerance to opioid effects; huge opioid doses may be needed to provide adequate perioperative analgesia in patients receiving chronic, high-dose opioid therapy.[110] However, more recent evidence suggests that even brief exposure to opioids may result in an increased dose requirement.

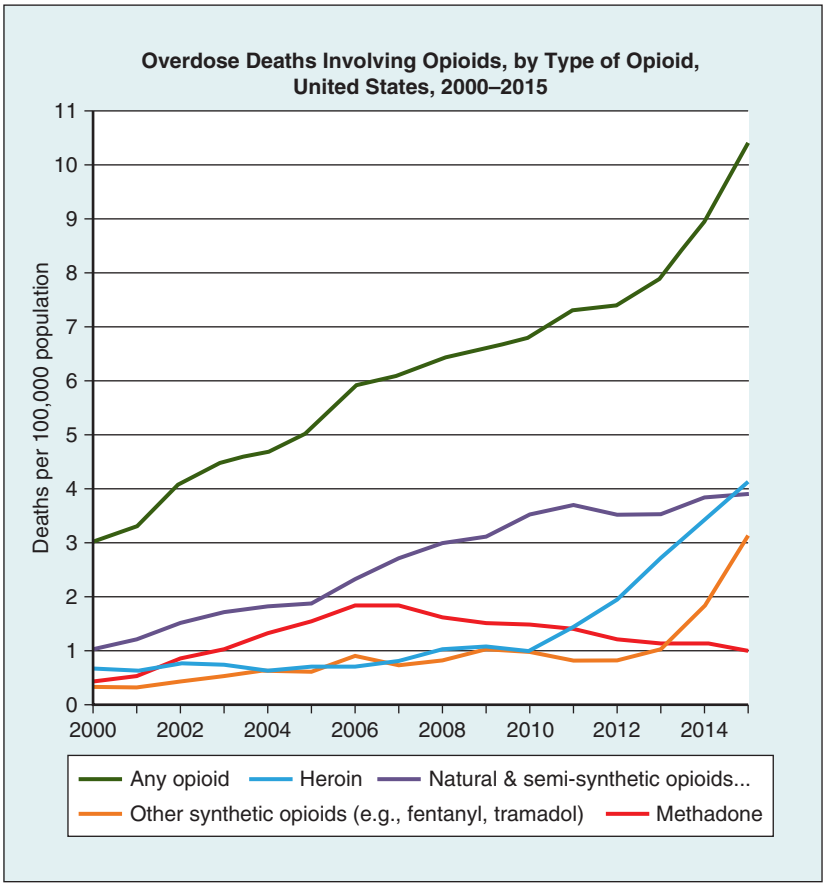
Acute tolerance and opioid-induced-hyperalgesia are pharmacologically distinct phenomena that can both result in the need for a dose escalation to maintain adequate analgesia. In general pharmacologic terms, tolerance is a decrease in the analgesic response to an opioid owing to its continued administration. Hyperalgesia, in contrast, is an increased response to a stimulus that is normally painful.[111]

Considered in terms of the dose-response relationship, opioid tolerance shifts the curve to the right, whereas opioid-induced hyperalgesia shifts the curve downward because of a change in pain sensitivity (Fig. 17.19).[112] Both phenomena manifest clinically as a need for a higher dose to achieve the same analgesic effect. Distinguishing between the two can be therapeutically important because tolerance calls for an increased dosage, whereas opioid-induced hyperalgesia may be more prudently addressed with non-opioid analgesics and other adjuncts (i.e., because opioids exacerbate the problem).

Whether acute tolerance and opioid-induced hyperalgesia play important roles in the management of perioperative patients is controversial.[111] Although numerous animal studies have demonstrated the occurrence of opioid-induced hyperalgesia, the data in humans are more ambiguous.[113-117] Current thinking suggests that both phenomena may coexist to some degree in certain perioperative settings.[111] Risk factors for their occurrence include high opioid dose, prolonged use, and perhaps inhalation anesthesia (i.e., propofol may mitigate risk).[118-120] There is increasing evidence that NMDA receptor antagonism mediated through drugs such



• **Fig. 17.19** Tolerance versus opioid-induced-hyperalgesia in terms of the dose-effect relationship changes. Tolerance shifts the dose-response curve to the right (but does not alter pain sensitivity). Opioid-induced hyperalgesia shifts the dose-response curve downward because of increased pain sensitivity. The *striped area* represents the net increase in dose required to achieve 50% of the maximal analgesic effect. (Adapted with permission from Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. *Clin J Pain.* 2008;24:479–496.)



• **Fig. 17.20** Overdose deaths involving opioids by type in the United States, 2000–2015. (Adapted from the Centers for Disease Control and Prevention National Vital Statistics database, 2016.)

as ketamine may also mitigate the severity of opioid-induced hyperalgesia.[121]

The mechanism of opioid-induced hyperalgesia is unclear. It likely involves both central and peripheral nervous system adaptation including processes involving the NMDA receptor.[112] It appears that endogenous opioid systems do not play a role in its pathogenesis,[122] whereas neuroinflammation induced by activation of microglia and astrocytes may contribute to the phenomenon.[123] Some evidence suggests that different opioids (i.e., morphine, fentanyl, and remifentanil) do not behave uniformly with regard to opioid-induced hyperalgesia, and that the mechanisms underlying the hyperalgesia may also involve spinal 5-hydroxytryptamine type 3 receptors.[124] An especially intriguing recent observation is that opioid agonism at MOR expressed by peripheral nociceptors may trigger the pronociceptive, maladaptive changes that result in opioid-induced hyperalgesia.[125] The administration of methylnaltrexone, a peripherally restricted opioid antagonist, was sufficient to block the development of opioid-induced hyperalgesia in this rodent model.

Opioid Overdose Epidemic

In recent years, deaths related to the abuse and diversion of both illicit and prescription opioids have skyrocketed in the United States and elsewhere as illustrated in Fig. 17.20.[126] Opioid overdose now constitutes a major cause of death in certain demographic groups; opioid-related deaths now exceed deaths from motor vehicle accidents in the United States. In addition to fatalities, this pervasive pattern of prescription and illicit opioid abuse has resulted in a huge surge in admissions to opioid use disorder treatment facilities.[127]

The disturbing trend is at least in part thought to be due to opioid prescribing practices for acute and chronic pain conditions that may predispose some patients to addiction.[128,129] It is increasingly clear that opioid prescribing patterns have been too liberal; over the decade from approximately 2000 to 2010, the number of opioid prescriptions written in the United States quadrupled.[130] These copious prescribing patterns were likely driven in part by a greater emphasis on the treatment of pain by professional societies and accreditation bodies (e.g., pain as the "fifth vital sign"). There is increasing recognition that the risk of opioid addiction stems primarily from the drugs, rather than from some obviously identifiable risk factor in the patient.[130]

The epidemic is now termed a national emergency in the United States,[131] prompting federal and state government authorities to enact legislation and set aside funding to support research, prevention, and treatment of the problem.[132,133] State-approved, pharmacy-based naloxone dispensing (without a physician's prescription) for patients filling opioid prescriptions is a notable example of the efforts supported by such legislation.[134] In addition, professional societies and the United States Centers for Disease Control and Prevention have produced new guidelines for opioid prescribing.[135,136] This is currently an area of intense public discussion and medical investigation.

Key Points

- Most of the clinically useful opioids are chemical modifications of morphine (e.g., hydromorphone, codeine, oxycodone) or meperidine (e.g., the fentanyl family of opioids).
- Opioids produce their primary effects by interacting with opioid receptors. Existing in three distinct types (i.e., μ, κ, and δ), these receptors are coupled with G proteins that, when activated by drugs or endogenous ligands (e.g., β-endorphins), produce inhibitory effects that hyperpolarize the cell and thereby attenuate nociceptive impulses.
- For certain opioids, the metabolic pathway has very important clinical implications. M6G and normeperidine are active metabolites that accumulate in renal failure, potentially causing toxicity. Remifentanil's high clearance because of esterase metabolism results in an extremely short duration of action.
- Opioids can be differentiated pharmacokinetically by their latency to peak effect after bolus administration, the time required to reach a steady state after beginning an infusion, and the time required to achieve a specified level of drug concentration decline after stopping a continuous infusion (i.e., CSHT).
- Pharmacodynamically, the primary therapeutic effects for the perioperative use of opioids are analgesia and sedation. The most dangerous adverse effect in nonventilated patients is depression of ventilation. Other opioid effects can be observed in virtually every organ system, in part because of the wide distribution of opioid receptors.
- The most important drug interaction for opioids is the synergism for both therapeutic and adverse effects that results when opioids are combined with sedatives (e.g., volatile anesthetics and propofol). These "MAC-reducing" effects are a fundamental concept underpinning modern anesthesia.
- When treating certain special populations (e.g., the elderly, patients with severe hepatic or renal disease, morbid obesity, severe bleeding), significant dosage adjustments are necessary.
- The most common clinical applications of opioids in perioperative medicine include postoperative pain therapy, "balanced anesthesia," and total intravenous anesthesia.
- The rational selection of opioids for perioperative use focuses on pharmacokinetic considerations. The commonly used perioperative opioids can be considered pharmacodynamic equals with important pharmacokinetic differences (e.g., differences relating to the onset and offset of effect). TCI of opioids is an important new delivery model.
- The influence of perioperative opioid use on cancer recurrence after oncologic operations, the treatment and prevention of opioid-induced ileus with poorly absorbable opioid antagonists, the search for "biased" opioid agonists with less potential for ventilatory depression, and the phenomena of acute tolerance and opioid-induced hyperalgesia are among the most important emerging developments and areas of investigation in opioid pharmacology.
- Opioid addiction and abuse is a major public health problem that has reached epidemic proportions, particularly in the United States. This public health crisis is an area of intense public interest and research activity.

Key References

Egan TD, Lemmens HJ, Fiset P, et al. The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. *Anesthesiology*. 1993;79:881–892. This human volunteer study first described the unique pharmacokinetic profile of remifentanil, the esterase metabolized fentanyl congener that became the first true "ultrashort-acting" opioid. In combination with propofol, remifentanil revolutionized the practice of TIVA and has become a mainstay of modern anesthesia practice, particularly in regions where intravenous anesthesia techniques are popular. (Ref. 75).

Matthes HW, Maldonado R, Simonin F, et al. Loss of morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the mu-opioid-receptor gene. *Nature*. 1996;383:819–823. Using site-directed mutagenesis techniques, these investigators demonstrated that μ-receptor knockout mice failed to exhibit therapeutic effects to morphine but were otherwise phenotypically normal, confirming the importance of the μ-receptor in opioid pharmacology. The μ-receptor knockouts also showed no reward or withdrawal behavior or respiratory depression with morphine administration. (Ref. 8).

McEwan AI, Smith C, Dyar O, et al. Isoflurane minimum alveolar concentration reduction by fentanyl. *Anesthesiology*. 1993;78:864–869. This study quantitatively characterized the extent of isoflurane MAC reduction by fentanyl in humans, thus serving as a prototype pharmacodynamic drug interaction study. The concept of reducing the dose requirement of volatile anesthetics with opioids is one of the most important and widely applied concepts in anesthetic pharmacology. (Ref. 42).

Osborne R, Joel S, Trew D, et al. Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide. *Clin Pharmacol Ther*. 1990;47:12–19. This human volunteer study confirmed the importance of M6G as an active morphine metabolite, particularly after oral administration. Subsequent investigation has established M6G's role in patients with renal failure or in patients receiving longer-term morphine therapy. (Ref. 66).

Poulsen L, Brosen K, Arendt-Nielsen L, et al. Codeine and morphine in extensive and poor metabolizers of sparteine: pharmacokinetics, analgesic effect and side effects. *Eur J Clin Pharmacol*. 1996;51:289–295. This human volunteer study demonstrated the importance of pharmacogenetic factors in determining the response to codeine, a prodrug of morphine. "Poor metabolizers" do not convert codeine to morphine in significant amounts and thus have no analgesic response to codeine, although they respond to morphine normally. This polymorphism relating to codeine metabolism is perhaps the best-described pharmacogenetic issue in this area of therapeutics and serves as a prototype in understanding the potential clinical impact of these genetic nuances. (Ref. 57).

Shafer SL, Varvel JR. Pharmacokinetics, pharmacodynamics, and rational opioid selection. *Anesthesiology*. 1991;74:53–63. This simulation study demonstrated the importance of pharmacokinetic considerations in rational opioid selection for perioperative use. The context sensitive half-time was an outgrowth of this work. Two key points of this article are that opioid behavior is quite different for bolus administration compared with continuous infusion and that pharmacokinetic simulation is necessary to understand the implications of these pharmacokinetic differences. (Ref. 14).

Wang JB, Johnson PS, Persico AM, et al. Human mu opiate receptor. cDNA and genomic clones, pharmacologic characterization and chromosomal assignment. *FEBS Lett*. 1994;338:217–222. These investigators first cloned the human μ-receptor and identified its chromosomal location, launching the era of genomic research in opioid pharmacology. (Ref. 3).

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18

Nonintravenous Opioids

JILL E. SINDT AND ROBERT H. JENKINSON

CHAPTER OUTLINE

Historical Perspective

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- Structure-Activity
- Mechanism of Action
- Metabolism

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- Pharmacodynamics
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  - *Adverse Effects*
  - *Drug Interactions*
  - *Special Populations*
  - *Unique Features of Individual Agents*

Clinical Applications
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  - *Acute Pain*
  - *Cancer Pain*
  - *Opioids for Chronic Pain*
- Rational Drug Selection and Administration

Emerging Developments
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- Peripherally Restricted μ-Receptor Antagonists
- Opioids and Immunosuppression
- Opioids and Sleep-Disordered Breathing
- Opioids and Endocrine Dysfunction

Historical Perspective

The use of opium for treating pain dates back to at least ancient Egypt, but the modern opioid era began in 1804 when German pharmacist Friedrich Wilhelm Sertürner discovered the naturally occurring opioid morphine.[1,2] Morphine and opium were widely sold over the counter in liquid, pill, and powder forms throughout the 19th century, and in 1898 the Bayer Company released the first semisynthetic opioid, heroin, as a cough suppressant. Initially touted as less habit-forming than morphine, within a few years heroin was widely crushed and snorted.[3] This, in addition to the rising tide of iatrogenic morphine addiction, led to the Harrison Narcotics Tax Act of 1914 in the United States, requiring physician and pharmacist registration for distributing opioids and largely criminalizing possession of these drugs for nonmedical uses.

In addition to regulatory action, the "opium problem" of the early 1900s led to increased focus on drug development both in the United States and abroad. The desire to identify a substitute for morphine, a drug that would separate the analgesic and addictive properties, led to the synthesis of oxycodone in 1917 in Germany.[4] In the United States the Committee on Drug Addiction was formed in 1921 and tested a number of newly developed synthetic and semisynthetic opioids over the next 50 years, yet a powerful opioid pain reliever without habit-forming properties remains elusive.[5]

The second heroin epidemic of the mid-1900s led to the Controlled Substances Act of 1970 in the United States, requiring manufacturers, distributors, and providers who dispense or administer controlled substances to register with the Drug Enforcement Administration (DEA). Later, in response to the need for opioid abuse treatment, the Narcotic Addict Treatment Act of 1974 decriminalized the use of opioids, primarily methadone, to permit legally treating opioid dependence with opioid replacement therapy.[6]

The 1990s ushered in growing attention to the problem of undertreated chronic pain. With this came aggressive marketing of opioids by the pharmaceutical industry, new pain management standards implemented by The Joint Commission on the Accreditation of Health Care Organizations, and relaxed laws governing prescribing of opioids by state medical boards. Prominent physicians and medical societies promoted the use of opioids to treat chronic pain with the misinformed assertion that opioids are safe and effective, with no dose ceiling or long-term untoward effects. These and other factors culminated in a rapid rise in the number of opioid prescriptions dispensed in the early 2000s, followed by an even more rapid rise in opioid-related overdose deaths.[7]

While opioids unquestionably have a role in the treatment of some types of pain, it is now clear they carry tremendous risks if not used judiciously. This chapter focuses on the clinical application of oral and transdermal preparations of opioid analgesics (for a discussion of basic opioid pharmacology and intravenous opioids, see Chapter 17).

Basic Pharmacology

Structure-Activity

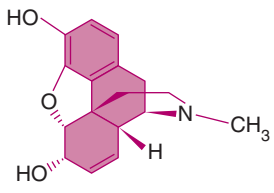
Clinically relevant nonintravenous opioids can be categorized into three structural groups: naturally occurring alkaloids, semisynthetic alkaloids, and synthetic opioids. Naturally occurring opioids can be extracted from the seeds of the poppy plant and include morphine and codeine (Fig. 18.1). Although the majority of codeine available worldwide is manufactured from morphine as a semisynthetic

Abstract

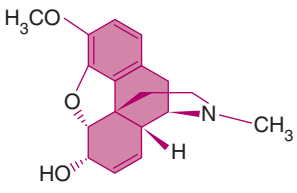
Oral opioids have been used for centuries for treating pain, with the modern era beginning in the 19th century with the discovery of morphine. Nonintravenous opioids can be categorized into three structural groups: naturally occurring alkaloids, semisynthetic alkaloids, and synthetic opioids. Most nonintravenous opioids are metabolized by the cytochrome P450 enzyme into inactive metabolites; however, morphine undergoes glucuronidation to produce metabolites that are renally cleared and may accumulate with renal insufficiency. Nonintravenous opioids have many routes of administration, including the ultrashort-acting transmucosal opioids, short-acting, extended-release and long-acting oral opioids, and continuous-acting transdermal opioids. Common side effects include constipation, nausea, sedation, pruritus, and respiratory depression. Tolerance develops to most of these effects, with the notable exception of constipation. Concomitant use of opioids and other central nervous system depressants can lead to profound sedation, respiratory depression, and death, particularly with benzodiazepines, propofol, and alcohol. Acute pain and cancer-related pain are long-standing indications for the use of nonintravenous opioids. However their use for chronic pain is controversial without established long-term efficacy and concerns for development of addiction and increases in opioid overdose deaths. Selection of a nonintravenous opioid is based on time to onset, needed duration, available routes of administration, opioid tolerance, and side effect profile. Emerging developments in nonintravenous opioids include buprenorphine for opioid dependence, peripherally restricted μ antagonists for opioid-induced constipation, concerns about suppression of immune and endocrine function, and increasing recognition of sleep-disordered breathing with opioids.

Keywords

Non-intravenous Opioids: Chemical Structure
Non-intravenous Opioids: Routes of Administration
Non-intravenous Opioids: Metabolism
Opioids: Renal Failure
Non-intravenous Opioids: Equivalency and Conversion
Cancer Pain: WHO Analgesic Ladder
Chronic Opioids: Side Effects

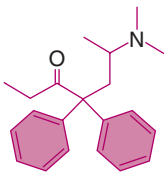


Morphine

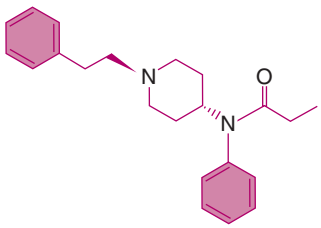


Codeine

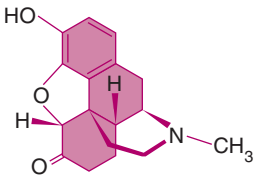
• **Fig. 18.1** Chemical structures of naturally occurring alkaloid opioids.



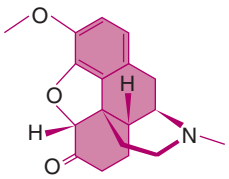
Methadone



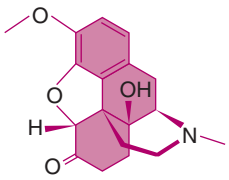
Fentanyl



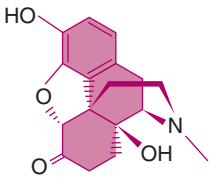
Hydromorphone



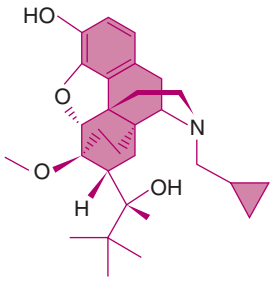
Hydrocodone



Oxycodone

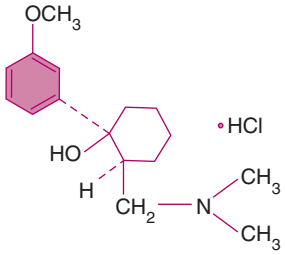


Oxymorphone

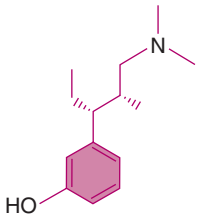


Bupenorphine

• **Fig. 18.2** Chemical structures of semisynthetic alkaloid opioids.



Tramadol



Tapentadol

• **Fig. 18.3** Chemical structures of synthetic opioids.

alkaloid, codeine is found naturally along with morphine in the poppy seed. Note that codeine simply adds a methyl group on the 3-hydroxyl of morphine.[8]

Semisynthetic alkaloids include hydromorphone (Dilaudid), hydrocodone (Norco, Vicodin), oxycodone (Percocet, Oxycontin), oxymorphone (Opana), and buprenorphine (Suboxone, Subutex). These drugs are derived from morphine, typically with substitutions of ester, hydroxyl, keto-, or methyl groups at the 3 and 6 carbon or 17 nitrogen positions of morphine (Fig. 18.2).[9]

Synthetic opioids are further characterized as phenylheptylamines, including methadone, and phenylpiperidines, including fentanyl. Tramadol and tapentadol are also included in this group. These drugs have unique chemical structures that do not follow a morphine-like pattern (Fig. 18.3).[10]

Mechanism of Action

All opioids exert their primary pharmacologic effects by interactions with opioid receptors at multiple sites in the central nervous system (CNS). The classic μ, κ, and δ opioid receptors are typical G-protein–coupled receptors (see Chapter 17). Binding of the opioid leads to an overall reduction in neuronal excitability via membrane hyperpolarization as the result of decreased cyclic adenosine monophosphate production, decreased calcium ion influx, and increased potassium ion efflux.

Tramadol and tapentadol are unique among nonintravenous opioids in that they bind to opioid receptors, but they also exert an analgesic effect through inhibiting reuptake of serotonin and norepinephrine; tramadol primarily inhibits serotonin reuptake and tapentadol primarily inhibits norepinephrine reuptake.[11] Fentanyl also inhibits serotonin reuptake, although the contribution to its clinical analgesic effect is unclear.[12]

Metabolism

The majority of nonintravenous opioids are metabolized by the cytochrome P450 system, primary via the 3A4 and 2D6 isoforms. Notable exceptions include morphine, hydromorphone, and oxymorphone. Morphine is chiefly metabolized via glucuronidation to the metabolites morphine-3-glucuronide (M3G), which has CNS neuroexcitatory effects, and morphine-6-glucuronide (M6G), an analgesic 50 times more potent than morphine. Hydromorphone and oxymorphone are the cytochrome P4502D6 metabolites of hydrocodone and oxycodone, respectively. They undergo glucuronidation as well as some reduction. Less is known about the activity of their metabolites, although hydromorphone-3-glucuronide may have CNS neuroexcitatory effects.

Most opioids are metabolized to inactive metabolites, although some, such as tramadol and codeine, are prodrugs that require metabolism to an active metabolite for clinical effect. Morphine is again a notable exception in having active metabolites. See Table 18.1 for a summary of opioid metabolism, metabolites. and their activity.[8–11,13–15]

TABLE 18.1 Metabolism of Opioid Analgesics

Medication	Metabolism	Metabolites	Metabolite Activity
Morphine	Glucuronidation	M3G M6G	Neuroexcitatory Active
Codeine	Glucuronidation (80%) CYP2D6 CYP3A4	C3G C6G Morphine Norcodeine	Possibly neuroexcitatory CNS-toxic Active Active Inactive
Hydrocodone	CYP2D6 CYP3A4	Hydromorphone Norhydrocodone	Active Inactive
Hydromorphone	Glucuronidation Reduction (minor)	H3G	Possibly neuroexcitatory
Oxycodone	CYP2D6 CYP3A4	Oxymorphone Noroxycodone	Active Inactive
Oxymorphone	Glucuronidation Reduction (minor)	6-OH-OXM OXM3G	Inactive Inactive
Buprenorphine	CYP3A4	Norbuprenorphine	Active
Methadone	CYP3A4 CYP2B6 (minor)	EDDP	Inactive
Fentanyl	CYP3A4	Nor-fentanyl	Inactive
Tramadol	CYP2D6	M1	Active
Tapentadol	Glucuronidation	TAP-OG	Inactive

EDDP, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; *H3G*, hydromorphone-3-gulcuronide; *M1*, O-desmethyltramadol; *M3G*, morphine-3-glucuronide; *M6G*, morphine-6-glucuronide; *6-OH-OXM*, 6-OH-oxymorphone; *OXM3G*, oxymorphone-3-glucuronide; *TAP-OG*, tapentadol-O-glucuronide.

Clinical Pharmacology

Pharmacokinetics

Opioids are unique in their availability across many routes of administration. In addition to intravenous and neuraxial administration, covered in previous chapters, they can be administered clinically by transmucosal (buccal, sublingual, or intranasal), oral, and transdermal methods. Experimental methods include inhaled opioids.

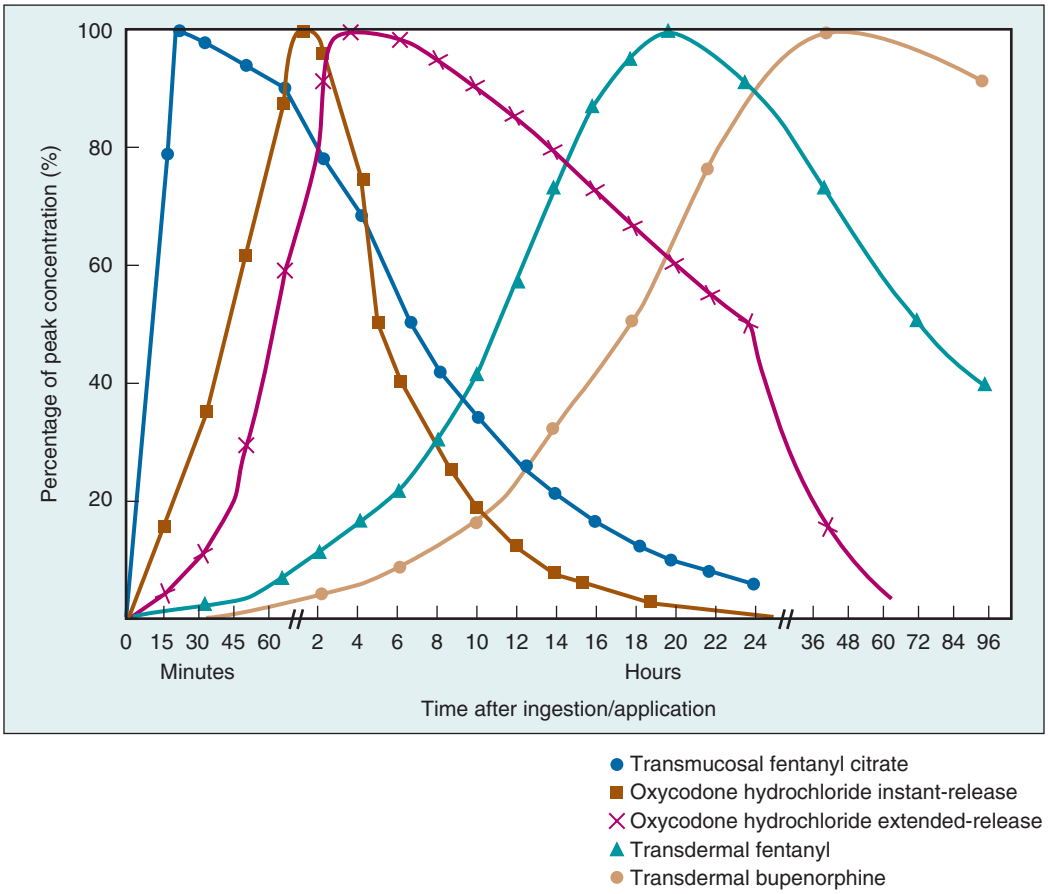
Transmucosal opioids are considered ultrashort-acting as they achieve peak plasma concentration within 10 to 20 minutes with an analgesic effect of 60 to 120 minutes.[16] Among oral opioids there are both short-acting and extended-release formulations of multiple agents such as hydrocodone, hydromorphone, and oxycodone. There are also long-acting agents such as methadone and buprenorphine. Short-acting oral opioids allow for "as-needed" dosing for episodic or breakthrough pain and generally achieve peak plasma concentrations within 30 to 60 minutes. Extended-release formulations and long-acting agents allow for less frequent dosing and more stable analgesia in patients with constant pain as they can ameliorate large fluctuations in serum opioid levels or the so-called "peak-and-trough" effect seen with short-acting opioids. However, they differ widely in their individual pharmacokinetic properties (Fig. 18.4 and Table 18.2).[17–26]

Fentanyl and buprenorphine are unique because transdermal delivery systems enable continuous delivery. Modern transdermal patches use an inert polymer matrix impregnated with dissolved drug that has evolved from early transdermal systems that consisted of a simple drug reservoir separated by a rate-limiting membrane. Drug delivery with transdermal patches is a result of the concentration gradient between the patch and skin, is proportional to the area of exposed skin, and allows for a near zero-order delivery of medication at steady state without being subject to first-pass metabolism.[27] This reduces, though does not eliminate, variability in serum opioid concentration. Additionally, this gradient is in part temperature-dependent, with increased absorption occurring at higher temperatures. Serious adverse effects and deaths have occurred with concurrent application of external heat, such as with electric heating blankets, saunas, and hot tubs.[28]

Pharmacodynamics

Like intravenous opioids, nonintravenous opioids exert their activity through agonism of the μ-opioid receptor (see Chapter 17). Given their common mechanism of action, most μ-opioid receptor agonists are pharmacodynamically equivalent and produce similar effects when used in equivalent equipotent doses.

The μ-opioid agonist-antagonists are exceptions to this general rule because of their more complicated μ-receptor activity profile. Buprenorphine, the most commonly used partial agonist outside the perioperative setting, is a partial agonist at the μ receptor



• **Fig. 18.4** Comparison of common nonintravenous opioid pharmacokinetics.

TABLE 18.2 A Comparison of Pharmacokinetic Properties Among Opioids

Opioid	Time to Peak Plasma Concentration	Duration of Effect	$t_{1/2}$
Transmucosal			
Buccal fentanyl	10–20 min	1–2 hr	4.5 hr
Intranasal fentanyl	5–10 min	60–90 min	4.5 hr
Oral Short-Acting			
Oxycodone	1–1.5 hr	2–4 hr	3.5 hr
Hydrocodone	1–1.5 hr	2–4 hr	3.5 hr
Oral Extended-Release			
Morphine	4.5 hr	8–12 hr	2–3 hr
Oxycodone	4.5–5 hr	12 hr	3.5 hr
Oral Long-Acting			
Methadone	1–7 hr	6–12 hr[a]	8–59 hr
Buprenorphine	100 min	24–36 hr	24–42 hr
Transdermal			
Fentanyl	24 hr	48–72 hr	24 hr
Buprenorphine	~48 hr	7 days	26 hr

[a]Methadone has a duration of analgesia that is much shorter than the duration of effect used to suppress withdrawal symptoms when used as maintenance therapy for opioid dependence.

and an antagonist at the κ receptor. Buprenorphine exhibits a ceiling effect for analgesia and respiratory depression compared with full agonists. Tramadol has a low affinity for the μ receptor, and analgesia is only partially reversed by administration of the specific μ-receptor antagonist naloxone, presumably because of its serotonin reuptake inhibition activity. Because of this low μ-receptor affinity, the analgesia produced by tramadol might be suboptimal for severe pain.

Therapeutic Effects

Activation of μ-opioid receptors produces analgesia, which is the primary therapeutic effect of opioids. Other effects such as sedation, decreased gastrointestinal motility, and antitussive properties have clinical applications but are typically secondary considerations for opioid selection and administration (see Chapter 17).

Adverse Effects

Common side effects of opioid analgesics prescribed in the ambulatory setting include constipation, nausea, sedation, confusion, dry mouth, pruritus, and respiratory depression. Less frequent side effects include urinary retention, myoclonus, and mood effects, both euphoria and dysphoria. These side effects can be dose-limiting and even life-threatening, but tolerance to most side effects occurs with continued opioid therapy, the major exception being opioid-induced constipation (OIC).

Respiratory Depression

Respiratory depression is the most dangerous adverse effect associated with μ-agonist drugs in either ambulatory or inpatient settings. Unrecognized respiratory depression when manifest in its severe

form can lead to fatal respiratory arrest. More than 165,000 deaths were attributed to overdoses related to prescription opioid medications from 1999 to 2014 in the United States; the overwhelming majority of these deaths are due to respiratory arrest.

Managing and monitoring opioid-induced respiratory depression in the ambulatory setting is challenging. The Centers for Disease Control and Prevention (CDC) Guideline on Prescribing Opioids for Chronic Pain released in 2016 recommends an increase in the frequency of follow-up as well as consideration of prescribing naloxone for emergency rescue if a patient's dosage from all combined sources of opioids reaches or exceeds 50 mg oral morphine equivalents (OME) per day because of the higher likelihood of respiratory depression.[29]

Sedation

Centrally mediated μ-receptor agonism is responsible for the sedation observed with opioid administration. Sedation is a common dose-limiting side effect outside the perioperative setting, particularly in the setting of patients with cancer pain and pain in the elderly, although it is generally temporary as tolerance occurs over time with stable opioid dosing. Combining oral and transdermal opioids with other CNS-active medications can lead to a greater than anticipated sedating effect.

Constipation

μ Receptors are highly concentrated throughout the mucosa and submucosa of the gastrointestinal tract. The concentration of μ and κ receptor is most dense in the stomach and proximal colon.[30] OIC is multifactorial but is due in part to an increase in nonperistaltic motility, delayed transit time, and increased sphincter tone at the pylorus and ileocecal junction. Given the high frequency of OIC, a prophylactic bowel regimen should be considered when initiating opioid therapy. In addition to traditionally used agents such as stool softeners, osmotic laxatives, and stimulant laxatives, newer therapies are available for treatment of OIC (see "Emerging Developments").

Nausea

Opioid-induced nausea and vomiting are common side effects, particularly for opioid-naive patients. Fortunately, habituation frequently occurs within several days but may necessitate treatment with antiemetic medications. Ultimately, switching to an alternative opioid, altering the route of administration, or reducing the dose may be required to manage the nausea effectively.[31] Patients can have idiosyncratic responses to different opioid analgesics and switching to a different opioid may reduce or resolve nausea, although the scientific foundation for this observation is not well established.

Pruritus

More commonly seen with parenteral or neuraxial administration, pruritus can still occur with oral, transdermal, and transmucosal administration. Patients typically become tolerant to opioid induced pruritus and infrequently require treatment. With rotation to another opioid, pruritus often resolves. If opioid-induced pruritus does require treatment, antiemetics such as ondansetron or promethazine or antihistamines such as diphenhydramine or hydroxyzine, can be used.[32]

Tolerance and Dependence

Tolerance and dependence are considered normal adaptive physiologic responses to ongoing opioid therapy. Tolerance is the need for increased dosing to maintain a defined degree of analgesia in the absence of disease progression or changes in other external factors. Dependence can be physical and/or psychological. Physical dependence occurs from a progressive tolerance to both the therapeutic and adverse effects of opioids and is characterized by the appearance of withdrawal symptoms with rapid dose reduction, abrupt discontinuation, or exposure to opioid antagonists.[33]

Tolerance and dependence should be distinguished from opioid abuse. As defined by numerous professional societies, opioid addiction is "a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving."[33]

Other Adverse Effects

Myoclonus can occur with high-dose opioid therapy, particularly with morphine, secondary to accumulation of the metabolite M3G. Transitioning to a new opioid often results in improvement or resolution of myoclonus. Urinary retention can result from opioid administration, although this effect is variable. μ Agonists increase urinary tract smooth muscle tone, although in some cases this can produce urinary urgency as opposed to true urinary retention. Conversely, opioids reduce gastrointestinal tract sphincter tone. This can result in dysfunction of the sphincter of Oddi, which controls the flow of bile and pancreatic secretions into the duodenum. Acute biliary-type pain attacks and dilation of bile duct have been reported and these effects are reversed with naloxone.[34] Opioids can affect reward pathways in the brain and induce euphoria in select patients, but can cause dysphoria in others. These responses are due in part to opposing effects of μ receptor and κ receptor agonism on dopamine levels in the nucleus accumbens, substantia nigra, and striatum, offering an explanation for seemingly idiosyncratic dysphoric reactions to different opioids.[35,36]

Drug Interactions

Concomitant use of opioids and other CNS depressants can lead to profound sedation, respiratory depression, and death, particularly with gamma aminobutyric acid $(GABA)_A$ agonists such as benzodiazepines, barbiturates, propofol, and alcohol. These interactions are synergistic. Opioid-associated urinary retention and constipation are compounded by the coadministration of drugs with significant anticholinergic activity. Of particular clinical significance is the increased incidence of constipation in the setting of concomitant use of opioids and ondansetron owing to the effect of ondansetron on serotonin-mediated gastrointestinal peristalsis.[37] Constipation is a common adverse effect associated with ondansetron, occurring in nearly 10% of patients treated for nausea and vomiting associated with chemotherapy, and can be worsened by opioid therapy in this patient population. The synthetic opioids, including fentanyl, methadone, tramadol, and meperidine, are all weakly serotonergic and have been implicated in multiple reports of serotonin syndrome when used in combination with other serotonergic medications such as monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, and lithium.[38,39]

Multiple opioids undergo phase I metabolism via the cytochrome P450 system, particularly CYP2D6 and CYP3A4. These enzymes are affected not only by allelic variations but also by many other medications that act as substrates, inhibitors, and inducers. Common inducers include anticonvulsant agents and pentobarbital. Calcium channel blockers, selective serotonin reuptake inhibitors, benzodiazepines, many psychotropic agents (see Chapter 12), and multiple antibiotics act as both a substrate and an inducer of CYP 450

enzymes, and many opioids have substantial interaction potential with these commonly used agents. See Table 18.3 for a summary of these interactions.

Special Populations

Renal Insufficiency

The liver is the major site for biotransformation and elimination of most opioids; however, the majority of opioid metabolites are renally cleared. Although these metabolites are often inactive or minimally active, an important exception is morphine. Morphine is metabolized to the inactive metabolite M3G and the active analgesic metabolite M6G, which has an analgesic potency near that of morphine. Accumulation of M6G leading to respiratory depression in patients with altered renal clearance mechanisms constitutes the basis for avoiding morphine therapy in patients with renal failure. Because codeine is metabolized to morphine it should also be avoided in patients with renal insufficiency.

Oxycodone and oxymorphone both have active metabolites. In uremic patients the elimination half-life is lengthened and excretion of metabolites is impaired; however, the clinical relevance of this is largely unstudied in the setting of renal insufficiency.[40] Tramadol produces the metabolically active metabolite M1, and an increased dosing interval of 12 hours is recommended in patients with compromised renal function.

Fentanyl, methadone, and buprenorphine are considered safe in patients with renal insufficiency and do not require dose adjustment. Hydromorphone is also a preferred opioid in patients with renal impairment, although it has a potentially active metabolite. In the setting of dialysis, hydromorphone levels are reduced to 40% of predialysis levels, whereas fentanyl and buprenorphine are not dialyzable and levels remain unchanged following dialysis.[41–43]

Hepatic Impairment

The liver is the major site of metabolism for most opioids; thus patients with liver disease who require opioid treatment present unique challenges. Impaired liver function not only leads to changes in the pharmacokinetic properties of drugs but can also lead to alteration in plasma protein binding and the plasma concentration of unbound "free" drug.[44] This altered drug disposition can lead to increased therapeutic effect and an increase in adverse effects, potentially manifest as sedation, respiratory depression, and potentiation of hepatic encephalopathy. Unfortunately, there is limited data to guide specific dosing recommendations of opioids in the ambulatory setting in patients with liver failure.

Because their metabolites are inactive, fentanyl and hydromorphone are often the preferred agents in patients with liver disease. However, lower starting doses, slower dose titration, and increased dose intervals are recommended when initiating ambulatory therapy with any of the commonly used opioids in patients with significant hepatic insufficiency. Limited data exists for buprenorphine, although it has been used without adverse effect in patients with concurrent liver dysfunction owing to hepatitis C and, with caution and close monitoring, appears to be safe in patients with liver disease.[45] See Table 18.4 for a summary of recommendations.

Elderly

Advanced age is known to be an important covariate that alters both the pharmacokinetic and pharmacodynamics properties of opioids. In general, opioid clearance is lower and opioid potency is greater in the elderly.[46,47] Compared with younger patients, a given dose produces higher plasma concentrations and more pronounced effects, both therapeutic and adverse, in the older patient.

Among elderly patients falls, fractures, sedation, and impaired cognition dominate concerns about the use of opioids. Unpredictable or greater than expected opioid effects can result from age-related reduction in renal function, drug-drug interactions owing to use of multiple prescription medications, and overall increased frailty in this population. Opioids as a class have been associated with an increased risk of falls and fractures and it does not appear that one opioid is vastly superior to another, although there is a lower incidence of fractures with transdermal buprenorphine compared with other opioids.[48]

In terms of selecting a specific opioid for elderly patients it appears that transdermal fentanyl and transdermal buprenorphine

TABLE 18.3 Opioid Analgesics in Hepatic Impairment

Medication	Dose	Dose Interval	Notes
Morphine	Reduced	Increased	
Codeine	Avoid	Avoid	Metabolized to morphine with unpredictable serum concentrations
Hydrocodone	Reduced	Increased	
Hydromorphone	Reduced	No change	Preferred agent
Oxycodone	Reduced	Increased	
Oxymorphone	Reduced	Increased	
Buprenorphine	Unknown	Unknown	Appears safe but limited data
Methadone	Reduced	Increased	
Fentanyl	Reduced	Increased	Preferred agent
Tramadol	No change	Increased	

TABLE 18.4 Morphine Equivalent Doses for Commonly Prescribed Opioids

Medication	Route	Equivalent Dose
Morphine	PO	30 mg
Hydrocodone	PO	30 mg
Hydromorphone	PO	7.5 mg
Oxycodone	PO	20 mg
Oxymorphone	PO	10 mg
Buprenorphine	SL	Unpredictable Approximately 0.8–1 mg
Methadone	PO	Unpredictable Approximately 7.5–10 mg
Fentanyl	TD	12 µg/hr

PO, Oral, *TD*, transdermal.

are generally safe and well-tolerated, with a lower incidence of constipation. The transdermal route, with infrequent need to change patches, also increases compliance. Transdermal buprenorphine (available in the United States) offers the advantage of a low dosage option (the 5-μg/hr patch is equivalent to approximately 15 mg of oral morphine over 24 hours) for the elderly patient. It is prudent to avoid morphine in the elderly to avoid M6G accumulation in patients with unrecognized, age-related renal impairment. All opioid analgesics in the elderly should be started at lower doses, with increased dosing intervals and slower up-titration with close monitoring of the therapeutic response and side effect proflie.[49]

Unique Features of Individual Agents

Morphine

Both short-acting and extended-release forms of enteral morphine are available. The two metabolites, M3G and M6G, are cleared by the kidney. M6G can contribute to sedation, hallucinations, and even respiratory depression in patients with altered kidney function. M6G is the primary active analgesic metabolite and crosses the blood-brain barrier.[50] M3G has no clinically significant analgesic effects but does have neuroexcitatory effects accounting for the myoclonus observed with high daily doses of morphine.[51] Approximately 10% of morphine is excreted unchanged in the kidneys with a small component of biliary excretion and enterohepatic recycling.

Morphine typically serves as the dosing reference for all other opioids used in ambulatory therapy. The OME is the standardized metric to compute "equianalgesic" doses of other opioids. The concept is useful when comparing the potential risks of adverse effects between opioids. Although widely applied when converting patients from one opioid to another, the main limitation of the OME concept is that the different pharmacokinetic and receptor profiles of the various drugs make the determination of "equal" doses difficult to achieve over time.

Codeine

Codeine is a prodrug that requires conversion by CYP2D6 in the liver to its active metabolites, codeine-6-glucuronide and morphine, that are ultimately responsible for codeine's analgesic effects. Patients with diminished or absent CYP2D6 activity have limited response to codeine, whereas patients who are ultrarapid metabolizers (e.g., CYP2D6 gene duplications) can have exaggerated responses to codeine owing to more extensive metabolism to morphine (see Chapter 17).[52,53] Because of this pharmacogenetic variability, codeine is now much less commonly prescribed in contemporary pain management.

Oxycodone

Oxycodone is a semisynthetic opioid synthesized from the opiate alkaloid thebaine. It is available in short-acting and extended-release formulations as well as preparations compounded with acetaminophen or aspirin. Oxycodone undergoes low first-pass metabolism and has a higher bioavailability (60%-87%) compared with morphine. It undergoes *O*-demethylation via both CYP3A4 and CYP2D6 to oxymorphone, its primary active metabolite, which is three times more potent than morphine.[54] Oxycodone also undergoes metabolism by CYP3A4 to noroxycodone, which has weak μ-opioid receptor activity compared with oxycodone or oxymorphone. It has been suggested that individuals with decreased CYP2D6 activity because of genetic polymorphisms require higher doses of oxycodone as the result of lower oxymorphone production, but there is limited evidence to support this assertion.[55] Oxycodone and its metabolites primarily undergo urinary excretion with less than 10% of the parent compound excreted unchanged.

Hydrocodone

Hydrocodone is a semisynthetic opioid structurally similar to codeine. It is available in short-acting and extended-release versions as well as preparations compounded with acetaminophen or ibuprofen. Hydrocodone undergoes a complex pattern of metabolism by CYP2D6 and CYP2C19 to hydromorphone, and by CYP3A4 to norhydrocodone, an inactive metabolite.[56] Although the parent compound hydrocodone exerts most of this drug's therapeutic effect, hydromorphone (which circulates at <3% of the original parenteral hydrocodone dose) contributes to the overall analgesic effect, and allelic variations in CYP2D6 can decrease the efficacy of hydrocodone.[57] Hydrocodone and its metabolites primarily undergo renal excretion, with only 6.5% excreted unchanged by the kidneys.

Oxymorphone

Oxymorphone is a semisynthetic opioid and is the primary active metabolite of oxycodone. It is available in both short-acting and extended-release formulations. It has poor oral bioavailability (approximately 10%), but it is much more potent that morphine. Oxymorphone primarily undergoes phase II metabolism via conjugation with glucuronic acid to form oxymorphone-3-glucuronide but is also metabolized to 6-hydroxy-oxymorphone, an active metabolite. Approximately 99% of the total administered dose is excreted in the urine in its conjugated form, while less than 1% is metabolized and undergoes renal elimination as 6-OH-oxymorphone; the active metabolite thus does not reach levels that contribute meaningfully to drug effect.[56] Therefore no dose adjustment is necessary for anticipated changes in cytochrome P450 activity as oxymorphone has no known pharmacokinetic drug-drug interactions.

Hydromorphone

Hydromorphone, a hydrogenated ketone of morphine, has very similar pharmacokinetic and pharmacodynamic properties compared with morphine and is similarly excreted by the kidneys. However, hydromorphone is four times more potent than morphine. Hydromorphone is available in short-acting and extended-release formulations. Hydromorphone primarily undergoes phase II conjugation with glucuronic acid to form hydromorphone-3-gulcuronide (H3G).[58] H3G has a low affinity for opioid receptors, and because of its hydrophilic properties and lower blood-brain barrier permeability, might cause fewer adverse cognitive effects compared with morphine. However, H3G can have a neuroexcitatory potential similar to M3G with accumulation in patients with renal failure, although this does not appear to be as clinically relevant as with morphine.[57]

Tramadol

A weak μ-receptor agonist, tramadol exerts additional central-acting analgesic effects via serotonin reuptake inhibition (and norepinephrine to a lesser degree). It is considered a weak opioid and is recommended for the treatment of mild to moderate pain.

Tramadol undergoes extensive metabolism by CYP2D6 and CYP3A4 as well as glucuronidation. The primary pharmacologically active metabolite is O-desmethyltramadol (M1) formed by CYP2D6.[59] Tramadol is thus affected by genetic polymorphisms of CYP2D6. Tramadol and M1 both exert analgesic effects, although M1 is a more potent μ-receptor agonist, and tramadol itself is a

more potent serotonin-norepinephrine reuptake inhibitor.[57] Tramadol and its metabolites are excreted in the urine with 30% excreted unchanged.

Because of this unique serotonin reuptake inhibition, clinicians must be aware of the potential for serotonin syndrome if tramadol is combined with monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants, or other serotonergic medications. Short-acting and extended-release oral formulations are available in the United States as well as a combination tablet with acetaminophen.

Tapentadol

Tapentadol is a synthetic analgesic indicated for the treatment of moderate to severe pain. It acts via both μ-opioid agonism and norepinephrine reuptake inhibition. It can be more effective for patients with primary or coexisting neuropathic pain such as painful diabetic peripheral neuropathy. It is available in short-acting and extended-release formulations and is less potent than morphine. There are no pharmacologically active metabolites. Tapentadol undergoes glucuronidation and is therefore less reliant on the cytochrome P450 system.[60] It then undergoes almost exclusively renal excretion with only 3% excreted in the urine unchanged.

Buprenorphine

Buprenorphine is unique in that it is available in enteral, transdermal, and transmucosal formulations. Buprenorphine is a partial agonist at the μ receptor but binds with higher affinity and slower dissociation than full agonist opioids. It also has κ-receptor antagonist properties. Because of its pharmacodynamic properties, it has been suggested that there is a ceiling effect for analgesia and also for respiratory depression, although profound respiratory depression and respiratory arrest can still occur with buprenorphine therapy, particularly with coadministration of benzodiazepines, alcohol or sedative hypnotics. The CYP3A4 isoenzyme plays a major role in metabolism of buprenorphine, and CYP3A4 inhibition can lead to a decrease in clearance of the drug. Norbuprenorphine is the only known active metabolite, but it produces analgesia or adverse effects only at concentrations well above clinically applicable dose ranges.[59] Buprenorphine undergoes hepatic metabolism and subsequent biliary and renal excretion.

For the transdermal formulation, the lowest available starting dose is a 5-μg/hr patch (available in the United States) that delivers drug for 7 days. In Europe the transdermal preparation is available in higher doses and delivers drug for 4 days. Buprenorphine is associated with QTc interval prolongation in higher doses and its use should be carefully considered in patients with a personal or family history of long QT syndrome or who are taking class IA or class III antiarrhythmics. As a partial μ-receptor agonist, buprenorphine can precipitate acute withdrawal in opioid-dependent patients; the severity of withdrawal depends on the degree of physical dependence and dose of buprenorphine administered.

Suboxone, a combination product of buprenorphine and naloxone, was approved in the United States in 2002 for use in the treatment of opioid dependence and maintenance therapy for opioid addiction. Naloxone has poor bioavailability with enteral administration owing to marked first-pass hepatic metabolism and was included in the formulation to deter intravenous abuse of buprenorphine.

Fentanyl

Fentanyl is a synthetic opioid that is frequently administered in injectable form but is also available in transdermal and transmucosal formulations. Fentanyl is primarily metabolized by CYP3A4 to norfentanyl and other inactive metabolites; CYP3A4 inhibitors can decrease the clearance of fentanyl. These metabolites primarily undergo renal excretion, although there is a small fraction that undergoes biliary excretion, and less than 10% of fentanyl is excreted unchanged.

Transdermal fentanyl is not indicated for opioid-naive patients and should be started after dose titration with a short-acting opioid. The lowest available starting dose is a 12-μg/hr patch that is intended for 72-hour use. Although as an intravenous formulation fentanyl is considered a short-acting drug, the transdermal preparation is considered a continuous opioid. Achievement of steady-state plasma levels can vary depending on patient characteristics such as variations in skin and subcutaneous tissues, skin temperature, and perspiration but generally requires 12 to 48 hours after initial placement. Peak plasma concentrations might not be reached until 72 hours after initial application in some patients. Some patients require more frequent patch replacement (e.g., every 48 hours instead of every 72 hours). Transdermal preparations have a more favorable side effect profile for constipation and higher patient satisfaction owing to convenience, particularly in cancer pain.[31]

In 2015 a novel transdermal fentanyl formulation using inotophoresis, a process in which low-intensity electric current is used to transport ionized drug molecules from the patch into the systemic circulation, was approved in the United States. The fentanyl HCI inotophoretic system (ITS) is a form of patient-controlled analgesia in which the patch is placed on the chest or outer upper arm. The ITS delivers a preprogrammed 40-μg dose over 10 minutes when the patient activates it by pressing a recessed button. It is indicated for the management of acute, moderate to severe postoperative pain in hospitalized adults.[61] Safe and effective pain control using the fentanyl ITS has been reported with multiple procedural types in both adult and geriatric populations.[1]

Transmucosal fentanyl delivery products are also available that allow for rapid-onset analgesia. These formulations include a buccal film and tablet, sublingual spray and tablet, oral lozenge, and nasal spray. The transmucosal delivery route avoids first-pass metabolism, substantially increasing the bioavailablity and speed of onset (see Chapter 17). Transmucosal fentanyl products are indicated for cancer-related breakthrough pain in opioid-tolerant patients only and their use is regulated under the U.S. Food and Drug Administration's (FDA) Risk Evaluation and Mitigation Strategies program.

Sufentanil

Sufentanil is a potent synthetic μ-receptor agonist currently available in a sublingual formulation in Europe and awaiting FDA approval in the United States. It has an onset of action similar to transmucosal fentanyl and substantially faster than that of other opioids such as hydromorphone and morphine. It undergoes extensive metabolism by cytochrome P450 3A4 and has no active metabolites. Inactive metabolites are excreted in the urine and feces. Small studies have not reported significant changes in sufentanil clearance in the setting of renal or hepatic impairment, although there are limited data in these populations.

Because of its rapid onset of action, sublingual sufentanil has been used and studied primarily for moderate to severe acute postoperative pain. The sufentanil sublingual tablet system is a novel method of patient-controlled analgesia in which a preprogrammed handheld device distributes a 15-μg sublingual microtablet with a preprogrammed lockout interval of 20 minutes. The device uses a radiofrequency identification thumb tag to ensure only

the patient operates the device. It has been shown to be at least as efficacious as intravenous morphine patient-controlled analgesia with a faster onset of action. Side effect profiles have been reported to be similar to intravenous morphine patient-controlled analgesia with greater patient and provider satisfaction and ease of use.[62]

Methadone

Methadone is a synthetic opioid for use in both opioid dependence as maintenance therapy and in chronic pain owing to its long duration of action, low cost, and lack of active or neurotoxic metabolites. Methadone is primarily metabolized by CYP3A4 and CYP2B6 but also undergoes metabolism by four additional cytochrome P450 enzymes. This complex metabolism profile complicates its interaction potential with other drugs.[63] Methadone undergoes both renal and biliary elimination.

Methadone is a μ-receptor agonist but additionally acts as a *N*-methyl-D-aspartate (NMDA) receptor antagonist and a weak serotonin and norepinephrine reuptake inhibitor. Methadone is dosed once daily for prevention of opioid withdrawal symptoms in the setting of opioid replacement therapy for opioid dependence. However, when used in the treatment of pain, its analgesic effect is much shorter, typically requiring dosing every 8 hours.

Methadone's clinical pharmacologic profile exhibits high interindividual variability.[31] Dose conversion ratios between other opioids and methadone are complex, and there is no clear expert consensus about dosing recommendations for converting patients to methadone from other opioids. Slow dose titration is necessary as the long and variable half-life increases the risk of unintended accumulation that can occur as the serum concentration slowly rises toward steady state once a dose is selected. Unfortunately, the increase in the utilization of methadone in the United States has been paralleled by an increase in methadone-related deaths, perhaps due in part to incomplete appreciation of its variable dose requirement.[64] The significant increase in iatrogenic overdoses with methadone therapy led the FDA to issue a black box warning cautioning clinicians regarding the risk of cardiac and respiratory related deaths when initiating and converting patients to methadone therapy. Methadone requires careful monitoring and slow dose titration by experienced clinicians.

Methadone has negative chronotropic properties and can prolong the QTc interval leading to torsades de pointes. Because of this risk, the American Pain Society, College on Problems of Drug Dependence, and the Heart Rhythm Society developed consensus guidelines for methadone use. These guidelines call for a pretreatment electrocardiogram (ECG) in patients with risk factors for QTc prolongation, documented prior QTc longer than 450 msec or a history suggestive of ventricular arrhythmias, and recommend considering a pretreatment ECG in all patients.[64] A follow-up ECG should be conducted in high-risk patients 2 to 4 weeks after initiation of methadone and some recommend annual ECGs, especially with dose increases above 30 to 40 mg/day or if the daily dose exceeds 100 mg/day.[66] Alternative therapy should be considered for patients with baseline QTc longer than 450 msec, and methadone should not be used in patients with QTc longer than 500 msec, as the risk of torsades de pointes increases substantially above this threshold.[65,66]

Combination Agents

Many combination agents exist in which select opioids—namely, hydrocodone, oxycodone, or codeine—are compounded with a nonopioid analgesic including ibuprofen, acetaminophen, or aspirin (e.g., codeine/acetaminophen, hydrocodone/acetaminophen, hydrocodone/ibuprofen, oxycodone/acetaminophen, oxycodone/aspirin). These agents provide some degree of convenience but present many challenges by combining opioids with agents that have clearly defined ceiling doses and their own unique side effect profiles. In 2014, the FDA began requiring that products containing acetaminophen limit the maximum amount of acetaminophen to no more than 325 mg per dose for nonintravenous agents to limit the risk of hepatotoxicity from inadvertent acetaminophen overdose.

Clinical Applications

Common Clinical Indications

Acute Pain

Acute pain related to surgery, illness, or trauma is the most common indication for nonintravenous opioid analgesics. Over the past two decades the importance of treating acute pain has been increasingly recognized. Unrelieved acute pain is associated with reduced quality of life, reduced social function, poor sleep, and impaired physical functioning. Additionally, severe acute pain has been identified as a risk factor for the development of chronic pain states. Although the mechanism for this phenomenon is poorly understood, it has been observed in various patient populations, including those with postsurgical pain, burn injury, acute herpes zoster ("shingles") infection, whiplash injury, after childbirth, and in patients hospitalized with severe medical illnesses.[67,68]

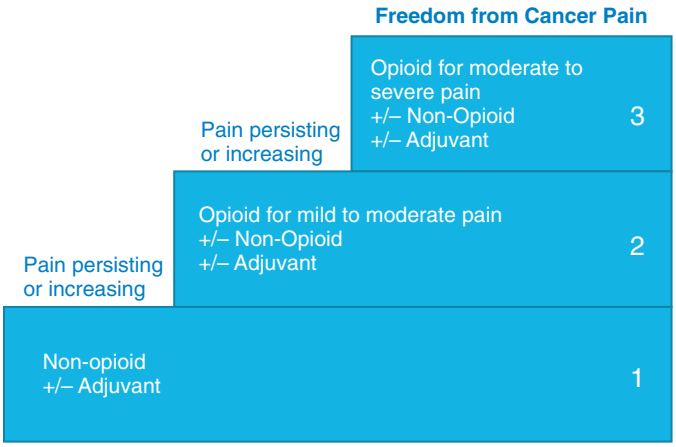
Opioid analgesics are reserved for patients whose moderate to severe acute pain is not relieved by acetaminophen and/or nonsteroidal antiinflammatory drugs and in combination with other nonopioid adjuvant medications and therapies.[69] Although most patients discontinue opioids themselves after recovery from illness, injury, or surgery within a matter of days, in patients who continue to experience pain it is less clear how long opioids should be reasonably continued. Although severe acute pain is a risk factor for the development of chronic pain, use of opioids for acute pain is associated with long-term opioid use, and this association is dose-related. In a study of patients hospitalized for medical opioid detoxification, 51% reported starting opioids for acute pain related to injury or surgical/dental procedure.[70] The Centers for Disease Control and Prevention (CDC) Guideline on Prescribing Opioids for Chronic Pain released in 2016 specifically addresses this issue and offers the following recommendation[29]:

> *Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.*

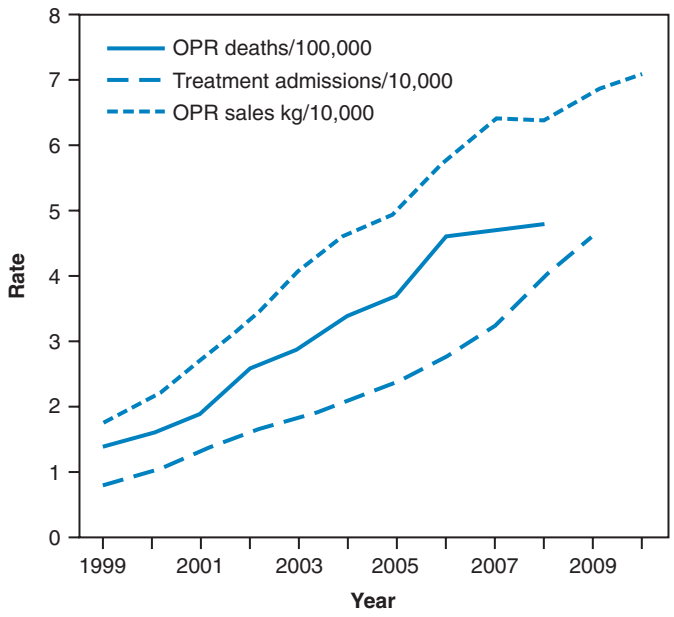
Cancer Pain

Pain is a significant burden in cancer patients; nearly 60% of patients with cancer report pain during their treatment, and among patients with advanced cancer nearly half describe their pain as moderate or severe. Cancer-related pain is associated with a reduced ability to tolerate treatment, depression, reduced life expectancy, and diminished quality of life for both patients and caregivers.[71]

In accordance with the World Health Organization's cancer pain ladder, opioids are the medication of choice for the treatment



• **Fig. 18.5** WHO Pain Relief Ladder for Cancer Pain. (From World Health Organization. WHO Pain Relief Ladder for cancer pain relief.)



* Age-adjusted rates per 100,000 population for OPR deaths, crude rates per 10,000 population for OPR abuse treatment admissions, and crude rates per 10,000 population for kilograms of OPR sold.

• **Fig. 18.6** Rates of opioid pain reliever *(OPR)* overdose death, OPR treatment admissions and kilograms of OPR sold—United States 1999-2010. (From *Morbidity and Mortality Weekly Report (MMWR).* This series is prepared by the Centers for Disease Control and Prevention. Available at http://www.cdc.gov/mmwr/pdf/wk/mm6043.pdf. Accessed October 22, 2016.)

of moderate or severe cancer pain (Fig. 18.5)[72] For pain that is not relieved by nonopioid medications such as acetaminophen or nonsteroidal antiinflammatory drugs, a weak opioid agonist such as tramadol, codeine, or hydrocodone should be initiated. If pain persists or worsens, a strong opioid agonist such as morphine, hydromorphone, or oxycodone should be used. Numerous studies, systematic reviews, and meta-analyses have confirmed the efficacy of this approach.[73,74]

Opioids for Chronic Pain

Chronic pain is defined as pain lasting for longer than 3 months, or past the time of normal tissue healing. Chronic pain is common in the United States, affecting approximately 20% of the population at any given time. Chronic pain is associated with reduced quality of life, lost productivity, martial and family discord, social isolation, impaired sleep, increased medical costs, financial stress, mood disturbance, and disability.[75]

The use of opioids for chronic, noncancer pain is a controversial topic. Comprehensive systematic reviews have reported unclear and/or weak evidence on the efficacy of long-term use of opioids for chronic pain. Despite this, prescribing opioids for chronic pain is a common practice; it is estimated that 20% of patients who present to physicians with chronic, noncancer pain receive an opioid prescription.[76] Opioid prescriptions dispensed by retail pharmacies rose in the United States from 76 million in 1991 to 219 million in 2011.[77] This trend was paralleled by a rapid rise in admissions for opioid abuse treatment and an even steeper rise in opioid overdose deaths (Fig. 18.6).[78]

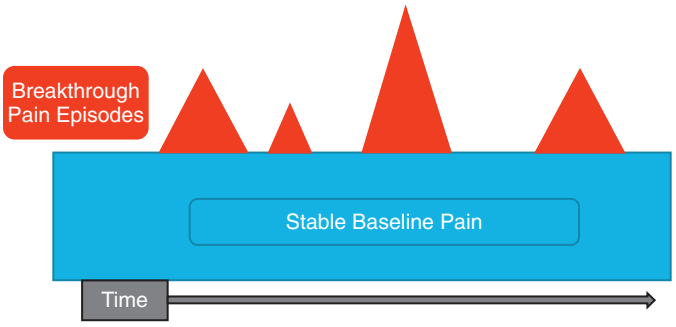
The CDCs Guideline for Prescribing Opioids for Chronic Pain lays out principles for navigating competing concerns. These include using opioids in combination with nonpharmacologic and nonopioid therapies, defining realistic goals for pain and function, discussing the risks of opioids frankly with patients, using the lowest effective dose, evaluating for objective improvements in function after initiating opioids when the OME dose exceeds 50 mg/day, and avoiding prescribing greater than 90 mg OME/day. The guideline also recommends screening for aberrant opioid-related behavior through use of drug testing and review of state prescription drug monitoring databases. Finally, avoiding concurrent use of benzodiazepines and offering take-home naloxone when the dose exceeds 50 mg OME/day are recommended to reduce the risks of opioid overdose and death.[29]

Rational Drug Selection and Administration

Similar to the choice of intravenous opioids, the selection of one oral or transdermal opioid over another is largely based on the desired temporal profile of effect, which is determined by its pharmacokinetic behavior. The time to onset of analgesia and needed duration of effect are primary considerations. However, unlike intravenous opioids, there are additional variables when selecting a nonintravenous opioid, including available routes of administration, level of baseline opioid tolerance, and the side effect profile.

For example, treatment of acute or cancer-related pain in an opioid-naive patient should start with a short-acting, low-dose opioid. Additionally, if pain is episodic, a short-acting oral opioid is appropriate, with escalation of dose as needed to achieve analgesia. However, if pain is continuous in nature such that frequent doses of short-acting opioids are required, initiation of a long-acting opioid should be considered. Long-acting opioids have the advantage of mitigating the "up-and-down" cycle of repeated dosing of short-acting opioids. However, these longer-acting formulations carry greater risk for serious side effect, such as respiratory depression and sedation, in opioid-naive patients.

Furthermore, there is the problem of breakthrough pain (Fig. 18.7), commonly defined as "a transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled baseline pain."[79] It is seen most in cancer patients, 40% to 80% of whom report breakthrough pain, with



• **Fig. 18.7** Breakthrough pain.

increased rates among patients with advanced cancer and in patients with more severe baseline pain.[80] Opioids are the rescue medication of choice in managing cancer-related breakthrough pain; opioids that act quickly but have a shorter duration are preferred. These include the short-acting or so-called immediate-release oral opioids, most ideal for opioid-naive patients, pain episodes lasting more than 60 minutes, and for preemptive dosing before volitional incident or procedural pain. For opioid-tolerant patients the transmucosal fentanyl products have been shown to be efficacious, safe, and well-tolerated and carry the advantage of a much more rapid onset and shorter duration, better matching the temporal profile of most breakthrough pain episodes.[81]

Finally, the optimal route of administration must be considered. Patients with impaired gastric or intestinal absorption, ileus, oral or esophageal irritation, gastrointestinal tract obstruction, or impaired swallowing may be unable to use oral formulations or may have unpredictable bioavailability and analgesic effect with oral formulations. Transdermal delivery of opioids is well suited for this population.

Emerging Developments

Buprenorphine for Opioid Dependence

Buprenorphine was approved in the United States for the outpatient management of opioid dependence in 2002. It is available as an abuse-deterrent sublingual film or tablet in combination with naloxone under the trade name Suboxone, or without naloxone as Subutex. It is typically taken as a once-daily dose of 8 mg to 32 mg and, when used for opioid dependence, must be prescribed by a physician who has completed specific training and holds a specialized Drug Enforcement Administration license.

Compared with in-person daily methadone dosing at a methadone maintenance clinic, buprenorphine permits more flexibility to patients and increases the availability of opioid replacement therapy to smaller towns and rural areas. Additional advantages include its long half-life (24–60 hours), lower incidence of euphoria, safety in renal insufficiency, possible ceiling for respiratory depression, and lower rates of tolerance.[82,83]

The efficacy of buprenorphine for opioid dependence is well established with numerous studies demonstrating reductions in cravings for opioids, withdrawal symptoms, and illicit drug use. A recent Cochrane review concluded that it is superior to placebo and, at doses greater than 7 mg/day, is equally effective as methadone for opioid dependence treatment retention and for suppressing illicit opioid use.[84,85] However, although buprenorphine is effective for opioid dependence, it appears most patients require long-term treatment. Rates of relapse to prescription opioid or heroin abuse with buprenorphine discontinuation are very high, approaching 80% in some studies.[86]

Illicit and accidental use of buprenorphine has raised safety concerns. Calls to U.S. Poison Centers regarding buprenorphine exposure or poisoning rose from 771 in 2010 to nearly 3500 in 2014.[87] There is an increasing number of reports of pediatric hospitalizations and deaths related to accidental ingestion of buprenorphine.[88] Additionally, owing to its high affinity for the μ receptor, typical doses of naloxone might not reverse the respiratory depression seen with buprenorphine overdose. Dose requirements of 2 to 4 mg of naloxone have been reported in several studies, with repeated doses or continuous infusion required.[89]

Finally, because of the long half-life and potency of buprenorphine (30–50 times as potent to morphine) there are anesthetic implications for pain control in the perioperative period. Patients treated with buprenorphine have significant tolerance/resistance to opioids. Additionally, full agonist opioids, both intravenous and oral/transdermal, often have diminished effects as the partial agonist buprenorphine acts as a competitive antagonist at the μ receptor. Several management strategies have been proposed, including discontinuing buprenorphine before planned surgery, continuing buprenorphine and adding full agonist opioids for perioperative pain control, and continuing buprenorphine and using additional supplemental buprenorphine postoperatively. At this time the preponderance of evidence supports continuing buprenorphine and adding full agonist opioids, sometimes at high doses, for perioperative pain control with close monitoring.[90–92]

Peripherally Restricted μ-Receptor Antagonists

μ-Receptor antagonists such as naloxone seem like a logical choice for the reversal of OIC. Unfortunately, naloxone easily crosses the blood-brain barrier, thus carrying a risk of inducing opioid withdrawal symptoms. Peripherally restricted μ-opioid receptor antagonists are a new class of medications developed in part to treat OIC. They are less likely to cross the blood-brain barrier owing to their hydrophilic nature and have low oral bioavailability. Two agents in this class include methylnaltrexone and naloxegol. Naloxegol was the first oral agent approved in the United States for OIC in 2014. An oral formulation of methylnaltrexone was approved for use in 2016 after being previously available only for subcutaneous or intravenous administration. A third peripherally restricted μ-opioid receptor antagonist, alvimopan, is restricted to short-term use because of an increased incidence of myocardial infarction. Alvimopan is approved only for the treatment of postoperative ileus and is contraindicated for use in patients taking opioids for more than 7 consecutive days, and therefore has a limited role for the treatment of OIC. These agents do not reverse analgesia in clinically relevant doses and do not cause opioid withdrawal syndrome.[93]

Opioids and Immunosuppression

In addition to the concerns regarding perioperative opioid administration and cancer recurrence (see Chapter 17), there is developing concern that exogenous opioid administration might lead to long-term immunomodulation. Opioids produce immune modulation in both animal and human studies; however, there are conflicting study results on the presence of μ, κ, or δ receptors on immunocytes.[94] There is no evidence of expression of opioid receptor messenger ribonucleic acid in peripheral blood mononuclear cells.[95]

Individual opioids differ in terms of immunomodulation; whereas most studies have examined the effects of morphine, other opioids can be either more or less immune-active. Limited data exist on the immunologic consequences of long-term opioid therapy. Paradoxically, both immunosuppressive and immunostimulatory effects have been reported in different groups of patients such as cancer survivors treated with long-term opioids and patients receiving methadone maintenance therapy.[96] Duration of therapy, as well as dose, likely has an impact on the nature of the immunomodulatory effect. However, existing data are variable and often conflicting such that more investigation is needed to refine our understanding.

Opioids and Sleep-Disordered Breathing

There is a growing body of evidence describing sleep-disordered breathing (SDB) in patients treated with oral and transdermal opioids, including both obstructive sleep apnea (OSA) and central sleep apnea (CSA) patterns. OSA is characterized by respiratory effort despite an obstructed airway, whereas in CSA there is cessation of both air flow and respiratory effort. CSA is commonly associated with a pattern of variable respiratory drive that may include periods of hyperventilation and hypocapnia. Patients with CSA can also have underlying airway obstruction, and in many patients both CSA and OSA contribute to the overall syndrome of SDB.

Chronic opioid use can lead to a disruption and imbalance between hypoxic and hypercapnic drivers of ventilation.[97] In a study of patients using stable methadone maintenance therapy, the incidence of CSA alone was found to be 30%.[98] In another study of 32 chronic pain patients using chronic opioid therapy, opioid dosage was found to be correlated with SDB and subsequent cessation of opioid therapy significantly reduced SDB.[99] A recently published review reported an overall prevalence of SDB in 70% to 85% in patients taking opioids, with moderate or severe SDB occurring in a high proportion of these patients.[100] Unfortunately, until recently this was a neglected and poorly described area and consensus recommendations for the screening and treatment of opioid-related SDB have yet to emerge.

Opioids and Endocrine Dysfunction

Although hypogonadism associated with chronic opioid use has been recognized for many years, there is an evolving understanding that long-term opioid therapy contributes to a variety of endocrine deficiencies. Opioids, administered by any route, disrupt the hypothalamic-pituitary-gonadal axis and have a well-documented effect on levels of gonadotrophin-releasing hormone (GnRH), luteinizing hormone (LH), and testosterone.[101] Exogenous opioids interfere with the release of GnRH from the hypothalamus. GnRH stimulates the release of follicle-stimulating hormone and LH from the pituitary. In males, LH stimulates testosterone release from Leydig cells in the testes. In females, LH drives ovarian follicular maturation and estrogen secretion. Evidence of hypogonadism associated with opioids has been shown in animals, healthy human volunteers, heroin abusers, patients with chronic pain, cancer survivors, and patients undergoing methadone maintenance therapy.[102] These effects can contribute to reduced libido, erectile dysfunction in males, menstrual irregularity in females, loss of muscle mass, and depression and anxiety.[103]

There is also a long-established association between opioid use and an increased incidence of fractures. The recent literature has suggested that the risk may be due in part to a direct effect via opioid-induced osteopenia. Studies have shown an association between opioid use and reductions in bone mineral density.[104] Although the mechanism by which opioids induce osteopenia has yet to be fully elucidated, there is a clear association between hypogonadism and osteoporosis. Additionally, some literature points to a possible direct effect on osteoblast growth and activity.[105]

Given this budding understanding of endocrine deficits observed in patients using chronic opioid therapy, some have called for recommendations for clinicians to screen patients for symptoms of hypogonadism and consider measuring serum hormone levels for patients on opioid therapy equal to or greater than 100 mg OME daily.[106] Screening thresholds for osteopenia in these patients are less well defined but should be considered as a clinical risk factor for early bone density testing.

Key Points

- Nonintravenous opioids can be categorized into three groups based on their chemical structures: naturally occurring alkaloids, semisynthetic alkaloids, and synthetic opioids.
- Most nonintravenous opioids are metabolized by cytochrome P450 enzymes into inactive metabolites. However, morphine is a notable exception in that it undergoes glucuronidation to produce metabolites M3G, which may have neuroexcitatory effects, and M6G, a potent analgesic. M6G is renally cleared and can accumulate in the setting of renal insufficiency with potentially deleterious clinical effects.
- Nonintravenous routes of opioid administration include transmucosal, oral, and transdermal. Transmucosal opioids are considered ultrashort-acting, whereas oral opioids are available in short-acting, extended-release, and long-acting forms. Transdermal preparations allow for continuous delivery of opioid medication.
- Common side effects of nonintravenous opioid analgesics include constipation, nausea, sedation, pruritus, and ventilatory depression. Tolerance develops to most of these effects, with the notable exception of constipation.
- Acute pain and cancer-related pain are long-standing indications for the use of nonintravenous opioids. Use of opioids in the treatment of chronic pain is controversial; clear evidence supporting their efficacy is lacking and there are concerns for the development of addiction and overdose related death.
- Selection of a nonintravenous opioid is based on the targeted time to onset, required duration of action, available routes of administration, baseline opioid tolerance, comorbidities, and side effect profile.
- Emerging developments in nonintravenous opioids include buprenorphine for opioid dependence, peripherally restricted μ antagonists for opioid-induced constipation, and concerns about suppression of immune and endocrine function and sleep-disordered breathing in patients treated with opioids.

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Chou R, Cruciani R, Fiellin D, et al. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. *J Pain*. 2014;15:321–337. This consensus guideline was developed by multiple national societies. The authors review the unique pharacokinetic and pharmacodynamic properties of methadone and present recommendations for appropriate patient selection, dose titration, monitoring for adverse effects, use of electrocardiograms, and implications in pregnancy. (Ref. 64).

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Nonopioid Analgesics

SHANE E. BROGAN, SRINAND MANDYAM, AND DANIEL W. ODELL

CHAPTER OUTLINE

NSAID History

Nonsteroidal Antiinflammatory Drugs and Acetaminophen
- Basic Pharmacology
  - *Structure-Activity Relationships*
- Mechanism
- Metabolism
- Clinical Pharmacology
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The term *nonopioid analgesics* seems to imply a motley group of agents self-consciously trying to establish their parity with their famously potent cousins: the opioid family. With contemporary understanding of the complexities of both acute and chronic pain, the importance of a multimodal approach to pain management pharmacotherapy has emerged, and the former outcasts have slowly been incorporated into the armamentarium of the anesthesiologist.

With the exception of the nonsteroidal antiinflammatory drugs (NSAIDs), most nonopioid analgesics have stumbled awkwardly from other specialties such as psychiatry and neurology into the field of pain medicine. As the specialty of pain medicine learned that opioids were not a panacea for all chronic pain conditions because of their long-term inefficacy, toxicities, and a propensity for misuse, greater emphasis was placed on nonopioid analgesics either as first-line treatment or as an adjunct to opioids.

Abstract

The role of nonopioid analgesics have become increasingly important given mounting evidence against the use of opioids in chronic, non-malignant pain. Furthermore, recent Centers for Disease Control guidelines for opioid prescribing recommend preferential use of nonopioid analgesics prior to initiation of opioid therapy. Nonopioid analgesics are a disparate group of compounds including nonsteroidal anti-inflammatories, anti-epileptic drugs, and tricyclic agents. This chapter will discuss each of these drug classes in detail with an emphasis on the evidence that supports their utility in the perioperative and pain management setting. Careful consideration will also be given to some of the perioperative controversies of certain agents; for example, the issues of surgical hemostasis and bone healing with nonsteroidal anti-inflammatories. A brief discussion on novel and emerging agents will also be presented.

Keywords

NSAID History
Nonsteroidal anti-inflammatory drugs
Analgesia
Post-operative pain
Chronic pain
Gabapentin
Pregabalin
Tricyclic antidepressants

In March 2016 the Centers for Disease Control and Prevention (CDC) released guidelines for prescribing opioids in chronic pain.[1] While these guidelines were directed at primary care physicians, all medical providers have likely felt the effects of the far-reaching effort to curb what has become known as an epidemic of opioid misuse and overdose. Paramount among these recommendations is the role of nonopioid analgesics in treating chronic pain, as evidenced by the first of 12 guidelines:

> *Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.*

Because of the pharmacologic heterogeneity of nonopioid analgesics, this chapter is broadly divided into two sections: one describing NSAIDs and another describing drugs used for treatment of neuropathic pain. An additional section discusses emerging developments of various drugs with potential utility in the perioperative and chronic pain population.

NSAID History

NSAIDs have been used for millennia in the form of the prototypical agent, aspirin. Hippocrates wrote about using powdered willow bark for pain and fever in the fifth century BC. In the late 18th century, Stone isolated salicylic acid from willow, myrtle, and a number of other plants. However, it was not until early in the 20th century that Hoffmann, a chemist with Bayer Pharmaceuticals, discovered acetylsalicylic acid and marketed aspirin for fever, pain, and inflammation. It was not until later in the 20th century that aspirin became the generic name for this compound. Aspirin continues to be an important drug, but now more for its antiplatelet activity than for its original indications.

The newer NSAIDs were released in the 1960s, the first being indomethacin, closely followed by ibuprofen. Since then several dozen agents have been released in the United States and elsewhere, competing for a lucrative commercial market. Over time, some of these agents have been withdrawn because of major toxicities, including hepatotoxicity, nephrotoxicity, and blood dyscrasias. The recent voluntary withdrawal of the blockbuster drug rofecoxib (Vioxx) generated considerable controversy and media coverage amid concerns of increased cardiovascular risk.

Despite these controversies, NSAIDs remain very useful and widely used drugs for their analgesic and antipyretic effects. In the management of postoperative pain, NSAIDs are probably underused despite good evidence for their safety and efficacy.[2]

Nonsteroidal Antiinflammatory Drugs and Acetaminophen

Basic Pharmacology

Structure-Activity Relationships

Nonsteroidal antiinflammatory agents are a diverse group of drugs broadly categorized into salicylates, acetic acid derivatives, propionic acid derivatives, oxicam derivatives, and the cyclooxygenase (COX)-2 selective agents (Fig. 19.1). All act by blocking prostaglandin synthesis, both in the periphery and in the central nervous system (CNS).

Mechanism

Prostaglandins are lipid-based compounds derived enzymatically from fatty acids that have important physiologic functions, including the mediation of the inflammatory response, the transduction of pain signals, and a central pyretic effect. The primary source of prostaglandins in humans is arachidonic acid, a 20-carbon polyunsaturated essential fatty acid that is, in turn, derived from cell membrane phospholipids. The NSAIDs act by inhibiting COX enzymes that catalyze the conversion of arachidonic acid to prostaglandins, thromboxanes, and prostacyclin (Fig. 19.2).

The COX enzymes are now known to exist as three isoforms: COX-1, COX-2, and COX-3. COX-3 is a splice variant of COX-1 and is now recognized as the once elusive enzyme inhibited by acetaminophen.[3] However, controversy still exists about the existence of COX-3 inhibition in humans and the mechanism by which acetaminophen-mediated analgesia occurs. COX-1 and COX-2 are the isoforms targeted by the traditional NSAIDs, while the more selective COX-2 inhibitors preferentially block COX-2. COX-1 is considered to be the constitutive enzyme (often called the *housekeeping enzyme*), generating prostanoids involved in normal physiologic functioning such as gastrointestinal mucosal protection and hemostasis. COX-2, on the other hand, has low baseline expression but is inducible during physiologic stress by agents including proinflammatory cytokines, neurotransmitters, and growth factors.

However, this schema is acknowledged to be an oversimplification in that there are exceptions to this rule: for example, COX-2 is constitutively expressed in the kidney and CNS, and COX-1 can be induced by certain stress conditions in nerve tissue.[4] Although both enzymes are structurally similar and act basically in the same fashion, their respective gene expression profiles and selective inhibition can determine NSAID side effects and toxicity.

Metabolism

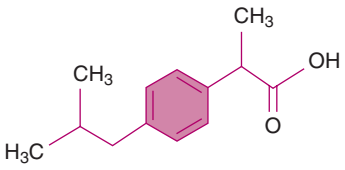
The primary mode of NSAID elimination is by hepatic biotransformation by cytochrome P450 (CYP 450)-mediated oxidation or glucuronide conjugation. Renal excretion of unmetabolized drug is much less important, accounting for less than 10% of the administered dose. Biliary excretion has been described for certain NSAIDs, although this route plays a small role. Because NSAIDs share common metabolic pathways, nuances relating to metabolism are not a basis for therapeutic decisions regarding the appropriate NSAID for a given patient.

Clinical Pharmacology

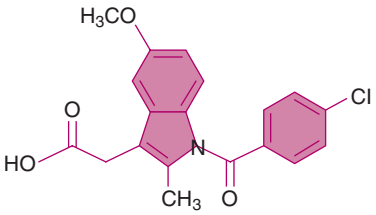
Pharmacokinetics

NSAIDs are weak acids with pK_a values typically lower than 5, and therefore they exist mostly in the ionized form at physiologic pH. NSAIDs, except aspirin, which is 50% to 80% bound, are highly bound to plasma proteins, primarily albumin. NSAID half-lives vary significantly between drugs (Table 19.1). Because oral NSAIDs are often prescribed for long-term use, a focus of modern NSAID development has been to design compounds that are relatively long-acting to facilitate improved patient compliance.

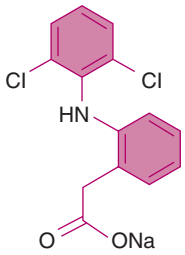
Most NSAIDs are rapidly absorbed following oral administration, with peak plasma concentrations generally reached within 2 to 3 hours. Factors affecting gastric emptying can profoundly affect the time course of the clinical effects of NSAIDs. In part because



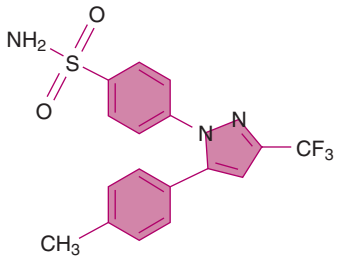
Propionic acid derivative – ibuprofen



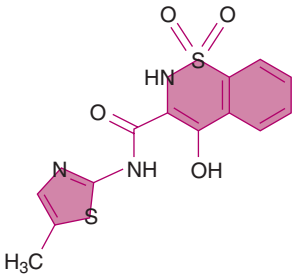
Acetic acid derivative – indomethacin



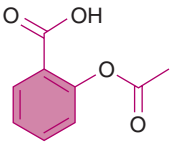
Fenamate NSAID – diclofenac



COX-2 selective NSAID – celecoxib

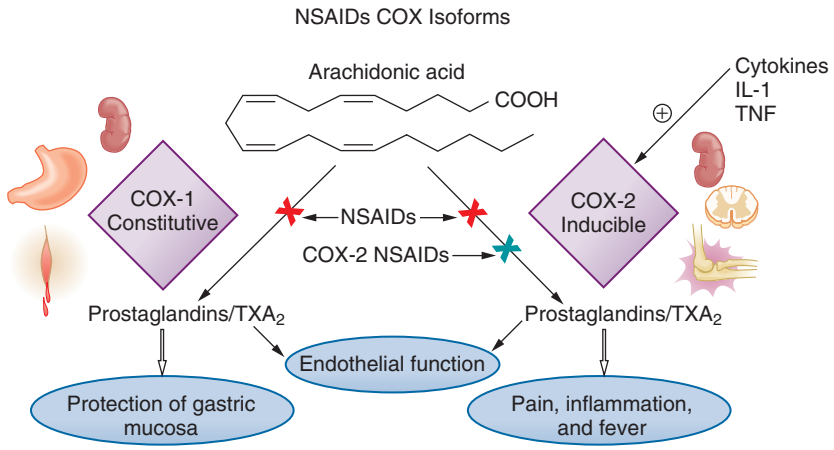


Enolic acid derivative (oxicam) – meloxicam



Salicylate – aspirin

• **Fig. 19.1** Nonsteroidal antiinflammatory drugs *(NSAIDs).* Molecular structures of an agent from each class of NSAID. Note the disparate chemical structures between classes.



• **Fig. 19.2** Mechanism of action of nonsteroidal antiinflammatory drugs *(NSAIDs),* with comparison of cyclooxygenase *(COX)*-1 and COX-2 inhibition effects. COX-3 effects not shown. *IL-1,* interleukin 1; *TXA_2,* thromboxane A_2; *TNF,* tumor necrosis factor.

TABLE 19.1 Summary of Nonsteroidal Antiinflammatory Drugs and Acetaminophen

Drug	Common Trade Name	Half-Life (hr)	Protein Binding (%)	Typical Daily Dose Range	Typical Dosing Schedule	Typical Pediatric Dosing (mg/kg per 24 hr)	Notes
Acetaminophen/ paracetamol	Tylenol, Panadol Ofirmev (IV)	2	20–50	2–4 g	325–650 mg q4hr	10–15 mg/kg q6–8 hr prn	No antiinflammatory effect
Propionic Acid Derivatives							
Fenoprofen	Nalfon	2–3	99	1.2–2.4 g	300–600 mg qid	NA	
Flurbiprofen	Ansaid	2	99	200 mg	100 mg bid	NA	
Ibuprofen	Motrin, Advil, Brufen, others	6	99	1.2–2.4 g	400–800 mg qid	7.5–10 mg/kg qid	Higher doses sometimes used for inflammatory conditions; maximum dose 3200 mg/day
Ketoprofen	Orudis	2–4	99	225 mg	75 mg tid	NA	
Naproxen	Naprosyn	14	99	750–1000 mg	250–375 mg bid	5–10 mg/kg bid	
Naproxen sodium	Alleve, Anaprox	14	99	550–1100 mg	275–550 mg bid	5–10 mg/kg bid	
Fenamates							
Diclofenac	Voltaren	1–2	99	150–200	50 mg tid 75 mg bid	2–3 mg/kg per 24 hr	Hepatotoxicity rarely reported. Also has topical formulations
Tolmetin	Tolectin	5	99	600–1800 mg	200–600 mg tid	20–30 mg/kg per 24 hr as 3–4 doses	
Ketorolac	Toradol	4–6	99	IV: 60 mg/day[a]	30 mg first dose; then 15 mg q6hr[a]	IV: 0.5 mg/kg per day, single dose only	[a]Half the dose if age >65 yr or weight <50 kg
Enolic Acid Derivatives (Oxicams)							
Meloxicam	Mobic	15–20	99	7.5–15	7.5–15 mg qd	NA	Higher dose typically used for rheumatoid arthritis Intermediate COX-1 and COX-2 selectivity
Piroxicam	Feldene	40–50	99	20 mg	10–20 mg qd	NA	
Nabumetone	Relafen	24	99	1000–1500 mg	500–750 mg bid	NA	
Acetic Acid Derivatives							
Etodolac	Lodine	7	99	400–1200 mg	200–400 mg tid/qid	15–20 mg/kg/24 hr	
Indomethacin	Indocin, others	2–5	90	100–200 mg	25–50 mg TID/QID	2–4 mg/kg/24 hr	
Sulindac	Clinoril	8–16	99	400 mg	150–200 mg	bid/tid	
COX-2 selective NSAID							
Celecoxib	Celebrex	6–12	97	200 mg	100–200 mg qd/bid	3 mg/kg bid	400 mg/day used for acute pain

bid, Twice daily; *COX,* cyclooxygenase; *IV,* intravenous; *NA,* nonsteroidal antiinflammatory drug; *prn,* as needed; *q,* every; *qd,* every day; *qid,* four times daily; *tid,* three times daily.

of the variability in the time course of oral absorption, the use of rectal NSAIDs is popular in Europe for the management of postoperative pain and has the added advantage of being possible even when oral intake is not.[5] Ketorolac and ibuprofen are the only parenteral NSAIDs currently available in the United States, but intravenous diclofenac and parecoxib are available elsewhere. Parenteral administration is advantageous in renal colic because of its more rapid onset than with oral administration, but it has demonstrated no obvious advantage over oral administration for any other indication.[6]

Pharmacodynamics

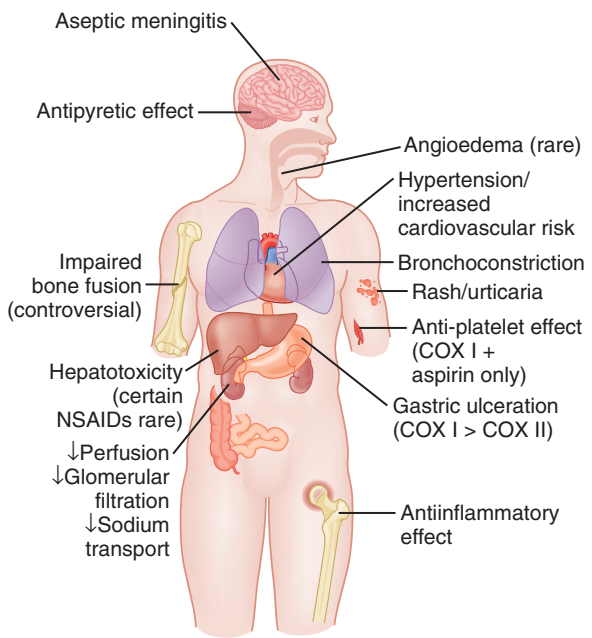
Therapeutic Effects

NSAIDs are widely used for their analgesic properties, particularly when pain has an inflammatory component such as in certain rheumatologic conditions. Tissue trauma results in cell membrane disruption and release of arachidonic acid, the substrate for COX enzymes, and consequently a rise in local prostaglandin (PG) concentrations. These prostanoids, particularly PGE_2, result in sensitization of nociceptors to mechanical stimuli and other chemical mediators such as bradykinin, leading to increased nociceptor firing and pain perception. COX enzyme activity has also been identified in the CNS, including the dorsal horn of the spinal cord, and it is postulated that COX inhibition also provides a central analgesic mechanism.[3]

The antipyretic effect of the NSAIDs is very predictable and has utility in the treatment of fever, both in adults and children. Perioperatively, NSAIDs are indicated in a multimodal analgesic approach, and the American Society of Anesthesiologists (ASA) recent practice guidelines for acute pain management in the perioperative setting encourage the use of NSAIDs unless contraindicated.[2] A less common NSAID indication (indomethacin is typically used) is in the prevention of ductus arteriosus closure when this would be detrimental in certain neonatal congenital heart conditions where an ongoing right-to-left shunt is desired before corrective surgery. Fig. 19.3 provides an overview of the pharmacodynamic effects of NSAIDs, including both therapeutic and adverse effects.

Adverse Effects

NSAIDs have a number of nonspecific adverse effects, including rash and gastrointestinal upset (e.g., dyspepsia, abdominal pain, and diarrhea), that are not related to their targeted mechanism.



• **Fig. 19.3** Overview of the common pharmacokinetic and pharmacodynamic effects of nonsteroidal antiinflammatory agents. *COX,* Cyclooxygenase; *NSAIDs,* nonsteroidal anti-inflammatory drugs.

Other adverse effects are manifest in multiple organ systems, reflecting the widespread expression of the COX enzymes.

Cardiovascular Effects

All NSAIDs, and not just the COX-2 selective agents, can increase the risk of serious cardiovascular thrombotic events such as myocardial infarction and stroke.[7,8] The mechanisms underlying these adverse effects are complicated but likely include an imbalance between the prothrombotic and vasoconstricting activity of thromboxane A_2 (TXA_2), and the antithrombotic and vasodilatory effects of prostacyclin (PGI_2), thereby favoring deleterious thromboxane effects.[9] In addition, NSAIDs increase blood pressure in a dose-dependent fashion, which may also be linked to the increased cardiovascular risks associated with their use.[10] Prolonged administration of COX-2–selective NSAIDs can cause adverse events through inhibition of PGI_2, including development of hypertension and the promotion of thrombus development in a ruptured plaque.[7] Recent reviews of both nonselective NSAIDs and COX-2 inhibitors have found that nonselective NSAIDs and celecoxib carry little risk of ischemic stroke, whereas rofecoxib and valdecoxib (both discontinued) are associated with significant risk.[11,12] However, the cerebrovascular safety of nonselective NSAIDs has been questioned in other studies, suggesting that all NSAIDs should be used with caution in patients with high risk for cerebrovascular disease.[8]

The perioperative administration of NSAIDs, especially the COX-2 selective agents for short-term use, has been subject to some controversy owing to their possible role in increasing morbidity after cardiac surgery.[13,14] However, a recent meta-analysis of studies using parecoxib and valdecoxib compared with placebo in noncardiac surgery concluded that there were no differences in cardiovascular events between groups.[15]

In 2005, a consensus statement issued by the Food and Drug Administration (FDA) Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee concluded that COX-2 selective agents are important treatment options for pain management and that the preponderance of data demonstrates that the cardiovascular risk associated with celecoxib is similar to that associated with commonly used, older, nonselective NSAIDs. The committee also concluded that short-term use of NSAIDs does not appear to increase cardiovascular risk and that rigorous scientific studies are needed to characterize the longer-term cardiovascular risks of these therapies. With respect to the longer-term use of NSAIDs, a careful risk-benefit analysis should be performed, particularly in those already at risk for cardiovascular events.[16]

Bone Healing

Bone healing is dependent on an inflammatory response involving numerous cytokines, including interleukin (IL)-1, IL-6, tumor necrosis factor, and fibroblast growth factor, so it is not surprising that agents that disrupt normal cytokine function can impair bone homeostasis and repair.[17] There are convincing animal data that nonselective and COX-2 inhibitor NSAIDs inhibit bone healing.[18–20] This inhibition of healing response has been used therapeutically to prevent heterotrophic bone formation after arthroplasty.[21] In a rat model of femoral fracture healing, celecoxib or rofecoxib delayed fracture healing compared with indomethacin.[22] At 8 weeks postoperatively, there was still evidence of the original fracture in these two groups.

However, human data on possible detrimental effect of NSAID use in the perioperative period are conflicted and controversial.[23] The issue of bone healing and NSAIDs has been addressed mostly in the spinal fusion literature. Successful spinal fusion surgery

demands a robust bone healing process, so spine surgeons place great importance on mitigating all risk of nonunion with measures such as smoking cessation and NSAID avoidance. A retrospective analysis of 288 patients who underwent instrumented spinal fusion from L4 to the sacrum demonstrated a five times higher nonunion rate when ketorolac was used in the immediate postoperative period.[24] In contrast, another retrospective study found that, in 405 consecutive patients who underwent primary lumbar spinal fusion, a subset of patients who had ketorolac 30 mg intravenously every 6 hours for 2 days had similar fusion rates to a group that had no NSAIDs.[25] A recent meta-analysis of five retrospective studies explored the relation of ketorolac dose and successful spinal fusion rates and concluded that high-dose ketorolac (>120 mg/day) might be associated with poor outcomes, whereas standard dose ketorolac (<120 mg/day) was not.[26] In the absence of any prospective or randomized studies, and realizing that bony nonunion is a high-morbidity outcome, use of perioperative NSAIDs in spinal fusion cases should be considered carefully, particularly when other risk factors for poor bone healing (e.g., smoking) exist. In nonspine orthopedic surgery, there is good evidence of NSAID analgesic efficacy and no significant association with compromised bone healing.[23,27]

Allergy and Hypersensitivity

All NSAIDs, including aspirin, can induce hypersensitivity reactions of two general types, both likely related to the inhibition of prostaglandin synthesis. Provocation of asthmatic attacks in patients with vasomotor rhinitis and nasal polyposis is likely related to inhibition of normal production of the bronchodilator PGE_2. NSAIDs also rarely induce the syndrome of urticaria and angioedema related to inhibition of prostaglandin effects that normally stabilize histamine stores in mastocytes and inhibit the inflammatory response.[28] In susceptible individuals, this unchecked inflammation can result in spontaneous degranulation of mastocytes with release of histamine in the respiratory tract and skin, which leads to bronchoconstriction and urticaria. This process is COX-1 mediated, and therefore COX-2 selective NSAIDs may be used, but with caution, in NSAID-intolerant patients.[29,30]

Gastrointestinal Toxicity

The long-term use of oral NSAIDs inhibits production of prostaglandins that maintain normal gastrointestinal mucosal integrity and results in gastric and colonic mucosal damage, including erosion and ulceration. In addition, oral NSAIDs can cause local irritation, and when erosion and/or ulceration is present, hemostasis is compromised by COX-1 inhibition. This constellation of physiologic derangements results in a spectrum of gastrointestinal problems, ranging from mild gastritis to peptic ulceration with perforation.

The morbidity and mortality of NSAID use is a significant public health problem, although it appears to be abating in recent years, likely because of the more widespread use of proton pump inhibitors, rather than the use of COX-2 inhibitors.[31] Risk factors identified for the development of NSAID-induced ulcers include advanced age, history of previous ulcer, concomitant use of corticosteroids, higher doses of NSAIDs (including the use of more than one NSAID), concomitant administration of anticoagulation agents, serious systemic disorders, cigarette smoking, consumption of alcohol, and concomitant infection with *Helicobacter pylori*. Short-term use of NSAIDs in the perioperative period carries little risk of mucosal injury, although intolerance or nausea can be an issue in patients given NSAIDs on an empty stomach.

Hemostatic Effects

Platelets, lacking a nucleus and the ability to generate new proteins like COX, are particularly susceptible to the effects of COX inhibitors. Aspirin irreversibly acetylates COX enzymes and inhibits platelet aggregation for the 10- to 14-day life span of the platelet. Other nonselective NSAIDs reversibly inhibit COX, causing only transient reduction in TXA_2 formation. Consequently, inhibition of platelet activation resolves after most of the drug is eliminated. For example, a single 300- to 900-mg dose of ibuprofen can inhibit platelet aggregation for 2 hours after administration, and the effect is largely dissipated by 24 hours. Overall, with the exception of aspirin, NSAIDs cause transient, dose-dependent, and modest bleeding time abnormalities, which often do not exceed normal limits.[9] However, clinical studies have revealed some significant issues with perioperative hemostasis and nonselective NSAID use. In total hip arthroplasty, patients taking nonselective NSAIDs had more intraoperative and postoperative blood loss than those who did not.[32] Despite concern on the part of many ear, nose, and throat surgeons regarding the use of NSAIDs for pain control after pediatric tonsillectomy, a thorough meta-analysis of studies addressing this concern failed to find any significant association between NSAIDs and perioperative bleeding requiring return to the operating room.[33] Importantly, the COX-2 enzyme has not been identified in platelets, so the COX-2 inhibitors are not thought to have deleterious antiplatelet effects.[34]

Renal Toxicity

Aspirin and all other NSAIDs, including COX-2 inhibitors, can transiently decrease renal function in selected patients, resulting in hypertension, edema, and even acute renal failure. These effects occur more often in patients with underlying renal disease and in those with intravascular volume depletion.[35] Renal perfusion and glomerular filtration are closely regulated by renal prostaglandin synthesis, particularly in the fluid-depleted state. Inhibition of this system is the postulated mechanism of NSAID-induced sodium ion (Na^+) retention and renal dysfunction. In the perioperative setting, NSAIDs seldom cause clinically significant renal impairment, but should be withheld in patients who are significantly volume depleted, have intraoperative oliguria, or have preexisting renal impairment.

Other Toxicities

Aspirin and diclofenac are the most potentially hepatotoxic NSAIDs and should be avoided in patients with preexisting hepatic failure.[36] NSAIDs have been implicated in hypersensitivity-induced aseptic meningitis, generally manifesting with meningeal signs commencing within weeks of starting therapy. It is a diagnosis of exclusion after ruling out an infectious cause of the meningeal irritation.

Drug Interactions

Hypoalbuminemia increases the free fraction of NSAIDs in the plasma, thus affecting their distribution and elimination. The high degree of serum protein binding increases interaction risk with other highly protein bound drugs. In clinical practice, however, this is rarely significant, and NSAIDs can be used safely in conjunction with other agents commonly used in perioperative practice. One exception is the potential for nephrotoxicity when NSAIDs are used concomitantly with other potentially nephrotoxic drugs such as the aminoglycosides, radiographic contrast media, and diuretics. Nonselective NSAIDs should be used with caution in patients who have been using other platelet-inhibiting drugs or anticoagulants.

Special Populations

Renal Failure

In general, NSAIDs are avoided in patients with renal failure. The use of NSAIDs in patients with preexisting renal insufficiency can have deleterious effects as discussed earlier. Renal failure influences NSAID kinetics by reducing renal excretion of the drugs and metabolites normally eliminated in the urine and by affecting their distribution and biotransformation.[37] All NSAIDs are very highly bound to plasma proteins, and hemodialysis will not likely increase elimination of these agents. No dosage adjustments are therefore necessary for hemodialysis patients receiving NSAIDs.

Liver Disease

The majority of NSAIDs have low hepatic clearance, so mild to moderate liver disease should theoretically not interfere with their oral bioavailability. Because NSAIDs are so avidly protein-bound, alteration of liver albumin synthesis would be expected to cause alterations in the unbound drug fraction in plasma. Diclofenac has been the agent most implicated with hepatic dysfunction and should be avoided in patients with liver disease.

Older Age

Advanced age is an independent risk factor for both cardiovascular disease and NSAID gastropathy, so NSAIDs should be used with additional caution in this population. However, the opioid-sparing effects of NSAIDs in the postoperative period make NSAIDs an attractive pain management adjunct, particularly when concerns exist regarding oversedation, delirium, or respiratory depression in older patients receiving opioids. In older adults, the relatively high lipid solubility of NSAIDs, potentially decreased plasma protein levels, and reduced renal function all contribute to an increased likelihood of toxicity. Therefore the lowest effective dose of NSAID should be administered, with frequent follow-up (sometimes including renal function tests) for assessment of side effects or toxicity.[38]

Unique Features of Individual Agents

Meloxicam

Meloxicam, an NSAID of the enolic acid type, is unique in that it selectively blocks COX-2 over COX-1, and is therefore considered an intermediate between COX-2 selective agents and the nonselective NSAIDs. Consequently, meloxicam might have a better gastrointestinal tolerability profile compared with nonselective agents and can be considered if celecoxib is unavailable or contraindicated.[28]

Ketorolac

Ketorolac, until recently, was the only parenteral NSAID available in the United States and was therefore used quite extensively in the perioperative period. Pharmacologically, it is a member of the pyrrolo-pyrrole group and is avidly protein bound, resulting in a low volume of distribution. Ketorolac is extensively conjugated in the liver and then excreted in the urine. Time to measurable effect is about 30 minutes, with a peak effect noted at 1 to 2 hours and a duration of action of 4 to 6 hours.

In the management of postoperative pain, ketorolac has proven very useful, with an opioid-sparing effect and efficacy similar to morphine in the treatment of moderate pain.[39,40] Concerns exist regarding the renal safety profile of ketorolac in the perioperative setting that have necessitated modifications of dosing guidelines. Previously, the drug was administered at a 60-mg initial dose followed by 30 mg every 4 hours, and cases of acute tubular necrosis were reported. Gastrointestinal bleeding and operative site bleeding have also been reported and are mostly associated with advanced patient age, duration of therapy beyond 5 days, and higher dosing regimens.[41] Subsequently, dosing recommendations were decreased by more than 50%. The ketorolac product labeling now advises the following intravenous dosing protocol: for a single dose, 30 mg intravenously or 15 mg if patient age is greater than 65 year or body weight less than 50 kg; for multiple dosing, patients should be commenced on 30 mg every 6 hours, not to exceed 120 mg in a 24-hour period; in those older than 65 years or weighing less than 50 kg, the dosing should be 15 mg every 6 hours, not to exceed 60 mg in 24 hours.[42] In no circumstance should dosing go beyond 5 days of therapy, and ketorolac is best avoided in patients with a history of peptic ulcer disease or renal impairment.

Acetaminophen

Acetaminophen, while strictly speaking is not an NSAID, is generally grouped in this therapeutic class and plays a major role in analgesic therapy. Acetaminophen is a para-aminophenol derivative with analgesic and antipyretic properties similar to aspirin. The very useful antipyretic effect is thought to be a direct effect on the hypothalamic heat-regulating centers via inhibiting action of endogenous pyrogens. Recent reports suggest that acetaminophen acts via serotonergic pathways, COX-3 inhibition, and/or endogenous cannabinoid potentiation to provide analgesia, but its mechanism of action remains poorly understood.[43–45] Although equipotent to aspirin in inhibiting central prostaglandin synthesis, acetaminophen has no significant peripheral prostaglandin synthetase inhibition and is therefore less useful than NSAIDs for painful inflammatory disorders.

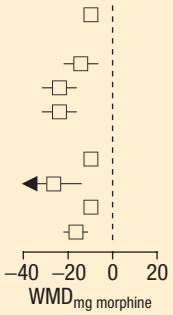
Acetaminophen has few side effects in the usual dosage range; unlike NSAIDs, no significant gastrointestinal toxicity or platelet function inhibition occur. Acetaminophen has, however, been associated with the development of hypertension but has not yet been associated with increased cardiovascular risk.[46] Nephrotoxicity also can occur with acetaminophen but less frequently than it occurs with NSAIDs.[47]

Acetaminophen is completely and rapidly absorbed following oral administration, and peak serum concentrations are achieved within 2 hours. About 90% of acetaminophen is hepatically metabolized to sulfate and glucuronide conjugates for renal excretion with a small amount secreted unchanged in the urine. Minor metabolites are responsible for the hepatotoxicity seen in overdose.[48] CYP 450 enzyme system induction in the liver by any agent, including ethanol, increases the formation of toxic free radial metabolites and thereby increases hepatotoxicity. In the healthy individual, daily doses of 2.6 to 3.2 g are generally considered safe, but acetaminophen dosing should not exceed 4 g/day.[49,50] In patients with a history of ethanol abuse or liver disease, acetaminophen should generally be avoided.

The bioavailability of rectal acetaminophen is variable and is approximately 80% of that following oral administration. The rate of rectal absorption is slower, with maximum plasma concentration occurring 2 to 3 hours after administration. Doses of 40 to 60 mg/kg of rectal acetaminophen have been shown to have an opioid-sparing effect in the management of postoperative pain.[51] In Europe, an intravenous prodrug form of acetaminophen, propacetamol, and intravenous acetaminophen are available for clinical use and have been shown to reduce

TABLE 19.2 24-Hour Morphine Consumption (in milligrams)

Regimens	NO. OF PATIENTS WITH Active	Control	Change in Morphine Requirement	WMD (95% CI)
Acetaminophen				
Multiple dose	379	334		–8.31 (–10.9 to –5.72)
NSAIDs				
Single dose	553	496		–8.31 (–10.9 to –5.72)
Multiple dose	495	398		
Continuous	276	253		–8.31 (–10.9 to –5.72)
COX-2 Inhibitors				
Single dose	70	69		–8.31 (–10.9 to –5.72)
Single dose	91	91		
Multiple low dose	272	273		–8.31 (–10.9 to –5.72)
Multiple high dose	535	411		



A weighted mean difference (WMD) less than 0 indicates less morphine consumption with active compared with control. When the 95% confidence interval (CI) does not include 0, the difference is considered statistically significant. COX-2 inhibitor = 200 mg celecoxib, or 50 mg rofecoxib; multiple high dose = valdecoxib and parecoxib 40 mg/12 hr and parecoxib 40 mg/6 hr; multiple low dose = valdecoxib and parecoxib 20 mg/12 hr.

*COX, C*yclooxygenase; *NSAID,* nonsteroidal antiinflammatory drug.

Reprinted with permission from Elia N, Lysakowski C, Tramer MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. *Anesthesiology.* 2005;103:1296–1304.

postoperative opioid consumption.[52,53] In 2011, an intravenous form of acetaminophen was introduced in the United States for the parenteral management of pain and fever.[54] Intravenous acetaminophen (1 g every 4 hours for 24 hours) was well tolerated, improved pain reporting, and decreased morphine consumption after orthopedic surgery.[55]

Oral NSAIDs

Common Clinical Indications

Postoperative Analgesia

While opioids continue to be the mainstay of analgesia during the perioperative period, NSAIDs and acetaminophen alone can be sufficient for the management of mild pain and are a very useful adjunct in the management of moderate to severe pain. The latest ASA practice guidelines for acute pain management in the perioperative setting encourage the use of NSAIDs and other adjuncts whenever possible.[2] The preoperative administration of oral COX-2 selective NSAIDs can reduce cerebrospinal fluid (CSF) and surgical site PGE_2 levels in humans during the perioperative period with an associated decrease in pain. In addition to reducing CSF PGE_2 levels, COX-2 selective NSAIDs decreased CSF IL-6 (a major proinflammatory cytokine) levels. The IL-6 modulation by COX-2 inhibitors is not well understood but is likely to be related to the PGE_2 pathway.[56]

A recent meta-analysis examined the effect of adding acetaminophen, nonselective NSAIDs, or COX-2 selective NSAIDs to opioid patient-controlled analgesia. The results suggested that all three analgesic agents provided an opioid dose-sparing effect (25% to 55%). Moreover, the addition of NSAIDs to morphine was associated with a decrease in the incidence of postoperative nausea and vomiting and sedation (Tables 19.2 and 19.3).[27] Clinical trials of COX-2 selective NSAIDs used preoperatively and into the postoperative period for patients undergoing both major surgery and minimally invasive surgery have demonstrated improved clinical outcomes, including reduction in postoperative pain, opioid use, and nausea.[27,57,58] A meta-analysis of clinical studies evaluating COX-2 inhibitors compared with nonselective NSAIDs for postoperative pain showed that the analgesic efficacy of COX-2 inhibitors in the 6 hours after surgery was similar to or better than ibuprofen.[59]

NSAIDs in Chronic Pain

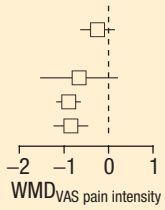
Chronic pain has been defined as pain that extends beyond the expected period of healing or beyond a certain arbitrary period of time, or more specifically as pain that extends beyond 3 to 6 months from the original injury. The use of NSAIDs in chronic pain has an important role in selected conditions. Conditions with a predominant inflammatory component such as rheumatoid arthritis are likely to respond favorably to NSAIDs, whereas noninflammatory conditions such as peripheral neuropathic pain are unlikely to respond.[60] An advantage of NSAIDs in chronic pain is their ability to offer an opioid-sparing effect so that opioid doses can be minimized, thereby lowering any potential opioid-related toxicity. However, the long-term (possibly lifelong) use of NSAIDs is not without its own risk, particularly in patients at risk for NSAID toxicity, including older adults and those with preexisting renal or cardiac disease.

Data on the long-term efficacy of NSAIDs for chronic pain are limited, whereas the long-term risk has been better defined.[16] In a meta-analysis of NSAID efficacy in chronic back pain, there was a small benefit with NSAID therapy when sciatica was not present; with sciatica, no difference was found.[61]

As is the case with all pharmacotherapeutic options for the management of chronic pain, any analgesic agent should

TABLE 19.3 Visual Analog Scale Score for Pain Intensity at Rest at 24 Hr (0–10 cm)

Regimens	NO. OF PATIENTS WITH: Active	Control	Change in Pain Score	WMD (95% CI)
Acetaminophen				
Multiple dose	175	180		–0.29 (–0.71 to 0.14)
NSAIDs				
Single dose	390	369		–0.75 (–1.61 to 0.11)
Multiple dose	288	265		–1.00 (–1.25 to –0.75)
Continuous	225	201		–0.97 (1.37 to –0.57)



A weighted mean difference (WMD) less than 0 indicates less pain with active compared with control. When the 95% confidence interval (CI) does not include 0, the difference is considered statistically significant. Meta-analyses were performed when data from at least three trials or more than 100 patients could be combined; this was not the case for cyclooxygenase-2 inhibitors.
NSAID, Nonsteroidal antiinflammatory drug.
Reprinted with permission from Elia N, Lysakowski C, Tramer MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. *Anesthesiology.* 2005;103:1296–1304.

be introduced only after careful consideration of the condition being treated and patient comorbidities. In the case of NSAIDs, close follow-up is essential to screen for efficacy and toxicity, with discontinuation if they are inefficacious or poorly tolerated.

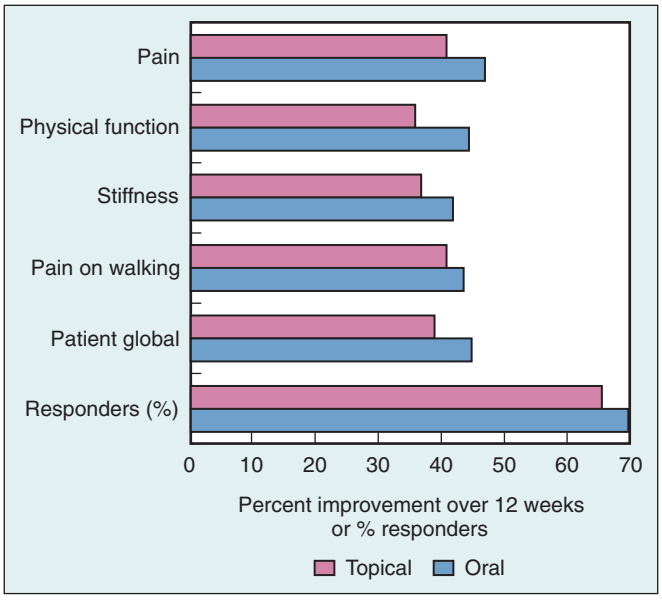
Rational Drug Selection

In general, NSAIDs have similar analgesic efficacy, and individual drug choice is more often determined by differences in tolerability, local availability, route of administration, and cost. In the perioperative setting, intravenous agents such as ketorolac and acetaminophen are often used for practical reasons, but thought should be given to alternative preoperative oral regimens that might significantly reduce cost. Many of the older nonselective NSAIDs can be purchased over the counter in the United States, whereas the COX-2 inhibitor celecoxib is available only by prescription. Celecoxib, owing to the presence of a sulfa moiety, is contraindicated in patients who report a history of sulfa allergy.

A summary table of the most commonly used agents is presented in Table 19.1. This information constitutes the rational basis for drug selection of these agents.

Topical NSAID Preparations

Because NSAIDs are the drugs of choice for musculoskeletal pain and adverse events occur commonly with systemic NSAID therapy, formulation of topical dosage forms to limit systemic exposure was a logical pharmaceutical development. Topical formulations are those that are applied locally in proximity to the affected area and that provide effective concentrations at the local target tissues without producing the systemic levels associated with common adverse effects.[62] These differ from transdermal dosage forms that deliver full systemic levels of the drug through the skin into the circulation. In the United States, diclofenac is the only approved topical NSAID and comes in gel, patch, and ointment form. Topical NSAIDs produce high drug concentration in dermis, muscle, synovium, and joint cartilage, while plasma drug concentrations are less than 10% of those obtained after oral administration. However, substantial interindividual variability exists in transdermal drug penetration. While the anatomic site of application has little effect on systemic drug absorption, individual skin and connective tissue differences can alter topical absorption of drugs. For selected conditions, topical NSAIDs have been shown to be comparable in efficacy to the oral route (Fig. 19.4).



• **Fig. 19.4** Efficacy of topical diclofenac is comparable to oral diclofenac for osteoarthritic knee pain at 12 weeks. These data illustrate that, compared to the oral route, topical administration of nonsteroidal antiinflammatory drugs may be similarly efficacious in selected indications. (Adapted from Simon LS, Grierson LM, Naseer Z, et al. Efficacy and safety of topical diclofenac containing dimethyl sulfoxide [DMSO] compared with those of topical placebo, DMSO vehicle and oral diclofenac for knee osteoarthritis. *Pain*. 2009;143:238–245.)

The specific topical NSAID formulation can greatly affect its absorption and penetration through the skin. Differences in formulations are based on the dosage form (gel, solution, or patch), different salts of the same molecule (diclofenac sodium, diclofenac potassium,

or diclofenac epolamine), carrier-mediated transport (lipid emulsions or solid nanoparticles), and penetration enhancement methods, either chemical (addition of penetration enhancer such as menthol or dimethylsulfoxide, physical [heat-mediated penetration enhancement], or electrical [charge-mediated penetration enhancement such as iontophoresis]).

The most common side effects reported in studies using topical NSAIDs are application site reactions, including dermatitis (reported in 7% of treated patients). Serious side effects are exceptionally rare.[63–65]

Drugs Used for the Treatment of Neuropathic Pain

Introduction and Historical Perspective

The International Association for the Study of Pain (IASP) defines neuropathic pain as pain that results from a lesion or disease affecting the somatosensory system.[66] It has been traditionally thought that opioids are ineffective in the treatment of neuropathic pain, but this is still considered controversial.[67,68] However, it is fair to say that opioids are generally *less* effective in the treatment of neuropathic pain compared with nociceptive pain and consequently are typically used as a second-line treatment after the typical neuropathic pain analgesics have failed to provide satisfactory results. The medical management of patients with neuropathic pain is a challenge to the medical community and has largely been steered by guidelines and systematic reviews of numerous pharmacologic interventions.

The drugs with the best efficacy in neuropathic pain are the tricyclic antidepressants (TCAs), certain anticonvulsants, selective norepinephrine reuptake inhibitors, and topical agents. Duloxetine, a selective norepinephrine and serotonin reuptake inhibitor, also is used in the management of certain neuropathic pain conditions.

The TCAs were introduced in the 1950s as the first agents used in the pharmacologic treatment of depression. Before this, they were used as antipsychotics, presumably because of their marked sedative effects. However, it was noted that TCAs sometimes produced the opposite effect, elevating the mood and even inducing mania. This stimulating effect was later harnessed in the treatment of depression, with the first publication of imipramine as an antidepressant by the Swiss psychiatrist Ronald Kuhn in 1957.[69] While often effective, the TCAs were plagued by their unpleasant antihistaminergic and anticholinergic side effects. In 1974 the first selective serotonin reuptake inhibitors (SSRIs) were discovered; the most promising of these was fluoxetine. It was not until 1986 that fluoxetine (Prozac) was released on the Belgian market, and the following year it gained FDA approval in the United States. This promptly curtailed the use of TCAs for the management of depression, and Prozac rapidly became a blockbuster drug, with more than 22 million U.S. prescriptions written in 2007 alone. However, the TCAs continue to be used, albeit at much lower doses, for the management of neuropathic pain. Perhaps surprisingly, their efficacy, in terms of numbers needed to treat, is actually better than the aggressively marketed anticonvulsant agents discussed later.[70]

Gabapentin is an anticonvulsant initially approved for the treatment of partial seizures, but in 1995 was anecdotally noted to be helpful in the treatment of certain pain conditions, leading to clinical studies in neuropathic pain conditions where it was found to be clinically helpful. Gabapentin is confusingly named because it was originally designed to be a gamma-aminobutyric acid (GABA) analog. Mechanistic studies eventually showed that it had no significant GABA activity; instead, it was involved with voltage gated N-type calcium channels. In 2005 pregabalin (Lyrica), with almost identical receptor activity to gabapentin, was released on the U.S. market with specific indications for neuropathic pain. Two years later, the FDA approved pregabalin for the management of fibromyalgia.

Tricyclic Antidepressants

Basic Pharmacology

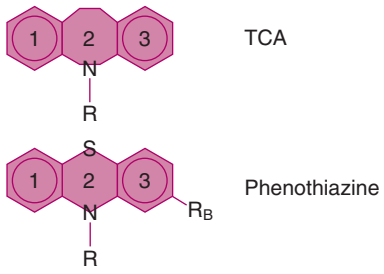
TCAs are heterocyclic compounds that were previously used in the treatment of major depressive disorder before the development of SSRIs. Since the release of the first SSRI, fluoxetine (Prozac) in 1987, TCAs are rarely used in the management of depression owing to a high burden of side effects at antidepressive doses, yet their low-dose use continues to have an important role in the treatment of chronic neuropathic pain.[70] The analgesic properties of TCAs are thought to be independent of their treatment effects on depression. TCAs are structurally related to phenothiazine antipsychotic agents and are named after their chemical structure composed of two benzene rings joined to a seven-member ring containing nitrogen, oxygen, and carbon (Figs. 19.5 and 19.6).[71]

Mechanism of Action

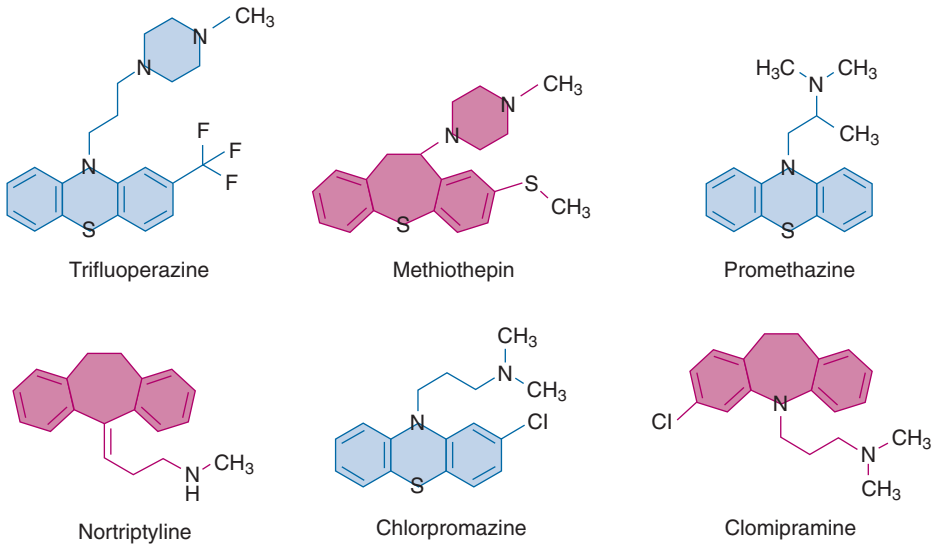
The mechanism of action for the analgesic properties of TCAs is unknown, but it is thought to be related to reuptake inhibition of serotonin and norepinephrine in the spinal cord and modulation of descending inhibitory pathways. In addition, many TCAs also have high affinity as *antagonists* at the 5-hydroxytryptamine (5-HT) receptors (5-HT2: 5-HT2A and 5-HT2C), 5-HT6, 5-HT7, α_1-adrenergic, and N-methyl-D-aspartate (NMDA) receptors. Sigma (σ_1 and σ_2) receptor (formally considered to be an opioid receptor) *agonism* is noted and may contribute to their efficacy as well as their side effects.[72–77]

Metabolism

The metabolism of tricyclics is dependent primarily on hepatic CYP 450 oxidative enzymes. Although the activities of some P450 isoenzymes are largely under genetic control, they may be influenced by patient variables, such as ethnicity and age, as well as the concomitant use of other medications or substances. Metabolism of TCAs, especially their hydroxylation, results in the formation



• **Fig. 19.5** The figure at the top shows the prototypical three-ring structure of a tricyclic antidepressant *(TCA)*. Notice its similarity to the structure of a phenothiazine-type antipsychotic drug pictured below it. TCAs were originally modeled after this class of antipsychotic medications. *R* and R_B represent different side chains for the various phenothiazines.



• **Fig. 19.6** A comparison of the molecular structures of select phenothiazine-type medications *(blue)* and tricyclic antidepressants *(red)*.

of active metabolites, which contribute to both the therapeutic and the adverse effects of these compounds. Tertiary amines like amitriptyline and imipramine are demethylated to secondary amines, which retain clinical activity. Therefore when parent compounds that generate active metabolites are prescribed, it is necessary to measure the total tricyclic concentration of clinically active substances when monitoring therapeutic concentrations.[78] The most important step in tricyclic metabolism involves forming inactive hydroxycompounds that are readily excreted in the urine. Renal clearance of TCA metabolites is reduced by normal aging, accounting for much of the increased risk of toxicity in older patients.[79]

Clinical Pharmacology

Pharmacokinetics

The most important factor influencing the pharmacokinetics of TCAs is their metabolism (discussed earlier). The pharmacokinetics of TCAs are characterized by substantial first-pass metabolism, a large volume of distribution, extensive protein binding, and an elimination half-life averaging about 1 to 3 days. The mean half-lives of amitriptyline and nortriptyline are about 21 and 32 hours, respectively, allowing for convenient once-daily dosing.[80] All of the tricyclic drugs are rapidly absorbed after oral administration and, at therapeutic plasma concentrations, are 90% to 95% bound to plasma albumin. They also bind to extravascular tissues, accounting for their large volumes of distribution.[81] TCAs are highly lipid-soluble drugs, are extensively metabolized in the liver, and are bound to tissues where their concentration is 10 to 20 times higher than plasma levels.[78]

Plasma concentrations of TCAs in the therapeutic range are thought to be between 50 and 300 ng/mL. Desipramine and nortriptyline, both secondary amines, have higher tissue and red blood cell concentrations compared with the tertiary amines.[81] Repetitive oral administration of TCAs at fixed doses and intervals increases the plasma concentration successively until a steady-state level is reached, which is generally attained within 1 to 3 weeks. The time required to achieve steady-state depends on the elimination rate and should be determined after five times the elimination plasma half-life. Individuals who metabolize TCAs very slowly ("slow hydroxylators") can manifest with unexpectedly high serum levels and toxicity and may require more than 3 weeks to reach steady-state plasma levels; these individuals, when identified, will require lower dosing and more stringent monitoring.[78]

Pharmacodynamics

Therapeutic Effects

Numerous clinical trials have shown the efficacy of TCAs in treating chronic pain conditions. It is postulated that TCAs exert their therapeutic effects by increasing the levels of serotonin and norepinephrine in the spinal cord, enhancing the descending inhibitory pathways of pain modulation. The dorsolateral pontine tegmentum is the major source of noradrenergic neurons that project to the spinal dorsal horn, while the rostral ventromedial medulla is the primary source of serotonergic neurons that project to the spinal dorsal horn. Both norepinephrine and serotonin can inhibit nociceptive dorsal horn neurons when applied locally. Additional studies conclude that opioid analgesia is enhanced in the presence of antidepressant therapy.[82]

Adverse Effects

The pharmacodynamic effects of TCAs on norepinephrine and serotonin reuptake are complicated by their simultaneous activity at multiple other receptor types, including muscarinic, α_1-adrenergic, dopaminergic, and histamine H_1 (Fig. 19.7), resulting in the side effect profile listed in Table 19.4.

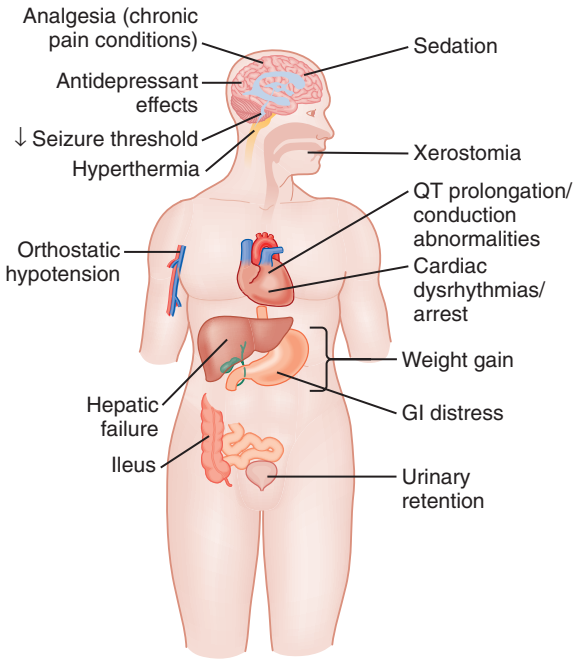
Common adverse effects of TCAs include sedation, urinary retention, gastrointestinal distress, dry mouth, and weight gain. Major adverse effects, typically only observed at higher doses, include QT prolongation, conduction abnormalities, cardiac arrest, hepatic failure, paralytic ileus, hyperthermia, orthostatic hypotension, and decreased seizure threshold (see Fig. 19.7 and Table 19.4).[83]

Therapeutic plasma concentrations of TCAs are in the 50- to 300-ng/mL range. Patients with plasma TCA concentrations greater

TABLE 19.4 Common Side Effects Associated With Selected Tricyclic Antidepressants

	Sedation	Anticholinergic Effects	Hypotension	Cardiac Effects	Seizures	Weight Gain
Amitriptyline	+++	+++	+++	+++	++	++
Clomipramine	++	+++	++	+++	+++	+
Desipramine	0/+	+	+	++	+	+
Nortriptyline	+	+	+	++	+	+

0/+, Minimal; *+*, mild; *++*, moderate; *+++*, moderately severe.
Note marked differences in the toxicity of certain tricyclic antidepressants compared with others.



• **Fig. 19.7** Tricyclic antidepressant pharmacodynamics: a summary of selected therapeutic and adverse effects. *GI,* Gastrointestinal.

than 450 ng/mL tend to develop CNS toxicity consisting of agitation, confusion, and memory impairment. Major toxicity and death is associated with concentrations above 1000 ng/mL.[81]

Drug Interactions

The degree of drug interactions with TCAs is largely dependent on the specific tricyclic agent used and its relative inhibitory potential of hepatic CYP 450 oxidative enzymes. Desipramine and nortriptyline have the least drug interactions because they are weak CYP 450 2D6 inhibitors and are unlikely to be involved in clinically relevant interactions unless the serum levels are high—for example, following overdose or in "slow hydroxylators." Amitriptyline, imipramine, clomipramine, dothiepin, and doxepin, all tertiary amines, are more potent CYP 450 inhibitors and therefore are more problematic in terms of drug interactions.[81]

It is important to use extreme caution when prescribing TCAs in patients taking monoamine oxidase inhibitors (MAOIs), SSRIs, or other anticholinergics. Cimetidine, haloperidol, and phenothiazines can increase TCA plasma levels. Drugs such as carbamazepine, a CYP 450 inducer, may reduce plasma levels of tricyclics. Concomitant use of NSAIDs or warfarin can increase the risk of gastrointestinal bleeding owing to the inhibitory effect of serotonin on platelet aggregation.[84–86]

TCAs are known to prolong the QTc interval, so care should be taken with the concomitant use of other agents associated with QT prolongation, potentially proarrhythmic medications, sodium channel blockers, cardiac glycosides, and noradrenergic drugs, such as cocaine and amphetamines.

Special Populations

In patients with cardiovascular diseases (e.g., coronary artery disease, hypertension, arrhythmias), the previously discussed cardiovascular risks of tricyclics are compounded. Older patients receiving TCAs may be more predisposed to orthostatic hypotension and falls, and they are more susceptible to the cognitive side effects related to factors such as altered renal metabolism and protein binding.[87] Selection of a TCA with less anticholinergic activity, a low initial dose, slow titration, and follow-up of blood pressure (measured both when supine and standing) is recommended in older patients.[81] Observational studies showed increased mortality after myocardial infarction in patients using type 1A antiarrhythmic agents; therefore TCAs are contraindicated after a recent myocardial infarction.[88]

It is recommended that patients with liver disease have laboratory screening of serum electrolytes and liver function tests before initiation of TCA treatment with caution advised during dose titration.

TCAs should be used with caution in patients with renal dysfunction because metabolites are excreted in the urine. Chronic kidney disease affects TCA elimination by changing glomerular blood flow and filtration, tubular secretion and reabsorption, and renal bioactivation and metabolism. It is therefore recommended to reduce the drug dose and slowly titrate based on serum drug concentration monitoring (including the active metabolites).[88]

Unique Features of Individual Agents

In general, TCAs are equally effective in their treatment of neuropathic pain and the choice of a particular agent is usually determined based on the side effect profile.

Amitriptyline blocks the reuptake of both norepinephrine and serotonin, but it more potently blocks the reuptake of the former. It has a high affinity for histamine H_1 and muscarinic M_1 receptors; compared with other tricyclics, it is highly sedating and

associated with weight gain and more anticholinergic side effects (see Table 19.4).

Desipramine also blocks the reuptake of norepinephrine and serotonin, but it has more affinity for norepinephrine reuptake blockade. It has less affinity for histamine H_1 receptors, thereby resulting in less sedation in comparison to other TCAs. It also has less affinity for muscarinic M_1 receptors and therefore has less anticholinergic effects.

Doxepin, also FDA-approved for anxiety disorders, has the highest affinity for histamine H_1 receptors, is highly sedating, and is associated with weight gain.

Imipramine is similar to amitriptyline in terms of its ability to block norepinephrine and serotonin reuptake, but it also has strong affinities for α-adrenergic, histamine H_1, and muscarinic M_1 receptors. Hence, it is associated with orthostasis, sedation, weight gain, and anticholinergic side effects; however, the intensity of these symptoms is less than those of amitriptyline. Imipramine is demethylated in the liver to desipramine.

Nortriptyline, the active metabolite of amitriptyline, is similar to desipramine in that it has more affinity for blocking the reuptake of norepinephrine over serotonin. It has relatively less affinity for histamine H_1 and muscarinic M_1 receptors and therefore has a more favorable side effect profile.

Common Clinical Indications

TCAs are now rarely used for the management of depressive disorders but have become a mainstay in the treatment of several chronic pain syndromes. According to guidelines published by the IASP, low-dose TCAs are recommended as first-line therapy in many neuropathic pain conditions, including diabetic neuropathy, postherpetic neuralgia, and central pain syndromes.[89]

Numerous studies show that TCAs are effective in treating chronic nonmalignant pain, including diabetic neuropathic pain, postherpetic neuralgia, radicular pain, and pain originating from conditions such as human immunodeficiency virus (HIV), complex regional pain syndrome, and autoimmune disorders. TCAs have also been used in fibromyalgia, temporomandibular joint disorder, interstitial cystitis, phantom limb pain, premenstrual pain, and pelvic pain and are a mainstay in preventive treatment of migraine and tension headaches. Mixed data support the efficacy of TCAs in surgical acute pain as an adjunctive medication in patients recovering from amputation and traumatic or surgical nerve injuries.[90,91]

Many prescribers take advantage of the sedating histaminergic side effects of tricyclics by prescribing them as sleep aids. In general, TCAs promote initiation and continuity of sleep while suppressing rapid eye movement sleep in a dose-dependent manner.[92]

Rational Drug Selection

As discussed earlier, the basic approach to prescribing TCAs is based on the side effect profiles in that they tend to vary from each drug in this class. In general, desipramine and nortriptyline have the most favorable side effect profiles. However, because they have more affinity for norepinephrine reuptake blockade as opposed to serotonin or histamine H_1, they may have an unpleasant psychostimulant effect and may not be suitable for use before bedtime.

Tricyclics (e.g., doxepin and amitriptyline) that have more affinity to histamine H_1 receptors, thereby possessing sedative qualities that can be useful in patients with insomnia.

Gabapentin and Pregabalin

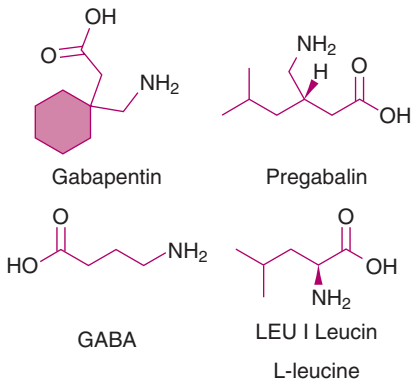
Pharmacology

Neuropathic pain resulting from peripheral nerve sensitization and ectopic transmission of noxious stimuli can resemble the abnormal hyperexcitability of neuronal transmission seen in epileptic disorders. The use of anticonvulsant agents by the mainstream pain medicine community has a long history but evidence of their efficacy often came later, as practitioners first used these antiepileptic agents "off label" before rigorous scientific validation was achieved. Numerous anticonvulsants have been used in the treatment of neuropathic pain, including phenytoin, topiramate, carbamazepine, and sodium valproate. While some of these agents continue to be used for certain conditions (e.g., carbamazepine for trigeminal neuralgia) the newer anticonvulsants with FDA approval for the management of pain—gabapentin and pregabalin—have largely supplanted their role. These second-generation antiepileptic medications, referred to as *gabapentinoids,* provide much better tolerability in terms of side effects and toxicity, and offer greater receptor selectivity than first-generation drugs.[83]

Gabapentin and pregabalin are branched-chain amino acids and chemical analogs of the neurotransmitter GABA. Despite their name, neither drug has activity in the GABAergic neurotransmission system. They are functionally similar to the essential amino acid leucine in that they competitively bind $\alpha_2\delta$ calcium channel subunits (Fig. 19.8).[87] Gabapentin is described as 1-(aminomethyl)cyclohexaneacetic acid ($C_9H_{17}NO_2$), while the chemical name of pregabalin is (*S*)-3-(aminomethyl)-5-methylhexanoic acid ($C_8H_{17}NO_2$).[93,94]

Mechanism

The mechanism of action for gabapentin and pregabalin is also uncertain, but both drugs have high binding affinities to the $\alpha_2\delta$-1 subunit of presynaptic voltage-gated calcium channels in the CNS.[95] Their analgesic effects may be related to calcium influx inhibition as well as inhibition of the release of excitatory neurotransmitters in spinal and supraspinal pathways.[83] It is hypothesized that conditions such as neuropathic pain and epilepsy may involve excessive formation of excitatory synapses. A recent study showed that by binding to this $\alpha_2\delta$-1 subunit, gabapentin prevents the binding



• **Fig. 19.8** A comparison of the chemical structures of gabapentin, pregabalin, the neurotransmitter gamma-aminobutyric acid, and the amino acid L-leucine.

of thrombospondin, a synaptogenic protein secreted by astrocytes, thereby impeding synapse formation between neurons.[96]

Although both drugs are structural analogues of GABA, neither modifies this neurotransmitter nor is converted metabolically into GABA or a GABA agonist. In addition, neither drug inhibits GABA reuptake or degradation.[93]

Animal studies using genetically modified mice show that selective binding to the $\alpha_2\delta$-1 subunit is necessary for these drugs to exert their antinociceptive, anticonvulsant, and anxiolytic effects.[97–99]

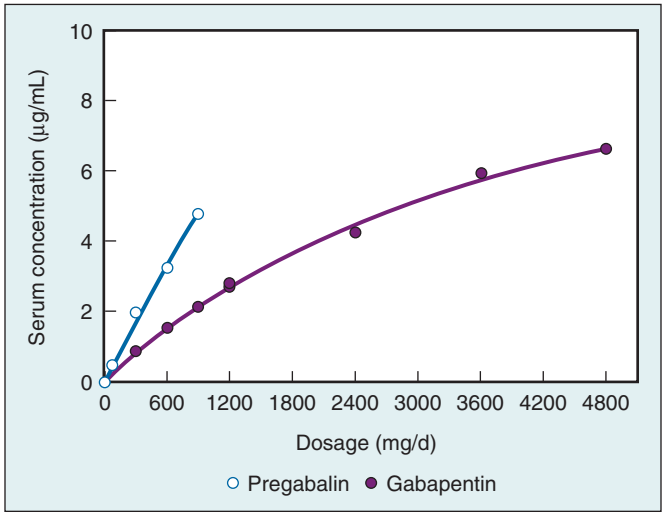
Metabolism

The metabolic profiles of gabapentin and pregabalin are very similar. Both drugs are metabolized to their corresponding N-methyl metabolite in dogs but undergo minimal metabolism in humans and are excreted unchanged.[87]

Clinical Pharmacology

Pharmacokinetics

Gabapentin and pregabalin readily disintegrate after oral administration, but there are some significant differences in the absorption of the two drugs related to the L-amino acid transporter (LAT) system that facilitates the absorption of large, neutral amino acids as well as the absorption of both gabapentin and pregabalin.[100] Preclinical data suggest that gabapentin is transported solely by the LAT1 transporter, which results in dose-limited absorption owing to nearly maximal transporter saturation at a dose of 2400 to 2700 mg/day. The absorption of pregabalin is also facilitated by the LAT family of transporters but is also mediated by an additional pathway allowing almost complete, nonsaturable incorporation into the bloodstream.[101] Therefore pregabalin displays linear pharmacokinetics over its recommended oral dose range of 75 to 900 mg/day (Fig. 19.9).[87,101] Gabapentin has an elimination half-life of 5 to 7 hours and is primarily excreted unchanged in the urine with 10% to 23% excretion in the feces. The renal clearance of gabapentin does decrease in patients with kidney disease, and the drug is dialyzable.[102] Pregabalin has a mean elimination half-life of 6.3 hours, does not undergo any protein binding in the plasma, and has negligible metabolism. Approximately 98% of the dose is excreted unchanged in the urine. Pregabalin blood concentrations can be reduced by 50% by hemodialysis but a supplementary pregabalin dose of 25 to 100 mg after dialysis may be used to restore a therapeutic level.[102]



• **Fig. 19.9** Mean steady-state minimum plasma drug concentration values in 33 healthy subjects given oral pregabalin or gabapentin every 8 hours. Note the more linear dose-to-serum concentration relationship of pregabalin compared with gabapentin. (From Bockbrader HN, Wesche D, Miller R, et al. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. *Clin Pharmacokinet*. 2010;49:661–669.)

Peak plasma concentration after gabapentin absorption occurs 1.5 to 4 hours after administration of an oral dose, and its oral bioavailability is dose-dependent with minimal additional absorption achieved after a dose of 2700 mg/day. Pregabalin is rapidly absorbed after oral administration with 90% bioavailability and peak plasma concentrations seen after just 1 hour. Steady-state concentrations of pregabalin in plasma are seen after approximately 1 to 2 days of treatment.[101,102]

Pharmacodynamics

Therapeutic Effects

As discussed earlier, the voltage-gated calcium channel receptor activities of gabapentin and pregabalin in dorsal horn of the spinal cord and brain are well elucidated, but the mechanism by which this modulates neuropathic pain signaling is not well understood.

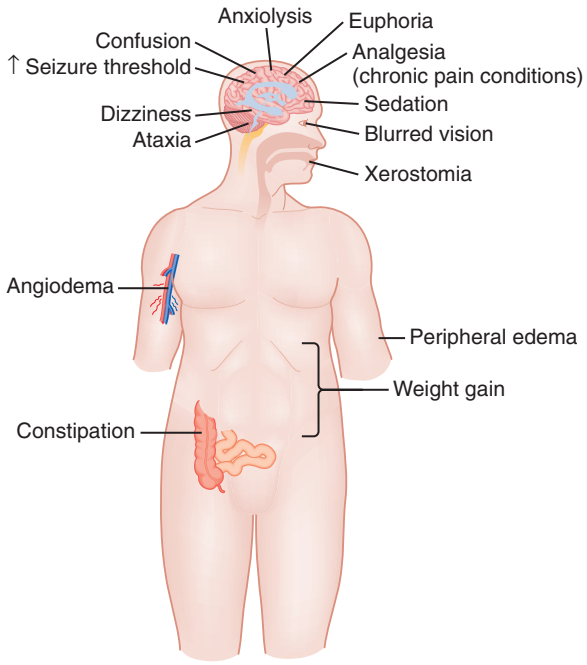
Adverse Effects

With careful dosing, gabapentin and pregabalin are typically well-tolerated medications. Dizziness and somnolence are the most commonly reported adverse effect of both drugs, and the latter is the most frequent reason for discontinuation. Other reported side effects include xerostomia, peripheral edema, angioedema, blurred vision, ataxia, dysarthria, tremor, lethargy, memory impairment, euphoria, constipation, decrease or loss of libido, and weight gain (Fig. 19.10). The adverse effects of gabapentinoids are reversible and dose dependent.

Abrupt discontinuation and withdrawal of gabapentinoids may precipitate seizures, particularly in a patient with a preexisting seizure disorder. Anxiety, insomnia, nausea, pain, and sweating are the most frequently reported adverse events following abrupt discontinuation. It is recommended that these medications be gradually tapered over the course of at least 1 week to avoid these symptoms.[93,94]

Drug Interactions

Because gabapentin undergoes minimal metabolism, it is unlikely to have any interactions with other medications. Concomitant administration of other antiepileptic drugs, including phenobarbital, carbamazepine, valproate, and phenytoin, does not alter gabapentin pharmacokinetics.[100] Gabapentin does not induce or inhibit hepatic enzymes and therefore it does not appear to be affected by drugs that are inducers or inhibitors of cytochrome P450 enzymes. The use of antacids aluminum hydroxide and magnesium hydroxide may reduce the bioavailability of gabapentin by up to 20%. It is therefore recommended that gabapentin should not be administered until at least 2 hours after antacid use. Agents that prolong the transit time of gabapentin in the small intestine could potentially increase its bioavailability. One study demonstrated that gabapentin's bioavailability was increased by 50% when a 600-mg dose was



• **Fig. 19.10** Gabapentinoid pharmacodynamics: a summary of selected therapeutic and adverse effects.

coadministered with oral morphine.[103] A statistically significant but clinically irrelevant decrease was reported in the oral clearance of gabapentin with the concurrent use of cimetidine.[100]

Pregabalin is also similarly unlikely to be associated with any pharmacokinetic drug interactions as it does not undergo hepatic metabolism and does not induce or inhibit cytochrome P450 enzyme systems. Studies in healthy volunteers and various other patient populations show that the pharmacokinetics of pregabalin were not significantly altered by simultaneous administration of lorazepam, oxycodone, alcohol, oral contraceptive drugs, antihyperglycemics, furosemide, and numerous other anticonvulsants. Concomitant use of pregabalin with oxycodone or alcohol had an additive effect on cognitive and gross motor functioning, but not respiration.[104] Furthermore, pregabalin does not demonstrate any changes in its bioavailability when administered with agents that reduce gastrointestinal transit time.

Special Populations

Gabapentinoids are excreted almost exclusively by the renal system and their clearance is directly related to creatinine clearance. Numerous studies have shown that serum levels of gabapentin and pregabalin increased with decreasing renal function, and that both drugs are readily dialyzable. Therefore dosage adjustments based on creatinine clearance are necessary in patients with renal dysfunction or those undergoing hemodialysis. The pharmacokinetics of both drugs are not affected by sex or race, but clearance is decreased in older patients secondary to age-related changes in renal function.[103–105]

Unique Features of Individual Agents

The slight differences in the chemical structure of gabapentin and pregabalin differentiate their pharmacokinetic and pharmacodynamic properties. Pregabalin is advantageous in that it possesses nonsaturable absorption at clinically relevant doses, resulting in linear pharmacokinetics. Pregabalin also has a steeper dose response relationship than gabapentin (see Fig. 19.9) and appears to achieve a greater treatment effect in postherpetic neuralgia and epilepsy.[87]

Pregabalin has more selective binding to the $\alpha_2\delta$-1 subunit, has a more favorable side effect profile, and has a simpler, twice-a-day dosing regimen versus gabapentin, which must be dosed three times per day.

Common Clinical Indications

Gabapentin is currently FDA approved for postherpetic neuralgia and partial seizures, while pregabalin is FDA approved for partial seizures, painful diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia. Furthermore, recent guidelines published by the IASP recommend both drugs as first-line therapy for these conditions as well as central pain syndromes, such as central poststroke pain related to spinal cord injury and multiple sclerosis.[89]

Numerous studies show the efficacy of gabapentin in HIV-related neuropathic pain, pain associated with Guillain-Barré syndrome, neuropathic cancer pain, complex regional pain syndrome, phantom limb pain, and neuropathic pain in patients with spinal cord injuries. In addition to its FDA-approved indications, pregabalin has also been shown to be effective in treating generalized anxiety and social anxiety disorders.[106]

Newer studies that have investigated the role of gabapentinoids in managing postoperative pain have yielded mixed results. While some studies that looked at the administration of gabapentin to patients undergoing craniotomies, thoracotomies, and thyroidectomies showed favorable results in terms of controlling acute pain as well as preventing chronic pain, others show that it is an inferior as a single agent compared with numerous other drugs used in this setting.[107]

The same holds true for pregabalin in that some studies show it may decrease perioperative opioid and epidural use in patients with more acute neuropathic pain than acute inflammatory pain, and it may also decrease the incidence of chronic pain when surgery involves a more neuropathic type acute pain process.[108] A large meta-analysis of numerous randomized controlled trials showed no clear beneficial effect of pregabalin in acute postoperative pain.[109]

Owing to the hypothesized spinal site of action of gabapentin, as well as its relatively short plasma half-life, intrathecal gabapentin administration would seem like a logical option for treatment of chronic pain conditions. However, a multiphase randomized, blinded, placebo-controlled, multicenter trial showed no difference in the numerical pain rating scale and response rate after 3 weeks of treatment in 170 patients.[110]

Rational Drug Selection

For the most part, gabapentin and pregabalin have minimal drug interactions, making them versatile drugs in combination with other neuropathic pain medications. Gabapentin is also relatively less expensive in that it is available in a generic form and available in most inpatient and outpatient settings.[93] Pregabalin has the advantage of high oral bioavailability that results in predictable dose-dependent responses, and has a short titration period that is better tolerated by patients. Because it is a newer drug, pregabalin

is relatively expensive with no generic formulation, and there are limited studies demonstrating its long-term safety.[71]

Emerging Developments

The quest for novel analgesics has been hampered by the complexity of "pain transmission" along neural pathways that share the same anatomic, physiologic, and receptor systems as more useful signaling pathways such as the motor system, proprioception, light touch, and mentation. It has proven difficult to modulate nociceptive and neuropathic signaling without also incurring intolerable side effects. Pain anesthesiologists lack the drug specificity of other fields within our specialty—consider the elegance of being able to selectively block peripheral nicotinic receptors and induce neuromuscular blockade, then reverse this effect with another specific agent, all within minutes. There is presently no such analogy to be made in the treatment of chronic pain. The lack of nonspecific analgesic targets has frustrated patients and their treating physicians alike, but in the emerging field of epigenetics, there are some glimpses of promising gene-based therapies.

The development of new NSAIDs has been somewhat tempered by the controversies surrounding NSAIDs and their associations with increased morbidity and mortality in cardiovascular disease. In perioperative medicine, practitioners in the United States do not yet have access to a parenteral COX-2 inhibitor and eagerly await this important therapeutic option.

In the battle against neuropathic pain, no new agents have been released since duloxetine in 2004. There has been some preclinical interest in the Nav1.7 sodium channel as a possible target for modulating neuropathic pain, but a clinical application should be considered futuristic.[111] A capsaicin receptor, known as TrpV1, is also an enticing target for antagonism and analgesia, but clinical trials of various TrpV1 antagonists have been discontinued because of unfavorable adverse effects.[112]

Novel Small-Molecule Therapeutics

Ziconotide is a novel conopeptide isolated from the venom of the marine snail, *Conus magus,* and has shown analgesic efficacy in the treatment of refractory chronic pain.[113,114] The unique analgesic properties of ziconotide are mediated by blockade of N-type voltage-sensitive calcium channels, inhibiting depolarization-induced calcium influx and reducing neurotransmitter release from nociceptive afferents. Ziconotide is suitable for intrathecal use only, and no development of tolerance, respiratory depression, drug dependence, or withdrawal symptoms have been reported in numerous studies.

Various other marine peptides have been isolated with often fascinating properties, but no analgesics have achieved clinical success since ziconotide was approved by the FDA in 2004.[115] However, Contulakin-G, a 16 amino acid conopeptide that is a neurotensin analog with no opioid or calcium channel activity, has shown potent antinociceptive activity in animal models with excellent tolerability and safety. A recent Phase 1A clinical trial in humans with central pain demonstrated good tolerability and promising analgesic effects.[116]

MicroRNAs as Biomarkers and Therapeutic Agents

The study of microRNA (miRNA) is an emerging field of interest in pain diagnosis and therapy. MicroRNAs are noncoding short fragments of RNA that play a role in target gene expression and are sometimes referred to as a "switch" for protein transcription. Their role of interest in the field of pain medicine is that of orchestrating neuronal plasticity, a process that seems to be deranged in certain neuropathic pain states. In a rat model, specific miRNA sequences have been identified as quite specific markers for neuropathic pain, and therefore it is conceivable that, as this field develops, miRNA may offer useful diagnostic tools.[117,118]

One particular type of microRNA, miR-124, has been shown to be downregulated in the dorsal root ganglia in certain animal pain models, and furthermore, the administration of intrathecal and intravenous miRNA-124 has demonstrated antinociceptive effects. Another microRNA subtype, miR-102, has been implicated in the regulation of L-type calcium channels, which are known to be involved in the development of neuropathic pain, and delivery of intrathecal miR-102 has attenuated this process.

While the study of microRNA in health and disease is still in its infancy, the concept of performing an assay on an individual's miRNA expression and function, with the potential identification of a personalized therapeutic agent to restore healthy homeostasis in pain pathways, is certainly an exciting prospect[119] (Fig. 19.11).

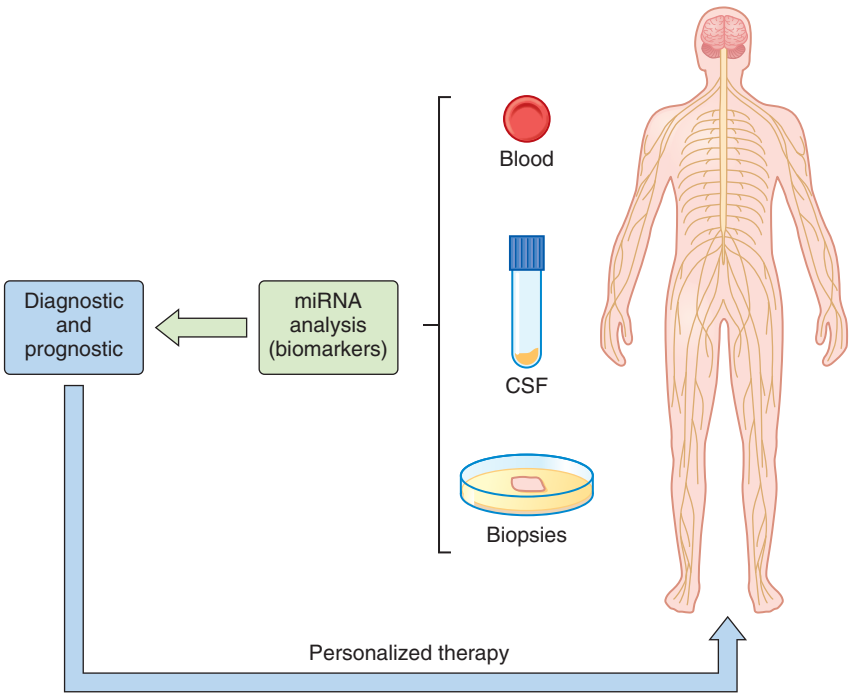
Cannabis Derivatives for Pain Management

In the United States, selected states have legalized the use of cannabis for medicinal purposes including pain management. This has been met with some controversy given the questionable scientific foundation, the pharmacologic heterogeneity of the cannabis in terms of its numerous active compounds, and the awkward political reality that cannabis continues to be seen as an illicit substance in the eyes of the Drug Enforcement Agency.

Endocannabinoids, cannabis plant–derived products, and synthetic cannabis compounds act with varying degrees of affinity on the endocannabinoid receptors CB1 and CB2. However, it has been postulated that specific cannabinoids, such as cannabidiol (CBD), demonstrate activity at receptor sites known to modulate pain including serotonin[120] and adenosine[121] receptors. Considering these developments it is no surprise that the use of cannabis for treatment of symptoms common to many disease states continues to dominate political debates both in the United States and worldwide.

In January 2017 the National Academies of Sciences, Engineering, and Medicine released a comprehensive review of research on the health effects of cannabis use. Among the nearly 100 conclusions made by the expert ad hoc committee was the following statement with regards to use of cannabis in the treatment of chronic pain: "There is substantial evidence that cannabis is an effective treatment for chronic pain in adults."[122] This conclusion was drawn almost exclusively from a meta-analysis performed by Whiting et al. in 2015 that demonstrated that plant-derived cannabinoids increase the odds for improving pain relief by more than 30% versus placebo (odds ratio 1.41) in various disease states, including neuropathic pain, cancer pain, fibromyalgia, musculoskeletal pain, multiple sclerosis, and rheumatoid arthritis.[123]

While measured optimism may be appropriate for the use of cannabis in pain management, the effects are likely modest and useful as an adjunct rather than a sole, or primary, agent. Furthermore, the long-term, systemic effects of chronic cannabis use remain largely unknown.[122] Additional research could elucidate these questions and determine the optimal role for use of cannabis in the management of pain and other common symptoms of various disease states.



• **Fig. 19.11** A schematic diagram illustrating how microRNAs *(miRNA)* might be harvested and processed for personalization of chronic pain therapy in humans in the future. Possible sources of miRNA include blood, cerebrospinal fluid, and biopsy tissue. As the field advances, it may be possible to identify diagnostic miRNA associated with selected pain diagnoses, personalize specific therapies, and monitor the treatment response. CSF, Cerebrospinal fluid. (From López-González MJ, Landry M, Favereaux A. MicroRNA and chronic pain: from mechanisms to therapeutic potential. *Pharmacol Ther.* 2017;180:1–15.)

Key Points

- NSAIDs inhibit the conversion of arachidonic acid to prostaglandins, thromboxane, and prostacyclin.
- NSAIDs are generally well tolerated, but distinct toxicities exist; patient comorbidities and the clinical scenario should be considered carefully when prescribing.
- Controversies exist regarding NSAIDs and perioperative hemostasis. While NSAIDs rarely cause clinically significant hemostatic derangement, they should be used with caution when other causes of coagulopathy exist.
- COX-2 inhibitors do not affect platelet function and should be considered when there are concerns regarding postoperative hemostasis.
- Gastrointestinal toxicity is rarely a problem with the short-term, perioperative use of NSAIDs, but it is a significant cause of morbidity and mortality with long-term use.
- NSAIDs are safe and useful adjuncts in the management of noncardiac postoperative pain.
- COX-1 and COX-2 inhibitors should be avoided in patients with renal insufficiency.
- Topical NSAIDs can produce local therapeutic effects without significant systemic drug levels, thereby avoiding the adverse effects of oral agents.
- Acetaminophen, available in oral, rectal, and intravenous formulations, is useful for the management of mild to moderate pain, and at appropriate therapeutic doses lacks the toxicity associated with NSAIDs.
- The analgesic properties of TCAs are thought to be related to reuptake inhibition of serotonin and norepinephrine.
- TCA adverse side effects include QT prolongation, conduction abnormalities, orthostatic hypotension, anticholinergic effects, weight gain, and sedation.
- Gabapentinoids bind to the $\alpha_2\delta$-1 subunit of presynaptic voltage-gated calcium ion (Ca^{2+}) channels in the CNS; their analgesic effects might be related to inhibition of Ca^{2+} influx and the release of excitatory neurotransmitters in spinal and supraspinal pathways.
- Gabapentinoids are structural analogs of GABA but have no GABA receptor effects.
- Dizziness and somnolence are the most commonly reported adverse effects of gabapentinoids.
- Gabapentin is approved for postherpetic neuralgia and partial seizures. Pregabalin is approved for partial seizures, painful diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia.
- There are mixed results regarding the efficacy of gabapentinoids in treating acute postoperative pain.
- MicroRNA is a relatively new field of interest with the potential to provide personalized therapeutic agents based on an individual's miRNA expression and function.
- Use of cannabis for the management of pain remains controversial with available evidence demonstrating modest improvement of pain in various disease states. Long-term effects of chronic cannabis use are unknown.

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20
Local Anesthetics

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Historical Perspective

Cocaine, the first local anesthetic, was isolated from leaves of the coca plant, *Erythroxylum coca,* by Albert Niemann in 1860. The medicinal use of coca had long been a tradition of Andean cultures but it was only after chemical isolation that it became readily available in Europe. Its pharmacologic properties after oral ingestion were investigated and described by Sigmund Freud in his publication *Über Coca* in 1884.[1] Freud's descriptions of the numbing effect of cocaine on skin and mucous membranes prompted his Viennese colleague Carl Koller to use cocaine as a topical anesthetic for cataract surgery, which up until then was performed with the patient awake and associated with severe pain.[2] Toward the end of the 19th century, cocaine was in widespread use for regional and local anesthesia for a myriad of medical indications, and it was also used as a food supplement—for example, in wine and soda beverages.[3] However, the chemical purification of cocaine from coca leaves also increased its toxic and addictive properties, and in the early 20th century the need was identified to synthesize safer medical alternatives to cocaine.[2]

Development of Modern Local Anesthetics

Both cocaine and the subsequent synthetic local anesthetics share as a basic property the reversible blockade of voltage-gated sodium channels. This resulted in two main clinical applications: (1)

Abstract

Local anesthetics are a group of structurally related compounds which share as principal mechanism of action the blockade of voltage-gated sodium channels, resulting in reversible interruption of nerve signal transduction. Currently used local anesthetics are divided into amino amides, or amino esters. Each substance has distinct physicochemical properties, and local anesthetics can be administered continuously or together with adjuvants, allowing clinicians to tailor their anesthetic to procedure and patient. Next to sodium channel blockade, local anesthetics interact with other targets, for example calcium and potassium channels, and G-protein coupled receptors. The latter mode of action explains the anti-inflammatory properties of local anesthetics. Clinical application of existing local anesthetics, and development of novel local anesthetics, is hampered by systemic and local toxicity. Among the additives to local anesthetics, epinephrine is helpful in prolonging duration of action of medium-acting local anesthetics, and to reduce systemic absorption of any local anesthetic. Buprenorphine is an effective additive and has local anesthetic properties but causes excessive nausea and vomiting. Dexmedetomidine and clonidine are popular additives as well but can cause dose-dependent systemic side effects such as sedation, bradycardia and hypotension. Dexamethasone has the least systemic side effects, and the longest prolongation of nerve block duration. Emerging developments in the field of local anesthetics include the development of subtype-specific sodium channel blockers, cell type-specific or heat-assisted delivery, and various modes of encapsulation.

Keywords

local anesthetics
pharmacology
toxicology
pharmacokinetics
pharmacodynamics

reversible interruption of nerve impulse propagation to achieve local or regional anesthesia, and (2) inhibition of cardiac ion channels as a class IB antiarrhythmic agent.

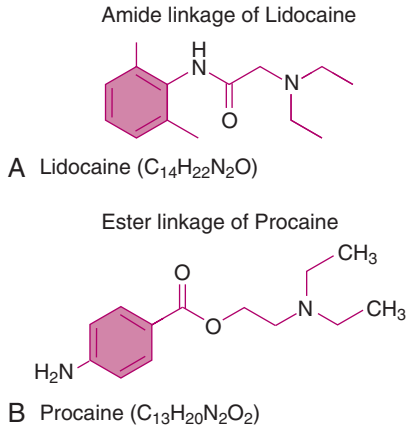
Using cocaine as the basic ester compound, the first derivative, procaine (also known by its trade name Novocaine), was synthesized in 1905. However, procaine was not the optimal local anesthetic because of its very long onset time, short duration of action, and low potency. A breakthrough came in the 1940s when lidocaine (Xylocaine) was introduced. Lidocaine was the first and a prototype compound of the amide class of local anesthetics, which are still in widespread use today. It had fewer undesirable effects than procaine and provided deeper anesthesia. Many new amide local anesthetics were subsequently introduced with differences in speed of onset, potency, and duration of action. Bupivacaine was synthesized in 1957 and rapidly gained popularity because of its long duration of action. However, because of the association of bupivacaine with cardiac toxicity, a less toxic long-acting drug was sought. Bupivacaine is a racemic mixture of the (+) and (−) enantiomers, with lesser toxicity associated with the S(−) form compared with the R(+) form. This led to the development of levobupivacaine and ropivacaine. Today many local anesthetic agents, including both ester and amide types, are available. Although they share the same basic structure, they have distinct physicochemical properties that allow clinicians to choose the optimal anesthetic for specific applications.

Chemical Structure and Physicochemical Properties

All currently available local anesthetics consist of a lipophilic phenyl ring and a hydrophilic tertiary amine joined by an intermediary ester- or amide-based linker (Fig. 20.1).

Ester- Versus Amide-Type Local Anesthetics

Based on the nature of the intermediary chain, clinically used local anesthetics are classified as amino amides (e.g., lidocaine, prilocaine, bupivacaine) or amino esters (e.g., cocaine, procaine, chloroprocaine, tetracaine). Amide and ester local anesthetics differ in their chemical stability, metabolism, and allergic potential. Amides are extremely stable, whereas esters are relatively unstable, particularly in neutral or alkaline solution. Amide compounds undergo enzymatic degradation in the liver, whereas ester compounds are hydrolyzed in plasma by esterases. Cocaine, an ester, is an exception, as it is metabolized predominantly by the liver.



• **Fig. 20.1** Local anesthetic structural classification. Amide linkage of lidocaine (A) and ester linkage of procaine (B).

Allergy

True allergy to local anesthetics is rare but is thought to occur more commonly with ester local anesthetics than with amide local anesthetics. The accepted explanation is that metabolites of esters include *p*-aminobenzoic acid (PABA), which is immunogenic.[4] Some preparations of amino amides contain methylparaben, which has a chemical structure similar to PABA and is a possible allergen in cases of allergic reaction to amide local anesthetics. Preservative-free preparations of local anesthetics are available to address the problems associated with methylparaben. Amide local anesthetics are considered to be one of the safest classes of drugs concerning allergy.[5]

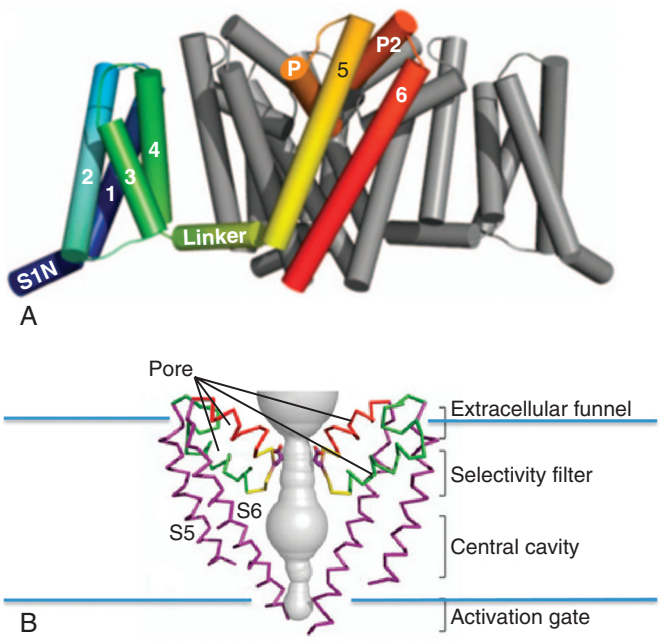
Chiral Forms

With the notable exception of lidocaine, the commonly used amide-type local anesthetics possess one chiral center in the amide piperidine ring. Therefore the plain solution of these substances is racemic, consisting of equal amounts of two possible stereoisomers, which are commonly designated on the basis of geometric configuration as LEVO (left) or DEXTRO (right). These two forms can possess different pharmacologic properties that are of clinical importance. For example, bupivacaine is a racemic mixture, and levobupivacaine is the pure levorotatory enantiomer. Levobupivacaine demonstrates potency and efficacy comparable to bupivacaine but has significantly less cardiac and central nervous system (CNS) toxicity, likely related to reduced affinity for subtypes of sodium ion (Na^+) channels expressed in brain and cardiac tissues.[6,7] Racemic- or R(+)-bupivacaine produces faster and more potent blockade of Na^+ channels in swine ventricular cardiomyocytes than levobupivacaine. In addition, racemic or R(+)-bupivacaine produces a greater reduction of the maximum rate of depolarization in animal cardiomyocytes, suggestive of the difference in Na^+ conductance.[8]

Physiochemical Properties of Local Anesthetics: Clinical Implications

In general, with increasing length of the carbon backbone, local anesthetics exhibit greater lipid solubility, protein binding, potency, and duration of action. However, these relationships are not linear and are often influenced by multiple other factors. Local anesthetics must penetrate through the lipid-rich nerve sheaths and cell membrane to reach their targets, voltage-gated Na^+ channels (Na_v). The binding site of local anesthetics is located inside the channel pore and is not readily accessible from the extracellular side as inferred from pharmacologic studies. This concept has gained support from the atomic resolution structure of a bacterial voltage-gated Na^+ channel (Fig. 20.2).[9] Therefore local anesthetics must cross the nerve membrane into the cell interior by diffusing through the lipid bilayer to reach their binding site. Consequently, the potency of each local anesthetic is closely related to its lipid solubility and its dependence on pH.[10,11]

The tertiary amine on the hydrocarbon backbone of local anesthetics is a weak base capable of accepting a hydrogen ion with low affinity to form a conjugated acid. Most local anesthetics have negative logarithm for the acid ionization constant (pKa) values relatively close to but higher than physiologic pH (with some exceptions such as prilocaine, which has a secondary amine



• **Fig. 20.2** Structure of a bacterial voltage-gated sodium channel. A, The structure consists of four identical subunits; the voltage-sensing domain of one subunit (S-S4) has been removed for clarity. Each subunit contains six transmembrane segments folded in a complex to form the ion-selective pore gated by voltage. One subunit (S1-6) is highlighted in color; the other three are in *gray.* Transmembrane segments S5 and S6 line the ion pore, the P loops form the selectivity filter, and S1-S4 form the voltage sensor. B, The transmembrane pore module, consisting of an outer funnel-like vestibule, a selectivity filter, the central cavity, and the intracellular activation gate. Four lateral openings lead from the cellular membrane to the lumen of the pore, giving hydrophobic access to lipophilic drugs, which are able to penetrate through these pores. (Modified from Payandeh J, Scheuer T, Zheng N, et al. The crystal structure of a voltage-gated sodium channel. *Nature*. 2011;475:353–358.)

and benzocaine that has a primary amine) (Table 20.1). Around physiologic pH (7.4), local anesthetics exist in two forms,[10] the positively charged acid and the neutral uncharged base form, with the respective ratio described by the Henderson-Hasselbalch equation:

$$[1]$$
$$pKa = \log([H+][B-]/[BH])$$
$$pKa = pH + \log([B-]/[BH])$$

where B is the base form and BH is the protonated acid form.

Local anesthetics cross the lipid membrane much faster in their neutral lipophilic form than their cationic form. Alkalinization by sodium bicarbonate addition to local anesthetics increases the pH and shifts the equilibrium in favor of the neutral base forms, which facilitates translocation of the local anesthetic into the cellular interior and speeds onset, but this is not advised for long-acting local anesthetics because of the risk of precipitation.[12,13] Once inside the cell, the lower pH shifts the equilibrium toward the positively charged protonated form. The charged form antagonizes Na^+ channels more potently than the neutral form.[14,15]

The onset of action of local anesthetic action depends on the route of administration and the dose or concentration of drug. In the subarachnoid space where the nerves lack a sheath, local anesthetics are able to reach their targets more readily, leading to a more rapid onset of nerve block with a much smaller dose compared with peripheral nerves. In peripheral nerve blocks, deposition of local anesthetic is in the vicinity of the nerves and the amount of drug that reaches the nerve depends on the diffusion of the drug and the proximity of the injection to the nerve. For a given route of administration, increasing the concentration can accelerate onset.[16] For instance, chloroprocaine is much slower in onset than lidocaine at equal concentrations because its pKa of 9.1 favors the positively charged form at physiologic pH. However, a 3% solution is the typical concentration of chloroprocaine used clinically, which provides a much faster onset than other agents at their clinically used concentrations (e.g., 0.25% bupivacaine, 0.5% ropivacaine, or 1.5% mepivacaine) simply because there are more molecules present to diffuse into the nerve.

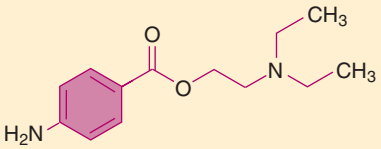
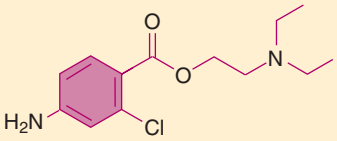
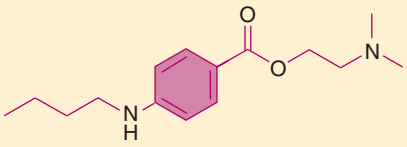
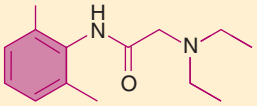
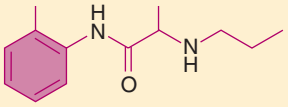
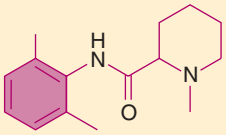
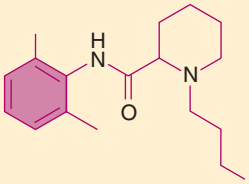
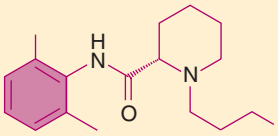
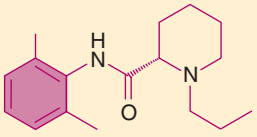
The duration of action of local anesthetics is determined primarily by their protein binding (see Table 20.1). Local anesthetics with a high affinity for protein remain bound to the nerve membrane longer. In other words, binding to Na^+ channels with higher affinity results in a channel blocking effect of longer duration. Duration of action is also influenced by the rate of vascular uptake of local anesthetic from the injection site. The duration of peripheral nerve blocks ranges from 30 to 60 minutes with short-acting agents such as procaine and chloroprocaine to nearly 10 hours with long-acting local anesthetics such as bupivacaine and tetracaine. The rate of vascular uptake significantly affects local anesthetic duration of action as local anesthetics provide their effect as long as they remain at the site of deposition. Therefore deposition of local anesthetics at a highly vascular site such as the intercostal space or inflamed tissue is associated with a higher rate of vascular uptake. Vasoconstriction slows the rate of vascular absorption and thus prolongs the duration of action. For this purpose, vasoconstrictive agents such as epinephrine and phenylephrine are frequently added to local anesthetics as adjuvants to increase duration. The prolongation of nerve block with vasoconstrictors is more prominent with local anesthetics of intermediate durations such as lidocaine and prilocaine than with longer-acting agents such as bupivacaine, possibly because the effect of long-acting local anesthetics outlasts that of vasoconstrictors. Local anesthetics themselves tend to have bimodal effects on vascular smooth muscle such that vasoconstriction results at lower doses, whereas vasodilation predominates at higher concentrations with some minor differences between individual agents.[17]

Pharmacodynamics

Nerve Anatomy

The surface of the nerve axon is formed by the cell membrane consisting of a lipid bilayer that contains various proteins, including ion channels. Myelinated nerve axons are surrounded by myelin, produced by Schwann cells, that wraps around the axons to form the *myelin sheath*. When seen in longitudinal cross section, the myelin sheath is punctuated by gaps called *nodes of Ranvier* (see also Chapter 8). Other axons such as postganglionic autonomic efferent and some of the nociceptive afferent fibers lack a myelin sheath (Fig. 20.3). Nerves are further organized within three layers of connective tissue: the *endoneurium, perineurium,* and *epineurium* (see Fig. 20.3). Nerve fibers are encased in endoneurium, loose connective tissue that consists of glial cells and fibroblasts along with blood capillaries. These fibers are grouped together into *fascicles* by dense collagenous perineurium. The fascicles are combined to form the peripheral nerve by a thicker layer of epineurium. The

TABLE 20.1 Physiochemical Properties of Selected Local Anesthetics

		pKa	Ionization at pH 7.4 (%)	Partition Coefficient	Protein Bound (%)
Ester Type					
Procaine		8.9	97	100	6
Chloroprocaine		9.1	95	810	N/A
Tetracaine		8.5	93	5822	76
Amide Type					
Lidocaine		7.9	76	366	65
Prilocaine		7.9	76	129	55
Mepivacaine		7.6	61	130	78
Bupivacaine		8.1	83	3420	96
Levobupivacaine		8.1	83	3420	98
Ropivacaine		8.1	83	775	94

N/A, Not available.

Modified from Liu SS. Local anesthetics and analgesia. In: Ashburn MA, Rice LJ, eds. *The Management of Pain.* New York: Churchill Livingstone; 1997:141–170.

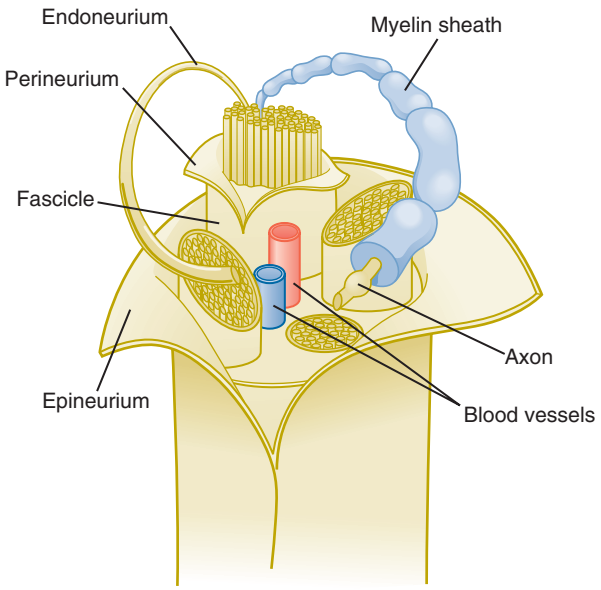
nerves are further encased in fascia. These are the structures that local anesthetics must penetrate to effectively block nerve conduction.

When looking at the sciatic nerve in the popliteal fossa as an example, three further peculiarities become evident. First, the share of nonneuronal tissue (connective tissue, fat, vessels) in peripheral nerves is high, at some locations more than half of the cross-sectional area.[18] Second, while travelling distally, nerve fibers form a plexus in peripheral nerves.[19] Third, before the sciatic nerve bifurcates into the tibial and common peroneal nerve, both nerves can be identified separately inside the thick connective perineurium of the sciatic nerve, at this point sometimes referred to as a paraneural sheath.[20]

Nerves are typically characterized by their degree of myelination, axonal diameter, and speed of impulse conduction (Table 20.2). They are classified as A, B, and C fibers, which roughly correspond to their decreasing cross-sectional diameters. A and B fibers are myelinated, and C fibers are unmyelinated. A and C fibers are further divided into subclasses by their anatomic location and physiologic functions.

Electrophysiology of Neural Conduction

The lipid bilayer of the axonal membrane is relatively impermeable to sodium ions but selectively permeable to potassium ions. The adenosine triphosphate (ATP)-dependent Na^+/K^+ pump (sodium-potassium adenosine triphosphatase) exports Na^+ and imports potassium ions (K^+) in a 3:2 ratio to maintain a concentration gradient of these ions across the axonal membrane.[21] The higher concentration of K^+ in the intracellular space and the greater permeability of the membrane to K^+ lead to the relative negative electrochemical potential of the cell interior. Resting neural membranes have an electrochemical potential of around −70 mV. When Na^+ channels open, sodium ions rush inward down the concentration gradient. Other channels, including Ca^{2+} and K^+ channels, are sensitive to the change in electrical potential and open in response to the depolarization. Neurons are activated by the transduction of chemical, molecular, or thermal stimuli into electrical potential via the influx of cations to raise the electrical potential. The conduction of electrochemical impulses in axons is an *all-or-none* phenomenon. When the depolarization is strong enough, the stimulus is conducted by sequential depolarization of the neural membrane along the axonal length via the opening of Na^+ channels and net inward movement of sodium ions. The sodium ions inside the cell diffuse along the axon in both directions and passively depolarize the adjacent membrane, thereby triggering the opening of additional Na^+ channels by reaching their activation threshold potential. Because the upstream region of the membrane is already depolarized and in a refractory state, the electrical impulse can propagate only in an anterograde direction along the axon (Fig. 20.4A). In myelinated axons, the myelin sheath serves as insulation, and this local phenomenon takes place only at the nodes of Ranvier. Therefore the nerve impulse is able to "skip" the length of myelin to the next node (saltatory conduction), making much faster conduction possible (see Fig. 20.4B). As a rule of thumb, three nodes of Ranvier need to be blocked to reliably interrupt impulse propagation.[22]



• **Fig. 20.3** Schematic diagram of nerve structure. Each nerve fiber is surrounded by Schwann cells and encased within three layers of connective tissue: endoneurium, perineurium, and epineurium. Schwann cells wrap myelin layers around some of the axon, forming sequential units of myelin sheath with gaps in between each myelin unit. Unmyelinated fibers are simply embedded within the cytoplasm of Schwann cells. (Modified from Schematic structure of a peripheral nerve. The peripheral nervous system and reflex activity. In: Marieb EN, Hoehn K, eds. *Human Anatomy and Physiology*. 7th ed. San Francisco: Pearson Education; 2007:498.)

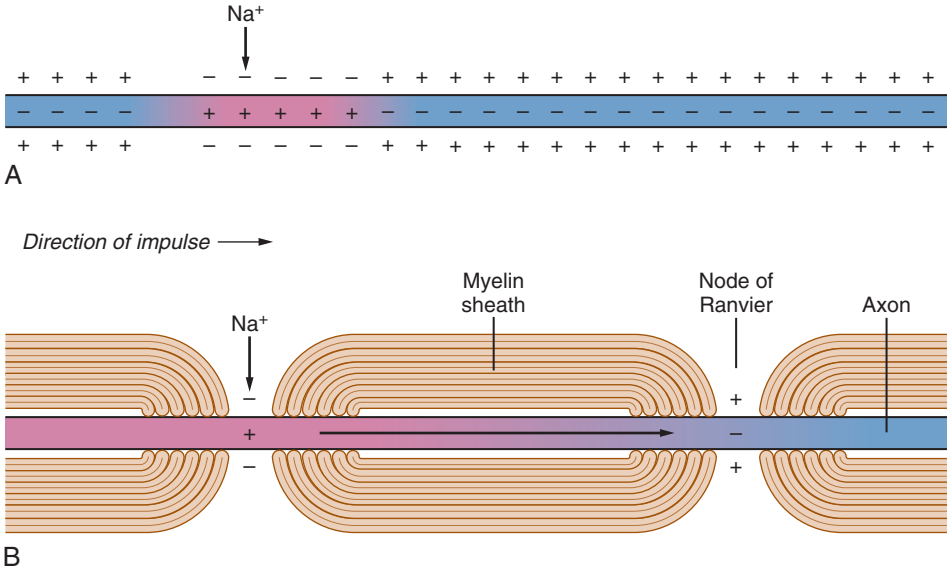
Voltage-Gated Na^+ Channels and Their Interaction With Local Anesthetics

Ion channels are multi-subunit transmembrane proteins that fold in a complex manner to form ion selective pores gated by voltage or ligands (see Fig. 20.2). Ion channels can switch between different conformations in a voltage-dependent manner that determines pore opening (activation), closing (inactivation), and reactivation (to the resting state) (Fig. 20.5). Voltage-gated Na^+ channels consist

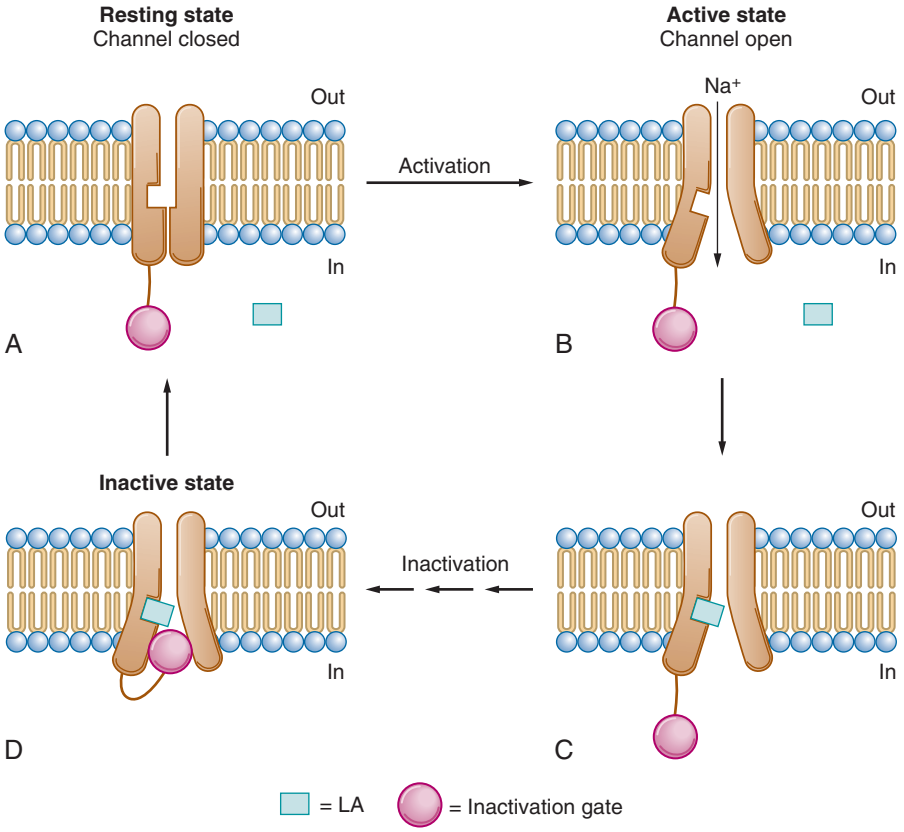
TABLE 20.2 Different Nerve Types: Characteristics and Sensitivity to Local Anesthetics

Fiber	Diameter (μm)	Conduction Speed (m/s)	Sensitivity to Block	Myelination	Anatomic Location	Function
Aα	15–20	80–120	++	+++	Afferent and efferent from muscles and joints	Motor, proprioception
Aβ	8–15	80–120	++	+++	Afferent and efferent from muscles and joints	Touch, pressure, proprioception
Aγ, Aδ	3–8	4–30	+++	++	Efferent to muscle spindles, sensory roots, and afferent peripheral nerves	Pain, temperature, touch/motor
B	4	10–15	++++	+	Preganglionic sympathetic	Autonomic—preganglionic
C	1–2	1–2	++++	–	Postganglionic sympathetic, sensory roots, and afferent peripheral nerves	Pain, temperature, touch

Modified from De Jong RH. *Local Anesthetics*. St. Louis: Mosby; 1994; and Goodman LS, Gilman A, Hardman JG, et al. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 9th ed. New York: McGraw-Hill, Health Professions Division; 1996.

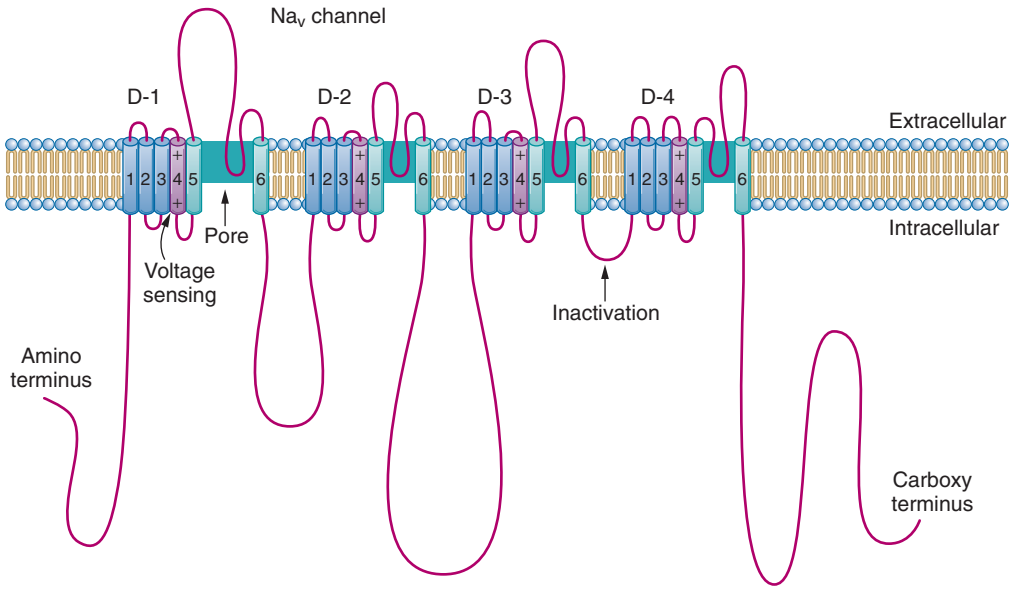


• **Fig. 20.4** Action potential propagates along the axon unidirectionally. The upstream region of the axonal membrane is still in the refractory period and unable to achieve the threshold for depolarization. A, Action potential propagates continuously along the unmyelinated axon by sequential depolarization of the nerve membrane. B, In myelinated axon, the action potential is conducted only at the nodes of Ranvier, skipping the distance between adjacent nodes *(saltatory conduction)*. *Na^+,* Sodium ion.



• **Fig. 20.5** Different states of voltage-gated sodium ion (Na^+) channel. A, Channels in the resting state. Activation leads to opening of the resting (closed) channel (A) to allow the passage of Na^+ in the activated (open) state (B). The inactivation gate closes the channel pore from the intracellular side and the channel inactivates (D). Local anesthetics *(LA)* preferentially bind to the activated and inactivated states (C and D). The local anesthetic binding site is in the pore of the channel (C and D).

of a single α subunit and varying auxiliary β subunits. The α subunit forms the ion-conducting pore of the channel and consists of four homologous domains, each with six α-helical transmembrane segments (Fig. 20.6). The loops that connect the S5 and S6 segments of these α helices of each of the four domains are positioned extracellularly and extend inward, which form the narrowest point of the channel pore and are thought to provide its ion selectivity (see Fig. 20.2). In the resting state, the ion pore of the Na^+ channel is closed (see Fig. 20.5A). Depolarizing voltage changes lead to movement of the voltage sensor (S1-S4) as the result of outward movement of positive charges in the S4 segment, which in turn leads to the rearrangement of S6 segments that results in opening

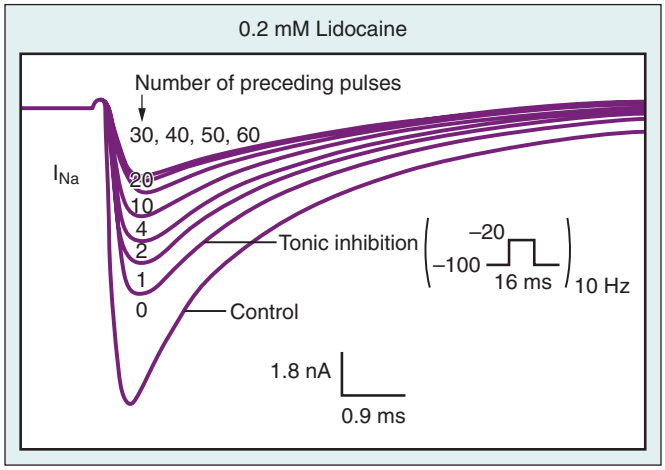


• **Fig. 20.6** Schematic structure of voltage-gated sodium ion (Na^+) channel α-subunit. It contains four homologous domains, each with six α-helical transmembrane segments. The intracellular loops that connect S5 and S6 of each of the four domains (P loops) are positioned extracellularly and extend inward to form the narrowest point of the channel pore and provide its ion selectivity.

of the channel pore (see Fig. 20.5B). The activated channel is inactivated within milliseconds by another conformational change, resulting in the movement of the S6 segment and the S5-S6 linker acting as an inactivation gate (see Fig. 20.5D).

The inactivated state differs from the resting state in its molecular conformation as well as its interaction with local anesthetics, which selectively bind and stabilize the inactivated state. Local anesthetics dose-dependently decrease peak Na^+ current through voltage-gated Na^+ channels.[23] The binding site for local anesthetics is located interior to the ion-selective pore and can be approached via two different pathways: diffusion of the uncharged form through the cell membrane followed by access to the binding site from the cytosolic side (hydrophilic pathway), and laterally through the lipid membrane (hydrophobic pathway) (see Fig. 20.2B). When bound, local anesthetics stabilize the inactivated state and prevent further activation. They can also bind in the ion channel pore to prevent ion flux (open-state block). Local anesthetics have a higher affinity for Na^+ channels in the activated (open) and inactivated (channel pore in open conformation but intracellularly closed by inactivation gate) states than those in the resting closed state (see Fig. 20.5C and D). The difference in the affinity is attributed to the difference in the availability of the two pathways for local anesthetics to reach their binding site. The binding site is more accessible in the activated state than in the resting state.

In the presence of local anesthetics, repeated depolarization results in an incremental decrease in Na^+ current until it reaches a newer steady level of inhibition, which is termed *use-dependent* or *phasic inhibition*.[24] With repeated depolarization, a greater number of Na^+ channels are in the active or inactivated state and are blocked by local anesthetics. Furthermore, the dissociation rate of local anesthetics from their binding site is slower than the rate of transition from inactivated to resting state. Therefore repeated stimulation results in accumulation of local anesthetic–bound Na^+ channels, which manifests as use-dependent inhibition or block (Fig. 20.7).[25] The positive charge introduced by the charged local anesthetic is thought to play a minor role.[26]



• **Fig. 20.7** Ionic (sodium ion [Na^+]) currents measured by voltage-clamp technique by depolarization applied infrequently ("tonic" test). After equilibration with 0.2 mM lidocaine, the currents measured tonically are reduced significantly compared with control currents. Application of repeated depolarizations results in a dynamic reduction of currents after each depolarization (use-dependent inhibition). (Modified from Butterworth JF, Strichartz GR. Molecular mechanisms of local anesthesia: a review. *Anesthesiology*. 1990;72:711–734.)

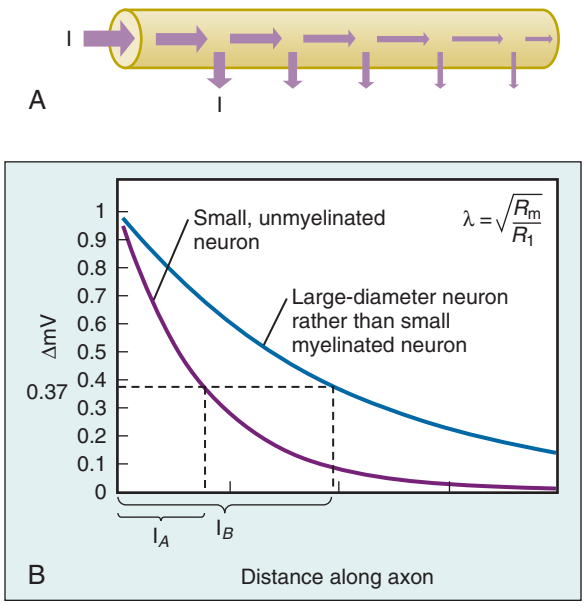
Na^+ Channel Diversity

There are multiple subtypes of voltage-gated Na^+ channels arising from variation in the homologous α-subunit genes. The 10 subtypes now known in mammals ($Na_v1.1$ through 1.9 and Na_x) are differentially expressed in various tissues with cell- and tissue-specific functions.[27] Sodium channels such as $Na_v1.8$, $Na_v1.9$, and Na_v 1.7 are expressed exclusively in peripheral neurons.[28] The $Na_v1.7$ subtype determines the ability of nociceptive neurons to transmit noxious stimuli. Rare loss-of-function mutations of $Na_v1.7$ are reported in patients with channelopathy-associated insensitivity to pain, in which patients have selective lack of pain and smell sensation.[28]

On the other hand, several gain-of-function mutations of genes related to the regulation or function of $Na_v1.7$ result in overactivity of this channel and are associated with the congenital pain disorders (erythermalgia, also termed *erythromelalgia*) and paroxysmal extreme pain disorder.[29] $Na_v1.7$ also appears to be involved in the development of inflammatory pain.[30]

Mechanism of Nerve Block

It was assumed that only a very small fraction (1%-2%) of local anesthetic reaches the nerve membrane even when placed in close proximity to the nerve.[31] With the advent of ultrasound-guided targeting, this fraction might be higher, but still a considerable amount of anesthetic is lost along the concentration gradient across different tissues. The quality of nerve blockade is determined by the potency, concentration, and volume of the local anesthetic. The potency of a local anesthetic can be expressed as the minimum local anesthetic concentration at which complete nerve block is established. The volume of local anesthetic is also important as a sufficient length of axon must be blocked to prevent regeneration of the impulse in the adjacent node of Ranvier. This is understood by the phenomenon of decremental conduction, whereby depolarization of the membrane decays with the distance away from the front of the action potential, and impulse propagation stops when the depolarization falls below the conduction threshold (Fig. 20.8). If less than the critical length of the axon is blocked (usually assumed to be three nodes of Ranvier), the action potential can be regenerated in the proximal membrane segment or node when the decaying depolarization is still above threshold for Na^+ channel activation.



• **Fig. 20.8** Decremental decay. A, Current flow along an axon, showing the flow across the membrane and within the cytoplasm gradually dissipating (*arrow* width is proportional to current flow). B, Depolarization of the nerve membrane is strongest at the site of activation and dissipates decrementally as an inverse first-order exponential with increasing distance from the site of activation. The length constant *(λ)* (which is the distance where the decrement is 1/e, or 37% of the initial voltage change) depends on the ratio of the resistance of the axonal membrane *(R_m)* to the longitudinal resistance of the cytoplasm *(R_i)* and therefore to the diameter of the neuron.

Other Mechanisms of Local Anesthetic Action

Local anesthetics block other ion channels besides Na^+ channels, including voltage-gated K^+ channels and calcium ion (Ca^{2+}) channels, but with lower potency compared with Na^+ channels. Local anesthetics also bind G-protein–coupled receptors and possibly influence the regulation of intracellular Ca^{2+}.[25] The significance of these local anesthetic actions is still unclear.

Lidocaine, one of the most studied local anesthetics, also possesses an antiinflammatory effect.[32] Lidocaine appears to inhibit release of proinflammatory cytokines and prevent leukocyte adhesion. Some local anesthetics have also been shown to be effective in treating predominantly inflammatory conditions such as irritable bowel diseases (see "Emerging Developments").

Difference Between Peripheral and Central Nerves

Peripheral nerves are covered by a nerve sheath, whereas nerves within the CNS are encased in three layers of meninges: the pia matter, arachnoid, and dura matter. The pia matter is adherent to the nerve itself and separated from arachnoid by cerebrospinal fluid that fills the space between the two layers. This space is the spinal or intrathecal space where "naked" or exposed nerves float in cerebrospinal fluid. The dura matter further outlines the arachnoid membrane, forming a tough covering around the central neuraxis. These meninges taper off as the spinal nerve roots exit the vertebral column via the foramina and course through the epidural space. The presence of these meninges around nerve roots in the epidural space means that 10 times the dose of local anesthetic is required to produce complete nerve block compared with that required in the intrathecal space.

Differential Block

Different nerve types show varying susceptibility to nerve block. Table 20.2 displays the characteristics of different nerve types. Clinically, sensory functions are blocked before motor function. This differential nerve block was initially attributed to differences in axon size.[33] Furthermore, fiber types do not only differ in myelin sheath thickness and neuron size, but also by functional differences in ion channel composition.[34] Nociceptive-selective nerve block (differential block) has been attempted with concentrations of local anesthetics that are just high enough for only certain nerve fibers (smaller diameter, thinly myelinated Aδ or unmyelinated C-fibers), but not for others (larger-diameter, myelinated nerves such as Aβ). Nevertheless, nerve block does not always follow this size principle in that Aγ is blocked at lower concentration than C fibers and some myelinated fibers before unmyelinated fibers.[35] The latter can be explained by the need to block only the nodes in myelinated fibers compared with the whole critical length of the nerve membrane in unmyelinated fibers. Therefore complete pain relief is generally accomplished only with concomitant simultaneous low-threshold sensory sympathetic and motor blockade. Current efforts are targeted at exploring specific nerve blocking mechanisms and developing agents that are more selective or exclusively pain-fiber selective than currently used local anesthetics.[36]

Pharmacokinetics

The plasma concentrations of local anesthetics are determined by intravascular absorption, distribution, biotransformation, and excretion (Table 20.3). All of these are affected by patient factors such as age, body size, pregnancy and organ function. Therefore clinical data must be synthesized with the pharmacology of the

TABLE 20.3 Pharmacokinetic Properties of Selected Local Anesthetics

	V_{dss} (L/kg)	Clearance (L/kg per hour)	$t_{1/2}$ (hr)
Chloroprocaine	0.5	2.96	0.1
Procaine	0.93	5.62	0.1
Lidocaine	1.30	0.85	1.6
Prilocaine	2.73	2.03	1.6
Mepivacaine	1.2	0.67	1.0
Bupivacaine	1.02	0.41	3.5
Levobupivacaine	0.9	0.3	3.5
Ropivacaine	0.84	0.63	1.9

$t_{1/2}$, Elimination half-time; V_{dss}, volume of distribution at steady state.
Adapted from Rosenberg PH, Veering BT, Urmey WF. Maximum recommended doses of local anesthetics: a multifactorial concept. *Reg Anesth Pain Med.* 2004;29:564–574.

local anesthetics to predict overall pharmacokinetics in each individual, and to estimate a safe maximum dose for an individual patient (Table 20.4).[37]

Absorption

The rate and extent of systemic absorption of local anesthetic depend on multiple factors: site of injection, dose, physiochemical properties of the drugs, and the presence of vasoconstrictive or other adjuvants. Injection in a more vascular tissue results in higher plasma concentration of local anesthetic in a shorter time. Thus a given dose of local anesthetic that can be administered safely for one type of block can result in higher plasma levels and potential systemic toxicity in another type of block. Clinically, the order of decreasing rate of systemic absorption is intravenous, intercostal, caudal, epidural, brachial plexus, femoral, sciatic, and subcutaneous injections.[38] For a specific block technique, the resulting plasma concentration of local anesthetic is generally directly proportional to the dose injected regardless of the concentration of the injectate or the speed of injection. Furthermore, lipid solubility can influence absorption such that more lipid-soluble agents are absorbed more

TABLE 20.4 Recommended Doses of Selected Local Anesthetics

	Route	Onset	Recommended Dose (mg/kg)	Maximum Dose (mg) With or Without Epinephrine		Duration (hr)
Ester type				Plain	+ Epinephrine	
Chloroprocaine	Subcutaneous	Fast	10	800	1000	0.5–1
	Peripheral block	Fast	10	800	1000	0.5–1
	Epidural	Fast	10	800	1000	0.5–1
Tetracaine	Topical	Fast	0.2	20	–	0.5–6
Amide type					–	
Lidocaine	Subcutaneous	Fast	4	300	500	0.5–3
	Intravenous	Fast	4	300		0.5–1
	Peripheral block	Fast	4	300	500	1–3
	Epidural	Fast	4	300	500	1–2
	Topical	Fast	4	300	–	0.5–1
Prilocaine	Subcutaneous	Fast	8	600	–	1–2
	Intravenous	Fast	8	600	–	0.5–1
	Peripheral block	Fast	8	600	–	0.5–3
	Epidural	Fast	8	600		1–3
Mepivacaine	Subcutaneous	Fast	5	400	500	1–4
	Peripheral block	Fast	5	400	500	2–4
	Epidural	Fast	5	400	500	1–3
Bupivacaine	Subcutaneous	Fast	2.5	175	225	2–8
	Peripheral block	Slow	2.5	175	225	4–12
	Epidural	Moderate	2	170	225	2–5
Levobupivacaine	Subcutaneous	Fast	2	150	–	2–8
	Peripheral block	Slow	2	150	–	14–17
	Epidural	Moderate	2	150	–	5–9
Ropivacaine	Subcutaneous	Fast	3	200	–	2–6
	Peripheral block	Slow	3.5	250	–	5–8
	Epidural	Moderate	3	200	–	2–6

Modified from Covino BG, Wildsmith JAW. Clinical pharmacology of local anesthetic agents. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain.* 3rd ed. Philadelphia: Lippincott-Raven; 1998:97–128; and Foster RH, Markham A. Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. *Drugs.* 2000;59:551–579.

slowly than less lipid-soluble ones.[39] This is likely due to sequestration of local anesthetic in lipophilic tissue as well as direct vasoconstriction of vascular smooth muscles by more potent lipid-soluble agents at low doses.[40] The use of vasoconstrictors such as epinephrine reduces the rate of systemic absorption after peripheral and epidural blockade.[39,41]

Distribution

Local anesthetics are distributed throughout the body, but their concentrations vary between different tissue types with preference to more vascular tissues. The rate of distribution can typically be described by a two-compartment model with rapid and slow phases. The rapid phase involves uptake in highly perfused tissues reaching rapid equilibration. For example, the lung is a major site of uptake for local anesthetic. The slow phase depends on the slow equilibration of less perfused tissues and on specific properties of individual local anesthetics.

Metabolism

The major difference between ester- and amide-type local anesthetics is their metabolism. Ester-type local anesthetics undergo hydrolysis by plasma esterases. An exception to this is cocaine, which is metabolized in the liver by carboxylesterase. Amide-type local anesthetics undergo biotransformation mainly in the liver. The rate of metabolism varies between different agents such that degradation of lidocaine is faster than mepivacaine, whose metabolism is still faster than bupivacaine. The metabolites of amide-type local anesthetics are excreted by the kidneys. About 5% of amide type local anesthetics is renally excreted unchanged. Therefore patients with decreased hepatic or renal function eliminate amide-type local anesthetics more slowly and are at increased risk for systemic toxicity. Two notable exceptions are prilocaine, which can be metabolized in the kidney, and articaine, which is inactivated by plasma carboxylesterase.

Toxicity

The toxicity of local anesthetics is the main limiting factor in their clinical applications. Local anesthetics are relatively safe if administered appropriately. However, significant systemic or localized toxicity can result from unintended intravascular, intrathecal, or intraneural injection or if excessive doses are administered, resulting in major systemic absorption.[37]

Systemic Toxicity

The classic cascade of local anesthetic systemic toxicity (LAST) occurs after the administration of a relative overdose of local anesthetic—for example, for a peripheral nerve block, resulting in increased absorption into the systemic circulation and escalating symptoms. These include CNS manifestations, followed by cardiovascular compromise. Other scenarios include inadvertent intravascular injection of local anesthetics, which can cause immediate cardiovascular collapse, and intraarterial injection during neck blocks that causes a short-lived seizure as local anesthetic directly enters the brain.[42] The initial symptoms depend on the plasma concentration of free local anesthetic and patient factors such as acidosis, protein binding, and comorbidities, and vary widely.[43]

Central Nervous System Toxicity

CNS toxicity can manifest from serum concentrations above 5 μg/mL, initially as anxiety, dizziness, circumoral numbness, lightheadedness, and tinnitus caused by blockade of inhibitory brain pathways. The net effect is central disinhibition. Objective symptoms include shivering, muscle twitching, tremors, and eventually generalized tonic-clonic seizure. With a high-dose intravascular injection, a brief period of early symptoms and seizure can be followed by respiratory depression and then arrest. Factors that increase susceptibility to CNS toxicity include use of more potent local anesthetics and the concomitant presence of respiratory or metabolic acidosis (by decreasing the convulsive threshold). Respiratory acidosis also reduces protein binding of local anesthetics, increasing local anesthetic availability for further toxic effects.[44] Elevated partial pressure of carbon dioxide in arterial blood ($PaCO_2$) leads to cerebral vasodilation and increased delivery of drug to the CNS. However, acidosis promotes amine protonation, leading to less diffusion into nerve cells. In the clinical situation of LAST, normocapnia should be sought.

Cardiovascular System Toxicity

Local anesthetics affect the cardiovascular system both directly by affecting cardiac myocytes and peripheral vascular smooth muscle cells, and indirectly by actions on the CNS or autonomic nervous system. The main mechanisms of cardiovascular toxicity of local anesthetics are blockade of cardiac sodium channels, leading to negative inotropy and arrhythmia. Local anesthetics act directly by decreasing conduction in Purkinje fibers and cardiomyocytes by prolonging recovery time. Moreover, fatty acid metabolism is inhibited, leading to energy loss,[45] interference with calcium homoeostasis, and disruption of the mitochondrial respiratory chain. The more potent, lipophilic local anesthetics such as bupivacaine, tetracaine, and etidocaine are more cardiotoxic than the less lipophilic agents such as procaine, prilocaine, and lidocaine (see Table 20.1).[46] Specifically, whereas the less lipophilic agents decrease inotropy, the lipophilic local anesthetics such as bupivacaine have an additional antiarrhythmic effect.[47] The dissociation of bound bupivacaine from the local anesthetic binding site is slower ("fast-in," "slow-out").[48] Local anesthetics are also direct myocardial depressants via a mechanism related to reduced Ca^{2+} influx and release from the sarcoplasmic reticulum.[49] The action of local anesthetics on peripheral vascular smooth muscle is biphasic with vasoconstriction at low concentrations and vasodilation at higher concentrations.[17] The exception is cocaine, which produces vasoconstriction at any dose.

Indirect cardiovascular effects of local anesthetics are related to the CNS or autonomic system. Patients experiencing the classic cascade of symptoms experience as first cardiovascular symptoms tachycardia and hypertension caused by central disinhibition. If toxicity progresses, this evolves into cardiocirculatory collapse. Considering the autonomic system, the use of neuraxial techniques induces hypotension, bradycardia, and cardiopulmonary collapse if not treated promptly. Mild to moderate symptoms are usually responsive to intravenous fluids and indirect- or direct-acting adrenergic agents such as ephedrine and phenylephrine. Severe symptoms and complications are associated with high dermatomal level blocks, use of sedatives, delayed recognition of unintentional subarachnoid or intravenous injection, and delayed treatment; these severe complications might require pharmacologic and even mechanical cardiopulmonary support.[50]

The severe cardiovascular toxicity associated with epidural use of 0.75% bupivacaine (and other local anesthetics) in the obstetric population in the late 1970s and early 1980s serves as a prototype example of the public health implications of local anesthetic systemic toxicity. The introduction of epidural analgesia for labor

pain was accompanied by multiple reports of local anesthetic–induced cardiac arrest and death in parturients. These tragic outcomes culminated in the relabeling of bupivacaine by the Food and Drug Administration (FDA), cautioning against the use of high concentrations in the obstetric population and refinement of epidural test dosing techniques.[51] Continued concern about the complications associated with local anesthetic toxicity decades later has resulted in further advancements in treatment, especially lipid rescue.

Treatment of Local Anesthetic Systemic Toxicity

Treatment of LAST depends on the detailed symptoms and circumstances of the local anesthetic overdose. The situation is highly dynamic and needs to be reassessed continually until symptoms have resolved. The priority is to maintain cardiocirculatory function and bridge the patient to the resolution of symptoms. When unintentional intravenous injection of local anesthetic is suspected or systemic toxicity is detected, seizures should be interrupted. Depending on the circulatory symptoms, short-acting benzodiazepines such as midazolam or anesthetics such as thiopental or propofol should be administered. Whereas guidelines prefer benzodiazepines because they cause less hemodynamic compromise,[52] it should be considered that their onset of action is substantially longer than with propofol or thiopental. During CNS toxicity, airway management and seizure control are the main priorities. Appropriate monitoring should be applied to assess cardiovascular and pulmonary function. Hypoventilation and respiratory acidosis should be aggressively treated by supplying oxygen or, if needed, establishing a definitive airway and instituting mechanical ventilation. Hypotension and bradycardia should be treated with intravenous fluids and cardiovascular drugs targeted to the signs. Epinephrine is considered the mainstay of immediate treatment, and use of vasopressin has also been suggested.[47] However, literature findings are conflicting as to their benefit, and further studies are warranted.[47] Intravenous administration of lipid emulsion has been used with immediate and successful resuscitation of patients with refractory local anesthetic–induced cardiac toxicity based on multiple case reports and is now a part of standardized treatment algorithms.[52]

The role of antiarrhythmic drugs in local anesthetic induced ventricular arrhythmia is not established. Amiodarone might be the safest option, but during lipid emulsion therapy, it can be sequestered with unpredictable effects. Calcium and sodium channel blockers are contraindicated because they can further depress myocardial function.

Lipid Rescue

The first report showing that the infusion of soybean oil emulsion improved resuscitation after bupivacaine-induced cardiovascular collapse in an animal model was published more than a decade ago.[53] Numerous case reports as well as experimental studies have shown the therapeutic effect of intravenous infusion of lipid emulsion in refractory systemic local anesthetic toxicity.[45] The exact mechanism behind lipid rescue is debated. It is currently thought that the main actions involve sequestration of lipophilic local anesthetics and a bolstering of fatty acid metabolism in cardiomyocytes. The clinical relevance of other mechanisms such as direct interactions between bupivacaine and the lipid emulsion at the receptor is unclear.[45] The sequestration hypothesis ("lipid sink") can also explain the similar antidote effect of lipid infusion for other lipophilic medications, including calcium channel blockers, β blockers, and tricyclic antidepressants. There is a limited number of cases reporting adverse outcomes after lipid rescue, mainly recurrent cardiovascular instability. A theoretical complication of lipid infusion is pancreatitis induced by hyperlipidemia and hyperamylasemia, but it should be considered that lipid administration is often performed in a life-threatening situation such that these theoretical adverse effects should not be weighed too heavily. In addition, careful monitoring of patients for several hours after even successful treatment with lipid infusion is essential as there can be a return of cardiovascular instability as plasma levels of the lipids decline.[54]

Neurotoxicity and Other Tissue Toxicity

Direct neuronal tissue toxicity (e.g., transient neurologic symptoms [TNS] and cauda equina syndrome) has been described with multiple local anesthetics, but the incidence appears to be significantly higher with lidocaine and mepivacaine than bupivacaine, prilocaine, and procaine.[55] TNS is characterized by transient hyperalgesia or dysesthesia in the low back, buttocks, and lower extremities following seemingly uneventful spinal anesthesia but without permanent neurologic damage. Risk of TNS is associated with the use of lidocaine, lithotomy position, and ambulatory procedures. The risk increases with dose, but it does not appear to correlate with the concentration of local anesthetic because there is no difference in the incidence of TNS with 0.5% and 5% lidocaine.[56] The etiology of TNS is unclear, but both mechanical and pharmacologic factors seem to contribute. Symptoms typically respond to nonsteroidal antiinflammatory drugs.[56]

Direct neurotoxicity can be demonstrated in vitro and in animal models.[57] The potential neurotoxic effects of local anesthetics came to the attention of public health officials in the United States after the introduction of microcatheters for spinal anesthesia in the late 1980s. Reports of cauda equina syndrome associated with typical "spinal" doses of local anesthetic solution injected through microcatheters appeared in the literature. Subsequent investigation using in vitro models of the subarachnoid space revealed that local anesthetic injection through microcatheters resulted in poor distribution and mixing of the drug (i.e., pooling), exposing the nerve tissue to unusually high concentrations of local anesthetic.[58] The incidence of the problem was high enough to culminate in voluntary withdrawal of the microcatheters by the manufacturer.

Today it is accepted that all local anesthetics are neurotoxic, depending on the dose.[59] Over the past two decades, concentrations of local anesthetics have, on average, decreased, and ultrasound has allowed for reduction in local anesthetic dose when applied for peripheral nerve blockade.[60]

Specific Local Anesthetics

Amide Local Anesthetics

Lidocaine

Lidocaine was the first widely used local anesthetic, and is available for infiltration as well as peripheral (including Bier block), spinal, and epidural blocks. Its use for spinal anesthesia has declined due to concerns about neurotoxicity and TNS (see previous text).[55] It can be applied topically as an ointment or jelly, or nebulized as an aerosol to anesthetize the upper airway. Intravenous injection of lidocaine to achieve low plasma levels (<5 μg/mL) results in systemic antiinflammation and analgesia, possibly not only owing to an action in the CNS but also by affecting peripheral nerves or cutaneous nerve endings. Clinically, lidocaine has been

administered as an infusion to treat chronic neuropathic pain and can predict efficacy for oral Na^+ channel blocking drugs such as mexiletine.[42]

Lidocaine causes vasodilation at most concentrations; the addition of epinephrine can significantly reduce absorption of lidocaine by nearby vessels, allowing more of the initially administered dose to enter the neural compartment, thereby prolonging the duration of action by as much as 50%.[61] Experimentally, intravenous lidocaine profoundly suppresses both increased peripheral neuronal firing induced by injury and inflammation as well as central sensitization of wide dynamic range neurons in the spinal cord dorsal horn.[62]

Prilocaine

Prilocaine has a clinical profile similar to lidocaine and is used for infiltration, peripheral nerve blocks, and spinal and epidural anesthesia. Because prilocaine causes significantly less vasodilation than lidocaine, addition of epinephrine is not necessary to prolong the duration of action, which can be an advantage when epinephrine is contraindicated. Prilocaine shows the least systemic toxicity of all amide local anesthetics and is therefore useful for intravenous regional anesthesia. However, it causes methemoglobinemia (>500-mg dose) owing to its metabolite o-toluidine, which has significantly limited its use.

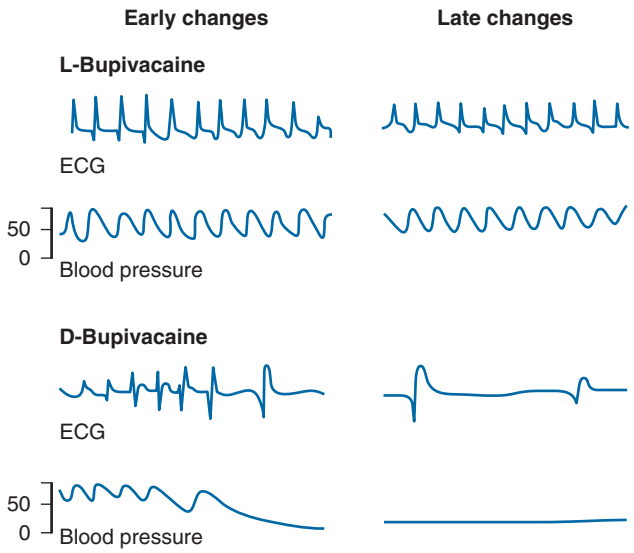
Mepivacaine

The anesthetic profile of mepivacaine is also similar to lidocaine but with a slightly longer duration of action. However, it is not as effective when applied topically. Although toxicity appears to be less than with lidocaine, metabolism of mepivacaine is prolonged in the fetus and newborn and therefore mepivacaine is not used for obstetric anesthesia. Vasodilation is mild, but adding epinephrine can significantly prolong action.

Bupivacaine

Bupivacaine (a racemic mixture of both the R and S enantiomers) provides prolonged and intense sensory analgesia, often outlasting the motor block. For epidural analgesia and anesthesia, bupivacaine is usually used at concentrations from 0.125% (postoperative analgesia) to 0.25% (intraoperative analgesia) to 0.5% (surgical anesthesia), with a 2- to 5-hour duration of action. Peripheral nerve blocks are also performed with these concentrations, depending on the amount of motor block sought. Peripheral blocks can last for 12 to 24 hours. Intrathecal use provides approximately 2 to 3 hours of anesthesia and 4 to 6 hours of analgesia. Other clinical uses include tissue infiltration and "trigger point" injections in treating myofascial pain. Epinephrine is sometimes added as a marker for intravascular injection and to prolong the duration of action owing to decreased vascular absorption. However, as vasoconstriction has less impact on the duration of more hydrophobic agents, epinephrine is more commonly added to more hydrophilic agents such as lidocaine.

LAST following bupivacaine injection is associated with particularly high morbidity and mortality. Its high affinity for Na^+ channels and high lipid solubility are probably the main causes. On the other hand, lipid emulsion seems to be most effective in treating bupivacaine-induced LAST. By consensus, the 0.75% concentration of bupivacaine is not used in obstetrics because of the associated mortality/toxicity (see above). In many countries, the highest concentration of bupivacaine used now is 0.5%. Because sufficient anesthesia can be achieved with bupivacaine 0.5%, the use of bupivacaine 0.75% does not offer any particular benefits and may be associated with increased local and systemic toxicity.



• **Fig. 20.9** Representative changes in the electrocardiogram (lead II) and arterial blood pressure 2 to 3 seconds after infusion of levobupivacaine (L-bupivacaine) or D-bupivacaine (2 mg/kg) in an anesthetized rat. The changes in rhythm and blood pressure are displayed. (Modified from Denson DD, Behbehani MM, Gregg RV. Enantiomer-specific effects of an intravenously administered arrhythmogenic dose of bupivacaine on neurons of the nucleus tractus solitarius and the cardiovascular system in the anesthetized rat. *Reg Anesth*. 1992;17:311–316.)

Levobupivacaine

Levobupivacaine is a single-enantiomer preparation consisting of the S enantiomer of bupivacaine. Compared with racemic bupivacaine, levobupivacaine has considerably reduced CNS and cardiovascular toxicity, allowing a larger dose to be given. An animal model demonstration of the lower potential for cardiovascular toxicity associated with levobupivacaine compared with dextrobupivacaine is shown in Fig. 20.9. The clinical profile and potency of levobupivacaine appears to be similar to that of bupivacaine, with a slightly longer block duration. Levobupivacaine is considered particularly useful when large doses are required, such as for plexus blocks performed without ultrasound guidance.

Ropivacaine

Concerns about the cardiotoxicity of bupivacaine led to the development of ropivacaine. Ropivacaine is structurally similar to bupivacaine but was developed as a single, less toxic enantiomer (as with levobupivacaine); it can be administered in larger doses than racemic bupivacaine before early signs of toxicity develop.[63] However, if equipotent concentrations/dosages are compared, the difference between bupivacaine and ropivacaine becomes less clear. Overall the clinical profile of ropivacaine is similar to racemic bupivacaine, considering that it is less lipid soluble and less potent than bupivacaine. Epidural application can allow for even greater sensory block without significant motor block ("differential block"). An intrinsic vasoconstricting effect (also true for levobupivacaine) might augment the duration of action and reduce the incidence of cardiotoxicity.

Ester Local Anesthetics

Procaine

Procaine was used mainly for infiltration and spinal blocks in the early 20th century before lidocaine became popular. However, low potency, slow onset (probably owing to its high pK_a), and short duration of action limit the use of procaine. Allergic reactions are possible due to the production of the metabolite PABA.

Chloroprocaine

Because of its relatively low potency and extremely low toxicity, relatively high concentrations of chloroprocaine can be used. It also has an extremely short plasma half-life because it is metabolized rapidly by plasma cholinesterase. Reports of CNS toxicity in the form of seizures are extremely unusual. It is thought to have the lowest CNS and cardiovascular toxicity of all agents in current use. Chloroprocaine is used commonly for epidural anesthesia. It is also used for peripheral blocks in combination with other long-acting, slow-onset local anesthetics for the combined effect of rapid onset and prolonged duration. In obstetrics, epidural chloroprocaine, with or without bicarbonate, is used to attain rapidly surgical levels of anesthesia in preparation for cesarean section. Another theoretical advantage in obstetrics is that there is virtually no transmission of chloroprocaine to the fetus.[64] Epidurally administered chloroprocaine can, however, interfere with the action of subsequently administered epidural amide anesthetics or opioids.[65]

Controversy exists regarding the use of chloroprocaine related to reports of persistent, serious neurologic deficits associated with accidental massive subarachnoid injection (i.e., adhesive arachnoiditis). Initially, the agent itself was implicated, but subsequent evaluation suggested that the preservative antioxidant bisulfite is responsible. However, after elimination of bisulfite a number of reports of back pain have appeared. Recently a renewed interest has actually suggested that bisulfite may be neuroprotective in an animal model.[66]

Tetracaine

Tetracaine is a slow-onset, potent, and intermediate- to long-acting ester-type local anesthetic. Even longer duration of action can be achieved when tetracaine is administered along with a vasoconstrictor such as epinephrine. However it is quite toxic, and has been suggested to cause neurotoxicity at high doses in animal studies, resulting in cauda equina syndrome with repeated spinal dosing. It is used mainly topically or sometimes for spinal anesthesia. Tetracaine is highly lipid soluble and a significant amount can be absorbed when used in the mucous membrane or wounded skin.[67]

Cocaine

The only naturally occurring local anesthetic used clinically is also the only local anesthetic that causes intense vasoconstriction. Thus it is often used as a topical anesthetic (e.g., when anesthetizing the cornea or the nasal airway before endotracheal intubation). Cocaine inhibits the neuronal reuptake of catecholamines and can therefore cause hypertension, tachycardia, dysrhythmias, and other serious cardiac effects.

Benzocaine

Benzocaine has a slow onset, short duration of action, and is both minimally potent and minimally toxic. Its clinical use is limited to topical anesthesia to anesthetize mucous membranes—for example, to anesthetize the oral and pharyngeal mucosa before fiberoptic endotracheal intubation. Excessive use of benzocaine is associated with methemoglobinemia.

Mixture of Local Anesthetics

The rationale for the mixture of local anesthetics is an attempt to benefit from their respective pharmacokinetics (e.g., a quick onset with the short-lasting drug while maintaining the long duration of the long-acting drug). However, the beneficial effects of the use of mixtures of local anesthetic agents might be overstated. For example, bupivacaine provides clinically acceptable onset of action as well as prolonged duration of anesthesia. In addition, the use of catheter techniques for many forms of regional anesthesia makes it possible to extend the duration of action of rapid- and short-acting agents such as chloroprocaine or lidocaine. Most importantly, one should be cautioned against the use of maximum doses of two local anesthetics. Toxicities of these agents are independent and should be presumed to be additive.[68] With the advent of ultrasound-guided regional anesthesia, the difference in onset time that can be achieved by mixing local anesthetics is down to a few minutes while losing total block duration at the end, such that this concept may be losing attraction.

Topical Local Anesthetics

EMLA

EMLA (eutectic mixture of local anesthetics) cream is a mixture of lidocaine and prilocaine, each at a concentration of 2.5%. It is eutectic because the mixture has a melting point below room temperature and therefore it exists as a viscous liquid, rather than a solid powder. EMLA should be applied to intact skin surfaces because application to breached skin surfaces can lead to unpredictably rapid absorption. It provides dermal analgesia by the release of the lidocaine and prilocaine from the cream into the skin, which leads to blockade of pain transmission originating from free nerve endings. The onset, quality, and duration of dermal analgesia are primarily dependent on the duration of skin application. Although there is considerable interpatient variation, EMLA cream should be applied under an occlusive dressing for about 1 hour to provide adequate analgesia for insertion of an intravenous catheter or the drawing of blood at roughly 2.5 g of the cream applied over a 25-cm^2 area of skin. Large application area, long duration of application, and impaired elimination can result in high blood concentrations of the local anesthetics. The maximum recommended duration of exposure is 4 hours, although exposures of up to 24 hours have not led to toxic plasma levels of local anesthetics. Caution must be taken in children or very small adults as plasma levels of lidocaine and prilocaine depend on patient size and rate of systemic drug elimination.

Lidocaine Patch (5%)

The lidocaine patch (Lidoderm) was approved by the FDA in 1999 for treatment of pain associated with postherpetic neuralgia, a severe chronic neuropathic pain condition. The patch is a topical delivery system intended to deliver low doses of lidocaine to superficially damaged or dysfunctional cutaneous nociceptors in an amount sufficient to produce analgesia without mechanosensory block. Its recommended dosing is an application of up to three patches to intact painful skin areas for 12 hours per day. Pharmacokinetic studies have demonstrated that clinically insignificant plasma levels are achieved with this formulation. The levels are $\frac{1}{10}$ of those required to produce cardiac effects and $\frac{1}{32}$ of those required

TABLE 20.5 Common Additives to Local Anesthetics

Agent	Main Mechanism	Common Indication	Usual Dose
Epinephrine	α_1-Adrenergic agonism Vasoconstriction α_2-Adrenergic agonism	Peripheral nerve block Infiltration anesthesia Epidural anesthesia Marker for intravascular injection	3–5 μg/mL
Opioids	Opioid receptor agonism	Neuraxial block	Intrathecal morphine 100–200 μg Intrathecal sufentanil 5 μg Intrathecal fentanyl 10–25 μg Epidural fentanyl 2–10 μg/mL Epidural sufentanil 0.25–1 μg/mL Epidural hydromorphone 20 μg/mL
Dexamethasone	Unknown	Neuraxial block Peripheral nerve block	Typically not used Dexamethasone 2–4 mg
Clonidine	α_2-Adrenergic agonism	Neuraxial block Peripheral nerve block	Up to 1 μg/kg ideal body weight Up to 1 μg/kg ideal body weight
Dexmedetomidine	α_2-Adrenergic agonism	Neuraxial block Peripheral nerve block	Spinal 10 μg Epidural 0.5 μg/kg Peripheral block 0.5–1 mcg/kg

to produce toxicity. However, patients often report pain relief even during the 12 hours between applications of a patch, despite the short plasma half-life of lidocaine, suggesting that some cumulative benefit results from prolonged local delivery of the drug.

Additives

Countless agents have been studied as additives to local anesthetics with the intent to accelerate onset (e.g., sodium bicarbonate) or improve the quality and prolong duration of neuraxial and peripheral nerve blocks (e.g., α-adrenergic agonists, opioids, dexamethasone; Table 20.5). Many substances have been found to enhance peripheral or neuraxial blocks in experimental or preliminary clinical investigations, including ketamine, benzodiazepines, tramadol, tricyclic antidepressants and cholinesterase inhibitors, but they have failed to gain widespread acceptance.

Nonselective α-Adrenergic Agonists

Epinephrine is used as a marker for detecting intravascular injection in both epidural and peripheral nerve blocks. α-Adrenergic agents also prolong and intensify the nerve block[61] owing to local vasoconstriction, which leads to decreased vascular absorption, making more local anesthetic available for nerve block. The extent of block prolongation depends on the specific local anesthetic and the site of injection and is most pronounced with shorter-acting local anesthetics such as lidocaine. Activation of central α_2-adrenergic receptors in the spinal cord also enhances epidural analgesia by epinephrine and other α-adrenergic agonists. Epinephrine also decreases neural blood flow, but the clinical relevance of this finding concerning adverse effects is not clear.

α_2-Adrenergic Agonists

Prolongation of nerve blocks by the α_2-adrenergic agonist clonidine has been the subject of ample research with mixed results. Its effects are mediated through supraspinal and spinal α_2-adrenergic receptors when used neuraxially, and inhibition of the hyperpolarization-activated cation (I_h) current has been described in experimental peripheral nerve blockade.[69] Higher doses are more effective; for example, 150 μg showed a higher probability of a positive result than 75 μg.[70] Some have recommended not to exceed 1 μg/kg body weight to avoid sedative and hypotensive side effects. The effect is more pronounced when clonidine is added to shorter-acting local anesthetics such as lidocaine and mepivacaine. On average, one can expect 2 to 4 hours of prolongation for peripheral blocks.[71,72]

Dexmedetomidine is much more selective for the α_2-adrenergic receptor compared with clonidine. Dexmedetomidine addition prolongs peripheral nerve blocks by 4 to 6 hours at a typical dose of 1 μg/kg body weight, while systemic administration was less effective. Both clonidine and dexmedetomidine are thought to be safe in terms of neurotoxicity.

Opioids

Opioids are also used in neuraxial blocks either alone or in combination with local anesthetics. Intrathecal morphine (0.1–0.2 mg) provides analgesia for up to 20 hours after cesarean section.[73] Fentanyl (10–25 μg) improves the spread and prolongs block in spinal anesthesia in a dose-dependent manner.[74] Sufentanil (5 μg) produces an effect comparable to 0.2 mg morphine (although much shorter) with a lower incidence of pruritus.[73]

Epidural morphine used as an adjunct to bupivacaine or ropivacaine provides effective postoperative analgesia for orthopedic surgeries[75] after cesarean section to prolong postoperative analgesia. Respiratory depression is an undesired side effect that can last longer than the analgesic effect and thus mandates monitoring. Epidural fentanyl (2–3 mcg/mL) is also used as an adjunct to local anesthetics or alone. In general, when administered above the conus medullaris, epidural lipophilic opioids are more effective than intravenous use.[76] Lipophilic opioids are also taken up into the systemic circulation, adding a second analgesic mechanism of

action, and it has been suggested by some that the systemic effect explains a substantial share of the clinical effect of lipophilic opioids.[77] Nevertheless, fentanyl or sufentanil (0.75–1 μg/mL) is a valuable adjuvant for epidural analgesia with improved analgesia and decreased intravenous opioid requirement.[78] Hydromorphone (20 μg/mL), which is less lipophilic than fentanyl or sufentanil, is also an effective adjunct to local anesthetics.[79]

In peripheral nerve blocks, evidence to support the use of opioids is limited and mostly focused on buprenorphine, a partial opioid agonist with activity at μ, κ, and δ receptors as well as sodium channels.[80] Block duration can be increased up to twofold to threefold, but the increase in nausea and vomiting limit its usefulness.[71]

Dexamethasone

Perineural administration of the antiinflammatory glucocorticoid dexamethasone can prolong both motor and sensory block, although the precise mechanism awaits clarification. Moreover, addition of dexamethasone seems to improve overall analgesia[80] and should decrease the incidence of postoperative nausea and vomiting. A currently debated issue is the dose dependency; there seems to be no benefit to add more than 4 mg perineurally.[81] Systemic dexamethasone can, within limits, mimic the effects of perineural administration.[82] An undesirable effect of dexamethasone is that motor blockade is also significantly prolonged.[81] Prolongation of peripheral nerve blocks of up to 10 hours can be achieved. A neurotoxic potential of high perineural doses of dexamethasone has been suggested in preclinical experiments,[83] but the clinical relevance is unclear because perineural steroid application has been performed for decades in pain medicine without significant untoward effects.

Other Agents

Other agents such as ketamine, tramadol, neostigmine, and midazolam have also been used as adjuvants with favorable results, but data are limited. Some preclinical reports show neurotoxicity,[84] and they are not recommended for routine clinical use.

Emerging Developments

Ultrasound and Intraneural Injection

Next to pharmacologic developments, the use of ultrasound has led to a substantial advance in the delivery of local anesthetics, allowing administration of smaller doses while achieving higher success rates. High-resolution surface ultrasound can provide direct real-time imaging of peripheral nerves and identify tissue planes that permit favorable local anesthetic distribution for conduction block and catheter placement. For safe and successful ultrasound-guided neural blockade, one must be familiar with the relevant cross-sectional anatomy and coordination of the imaging probe with the block needle. Real-time and continuous visualization of the procedure needle and the relevant anatomy enhances the safety of needling through structures and the quality of block compared with the blind or nerve-stimulator–guided techniques. If desired, ultrasound guidance can be combined with nerve stimulation to further confirm proximity to neural structures. Nonetheless, the quality of ultrasound-guided procedures is highly operator dependent and requires considerable dexterity and practice.[60,85]

The high resolution of contemporary ultrasound machines even allows discrimination of intraneural structures such as fascicles. It has been suggested that targeted intraneural but perifascicular injection of local anesthetic offers quick onset of anesthesia,[86] and that intraneural injection does not invariably result in nerve damage.[87] The latter contention challenges long-held beliefs that intraneural injection must be strictly avoided.[88–91] Indeed, for popliteal sciatic nerve blockade in which nerve stimulation is notoriously unreliable, intraneural injections frequently occur without apparent neurologic damage.[92] Both preliminary clinical[87] and some preclinical[93] evidence suggests that it is not as deleterious as once thought. But several factors should be considered. First, local anesthetics are toxic in a dose-dependent manner and intraneural injection theoretically increases the chance of direct toxicity. Second, the nerve contains blood vessels, and bleeding inside the nerve can lead to scarring and permanent loss of function. A potential exception may be the popliteal sciatic nerve block, where local anesthetic can be deposited beneath the thick paraneural sheath but still outside the tibial and common peroneal nerves, resulting in an injection that is in fact intraneural (in the sciatic nerve) but in practice not (outside the two constituent nerves). However, this injection depends on optimal visualization of anatomic structures, perfect block conditions, and a trained team, and it cannot be recommended for broad use. In general, even if intraneural injection does not invariably result in nerve damage, it is not recommended.

Subtype-Specific Sodium Channel Blockers

The observation that ProTX-II, a $Na_v1.7$-selective antagonist from spider venom, prevents propagation of action potentials in nociceptive fibers suggests that selective $Na_v1.7$ blockers might provide a novel target for analgesic therapy.[94] Similarly, selective blockade of $Na_v1.8$ has been reported to attenuate sensory neuron excitability.[95] However, no sensory-selective local anesthetic is currently available, and most contemporary research efforts are directed toward treating chronic pain rather than introducing new local anesthetics.

Cell Type–Specific Delivery

Another possibility is to target local anesthetics to specific cell types in nociception pathways. which has been explored using the permanently charged local anesthetics lidocaine-N-ethyl bromide (QX-314)[96] or EN3427.[97] Owing to their permanent cationic charge, these compounds do not readily cross the nerve cell membrane, but activation of nonselective ion channels such as the transient receptor potential vanilloid-1 (TRPV-1) receptor creates pores large enough for these compounds to enter the cytoplasm. Because TRPV-1 channels are expressed only on pain fibers, this could allow sensory-specific nerve block, a concept confirmed by several experimental investigations.[36] However, QX-314 is more neurotoxic than even lidocaine,[98] which hindered further development; neurotoxicity data for EN3427 are not yet available. Furthermore, activation of TRPV-1 requires a nociceptive stimulus such as concomitant application of capsaicin.[96] These limitations have precluded clinical introduction of cationic local anesthetics so far.

Heat-Assisted Delivery

Controlled heat-assisted drug delivery (CHADD), a disposable oxygen-activated system that allows controlled release of heat to enhance delivery of local anesthetics, has been used with lidocaine and tetracaine. The formulation is an emulsion in which the active ingredients are in oil phase as a eutectic mixture containing a 1 : 1

mixture of lidocaine and tetracaine by weight.[99] Heat is generated using a mixture of iron powder, activated carbon, sodium chloride, wood flour, and water. The local anesthetics are packed in a shallow chamber below the CHADD patch and sealed in an airtight packet.[99] When applied to the skin, the CHADD patch heats spontaneously and increases the temperature of the skin, thereby enhancing permeation of the drugs through the epidermis. The heating element produces a temperature of 39°C to 41°C for 2 hours and reduces the duration of onset compared with other topically applied local anesthetics such as a lidocaine/prilocaine combination.[100]

Local Anesthetics and the Inflammatory Response

Local anesthetics have antiinflammatory effects, affecting mainly polymorphonuclear granulocytes (PMNs), but effects on macrophages and monocytes are also implicated.[101] Overactive inflammatory responses that destroy rather than protect are critical in the development of a number of perioperative disease states, such as postoperative pain, adult respiratory distress syndrome, systemic inflammatory response syndrome, and multiorgan failure. Some local anesthetics (lidocaine or bupivacaine) reduce formation of leukotriene B_4 and interleukin (IL)-1. Leukotriene B_4 is a potent stimulator of PMNs that leads to their margination, degranulation, diapedesis, and superoxide release. It enhances vascular permeability and is also a potent chemotactic substance. Therefore preventing activation of PMNs is likely to suppress the inflammatory process. Additionally, local anesthetics (ropivacaine and lidocaine) attenuate tumor necrosis factor α and Ca^{2+}-dependent upregulation of the CD11b-CD18 complex, surface proteins that allow PMN adhesion to endothelium.[102] This is thought to be one of the key mechanisms for the therapeutic effect seen with low-dose topical application of ropivacaine in ulcerative colitis.[103] Wound healing is another area of interest in relation to the local anesthetic inhibition of PMN adhesion. But studies have yielded contradictory results such that in vivo investigations have demonstrated delayed wound healing, no effects, or improved wound healing after local anesthetic infiltration.[101]

Various substances such as tumor necrosis factor, platelet-activation factor, IL-8, lipopolysaccharide, and certain colony-stimulating factors "prime" PMNs for subsequent activation that leads to a potentiated response of PMNs. The mechanism of priming is not fully understood but might play a pivotal role in the overstimulation of inflammatory pathways. Lidocaine and other local anesthetics appear to block the priming of PMNs in a dose-dependent manner.[101] This could account for how local anesthetics can decrease tissue damage without significantly inhibiting PMN functions required for host defense.

Another immune-modulating effect of local anesthetics involves impaired release of lysosomal enzymes and inhibition of free radical release from macrophages.[104] Macrophage functions of cytokine release, respiratory burst, and phagocytosis are sensitive to intracellular pH changes, and are regulated by vacuole-type H-translocating adenosine triphosphatase (H^+-ATPase) and the Na^+-H^+ exchanger. Local anesthetics inhibit these transporters in human PMNs in vitro.[105]

Clinically, intravenous application of lidocaine results in a strong antiinflammatory effect that partly replicates the suppression of the surgical stress response seen with epidural analgesia.[106] Compared with placebo, lidocaine improves patient outcomes (function, bowel, time to discharge) in visceral surgery patients, while effects in other types of surgery are less clear.[107] In addition, antihyperalgesic and antinociceptive effects have been described, as well as antihypercoagulable effects.[42]

Liposomal Formulations

Liposomes are biocompatible microscopic lipid vesicles with a bilayer membrane structure that can be used to encapsulate and deliver drugs over a longer period. However, tissue reaction to such formulations has been problematic as conventional local anesthetics are intrinsically myotoxic, with increased toxicity over extended durations of exposure. They are also myotoxic when released from a delivery system, even when the delivery systems themselves are minimally toxic.[108] In contrast, site 1 sodium channel blockers (like saxitoxin) do not cause myotoxicity or neurotoxicity, which could make them desirable for an extended-release formulation.[109] However, these substances are very hydrophilic and thus difficult to encapsulate effectively in polymeric particles. Recently a liposomal formulation using saxitoxin was shown to produce sciatic nerve blockade up to 7.5 days in rats with minimal systemic or local toxicity.[110]

Liposomal bupivacaine (Exparel) has been approved for wound infiltration in the United States but not in Europe. Early studies support a prolonged mode of action after local infiltration compared with bupivacaine. However, a recent study failed to find a dose-response relationship during femoral block in volunteers such that more clinical research is needed to determine efficacy.[111]

Key Points

- Local anesthetics are classified as ester or amide types based on the linkage between the lipophilic phenyl ring and the hydrophilic amine. This difference is reflected in their physiochemical and pharmacokinetic properties.
- Local anesthetics bind to voltage-gated Na^+ channels and block depolarizing Na^+ current through these channels.
- Properties such as lipid solubility, protein binding, and pKa of individual local anesthetics affect their speed of onset, potency, and duration of action. Raising the pH of local anesthetic solution favors the membrane-permeable neutral form and accelerates onset of action.
- Voltage-gated Na^+ channels transition between resting, activated (open), and inactivated states via coordinated conformational changes. Local anesthetics have higher affinity for the activated and inactivated states than the resting state, leading to use-dependent block.
- There are multiple subtypes of voltage-gated Na^+ channels arising from expression of nine homologous α-subunit genes that are differentially expressed in various tissues. Na^+ channel subtypes such as $Na_v1.7$, $Na_v1.8$, and Na_v 1.9 are expressed exclusively on peripheral nerves and play important roles in nociception.
- The rate of systemic absorption decreases from intravenous, intercostal, caudal, epidural, brachial plexus, femoral and sciatic, and subcutaneous administration. The same dose of local anesthetic can result in higher plasma concentration and potential for systemic toxicity depending on the type of block.

- Ester-type local anesthetics undergo mainly hydrolysis by plasma esterases. Decreased activity or absence of plasma cholinesterase can also increase the risk for systemic toxicity with ester-type local anesthetics.
- Amide-type local anesthetics undergo biotransformation mainly in the liver. Their metabolites and about 5% of the unchanged drug are excreted by the kidney. Patients with decreased hepatic or renal function have longer elimination times and are at increased risk for systemic toxicity.
- The systemic and local toxicity of local anesthetics are the limiting factors in their clinical use. Systemic toxicity manifests primarily in central nervous system and cardiovascular effects and local toxicity (myotoxicity, neurotoxicity).
- Lipid emulsion infusion and avoidance of hypoxia and acidosis are recognized as crucial in the treatment of local anesthetic toxicity. Lipid emulsion should be available whenever local anesthetics are administered in large doses, such as during placement of peripheral nerve and neuraxial blocks.

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Physics: Medical Ultrasound

Bradley Stringer and Kai Kuck

OUTLINE

Background
Ultrasound Wave Generation: Transducers, Frequency, Attenuation
Ultrasound Wave–Tissue Interaction: Resolution
Enhancement of Echogenicity
Doppler Ultrasound
Safety of Ultrasound Imaging
Key Concepts

Background

Since the introduction of medical ultrasound imaging systems in the mid-20th century, advances in technology have propelled this point-of-care imaging modality to ubiquitous worldwide use in a multitude of clinical applications. Its low cost, portability, versatility, ease of use, quick results, reasonable learning curve, and safety—coupled with the fact that it does not subject patients and clinicians to ionizing radiation—have made this the first choice for many diagnostic and interventional imaging and therapeutic applications in clinical medicine.[1] To the practicing anesthesiologist, it is useful in many applications, including regional anesthesia, vascular access,[2,3] airway and lung assessment, transesophageal echocardiography (TEE) and Doppler, focused transthoracic echocardiography (TTE) and transcranial monitoring (e.g., of brain structures and cerebral blood flow.)

All medical ultrasound systems operate in the same basic fashion: **High-frequency** (pitch) **ultrasound waves** are generated by and transmitted into the body with an **ultrasonic transducer**. The sound waves are disrupted as they encounter interfaces between differing tissue types with different echogenicity. Some of the sound energy is reflected back to the transducer, now acting as a receiving antenna, the echoes are analyzed, and an image constructed and displayed using that information.[4–6]

Ultrasound Wave Generation: Transducers, Frequency, Attenuation

Medical ultrasound systems operate by exciting an array of **piezoelectric crystals**, causing them to vibrate at an intrinsic resonant frequency. Energy from the vibrating crystals is transmitted into the body in periodic waves of the same frequency. The crystals and supporting electronics and mounting materials are arranged in a pattern such that the sound energy is geometrically focused to a predetermined depth, typically ranging from a few millimeters to several centimeters. The crystals, electronics, and support materials as a functional unit are called a transducer, or **probe**. Variations in transducer shape, size, and frequency influence the **beam pattern** of the ultrasonic waves, which dramatically changes the way that the waves interact with tissue and how anatomic images are generated and displayed (Fig. P4.1).

Ultrasound waves will dramatically **attenuate** in air; there is a small layer of air at the interface between the probe and the patient no matter how firmly the transducer is pressed against the body. To eliminate significant attenuation with dry coupling, all air must be eliminated at the transducer–skin interface by applying a layer of viscous acoustic coupling gel between the skin and transducer before imaging.

Ultrasound Wave–Tissue Interaction: Resolution

As sound waves traverse the body, they encounter tissues of various density and elasticity. Each tissue type conducts sound at a specific speed. The differences in tissue characteristics are intrinsic and result in subtle differences in **acoustic impedance**, an indicator of the resistance to propagation that the ultrasound wave encounters. According to **Snell's Law**, when acoustic energy impinges on tissues of different impedance, an interface mismatch exists and predictable fractions of energy will be transmitted forward deeper into the body, while the balance will be reflected to the transducer as an echo (Fig. P4.2). The energy reflected back to the transducer varies directly with the difference in acoustic impedance encountered by the ultrasound.

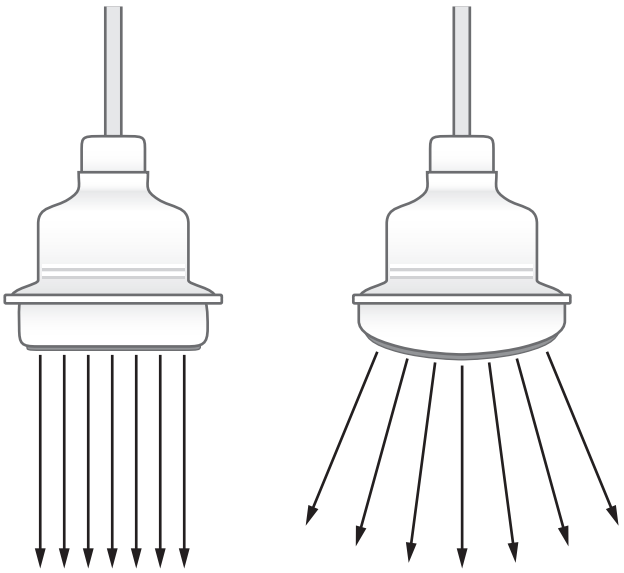
The time of arrival and relative strength of the echoes are mathematically analyzed and conclusions about the type, structure, size, density, and movement of the underlying tissues can be drawn. Images are then constructed and displayed (and possibly recorded) for viewing and clinical analysis.

For a given tissue type (and characteristic speed of sound), higher frequencies have shorter wavelengths, as related by the basic wave equation (Eq. 1):

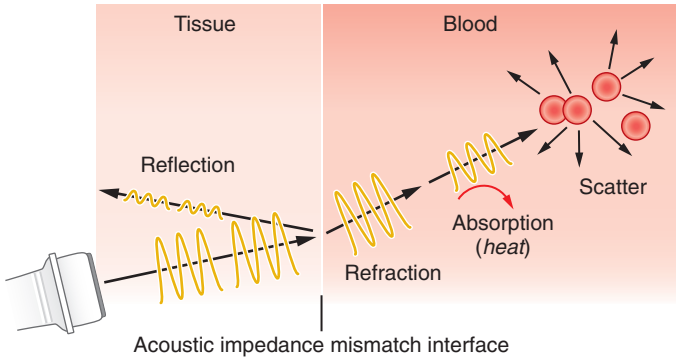
$$c = \lambda f$$

where

c is the constant speed of sound in a given tissue (mm/sec)
λ is the wavelength of the ultrasound wave (mm/cycle)
f is the frequency of insonification (cycles/sec)



• **Fig. P4.1** Linear transducers *(left)* use high frequencies, resulting in good resolution, but small depth. They are often used for guidance during nerve blocks, vascular access, and biopsies. Curvilinear probes *(right)* use lower ultrasound frequencies, are relatively large, have a depth of up to 30 cm, and are often used for abdominal and thoracic visualizations. (From http://famus.org.uk/modules/ultrasound-theory-module)



• **Fig. P4.2** Interactions of ultrasound with tissues in the body. Part of the ultrasound energy gets absorbed as it travels through tissue. As ultrasound encounters an interface of differing acoustic impedance, predictable fractions of the energy will be transmitted forward deeper into the body (albeit with refraction, i.e., at a changed angle), while the balance will be reflected to the transducer as an echo. When ultrasound strikes structures smaller than the wavelength, scattering occurs. (From Desjardins G, Vezina DP, Johnson KB, Cahalan MK. Perioperative echocardiography. In: Miller RD. *Miller's Anesthesia*. Philadelphia: Saunders Elsevier; 2015:1396–1429.)

The practical application of Eq. 1 is that the resolution of the image is directly proportional to the frequency of the transducer. According to Eq. 1, for a given tissue type with its associated speed of sound, increasing the frequency *must* be accompanied by a commensurate reduction in the wavelength of the sound. Resolution is inversely related to wavelength (i.e., higher-frequency transducers—hence, smaller wavelengths—typically provide better images than their lower-frequency counterparts). Higher-frequency transducers do suffer from higher attenuation in tissue and cannot penetrate as deeply (penetration is limited to about 200–400 times the wavelength). For example, ultrasound between 2.5 and 7.5 MHz can be used to image structures of 0.4 to 1.2 mm in size and penetrate not more than 24 cm in depth.

Enhancement of Echogenicity

The enormously large air–tissue impedance mismatch can be exploited to enhance an image during interventional use such as vascular access and regional nerve blocks. Because needles are typically manufactured with a high polish, the smooth barrel will act like a mirror, reflecting the incoming ultrasound waves *away* from the transducer and making the needle invisible because no reflective echoes from that structure are received. Because visualizing the needle as it advances into a nerve plexus or vein is critical, in such interventions the needles are often coated in a polymer layer embedded with micro air bubbles, making them extremely diffusively reflective and visible under ultrasonic imaging. In other cases, the polished needle barrel is intentionally etched to a dull finish so that the needle reflects ultrasound waves diffusely, making them more visible (opaque) during the procedure. These various needle modifications are said to be *echogenic*. Similarly, injectable liquid suspensions of microbubbles of air can be used as ultrasound contrast agents[7] when examining for intracardiac shunts.

Doppler Ultrasound

The Doppler effect has important applications in ultrasound imaging and can be used to determine blood flow velocity and direction. The real-world example of sound heard by a stationary observer when a moving train blares its whistle is often used as an example of the Doppler effect. The sound of a passing train whistle is higher in pitch if the train is advancing toward a stationary observer and lower in pitch if moving away. Similarly, the pitch (frequency) of an ultrasound wave is shifted higher or lower as the sound is reflected off a *moving* anatomic target, usually erythrocytes or heart valve leaflets (Fig. P4.3). The greater the velocity (v) of the target, the greater the Doppler frequency shift:

$$v = (c_{Ultrasound} \times \Delta f)/(2 \times f_{Ultrasound} \times \cos\theta)$$

where

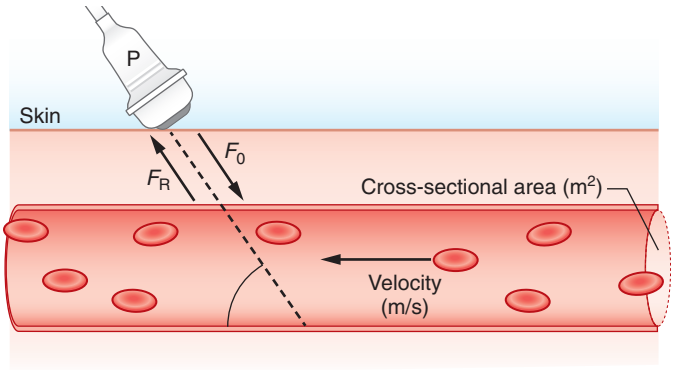
$c_{Ultrasound}$ is the speed of ultrasound in the tissue
Δf is the Doppler shift in frequency
$f_{Ultrasound}$ is the original frequency of the ultrasound
θ is the incident angle of the ultrasound beam with respect to the moving object

Blood flow can be calculated from velocity by combining it with the cross-sectional area and an assumption of the velocity profile is made. Also, the Bernoulli equation allows an estimation of the pressure gradient (Δp) across the heart valve:

$$\Delta p = 4v^2$$

Important uses of Doppler ultrasound in anesthesiology include TEE, TTE, vascular flow (patency, direction, flow rate, velocity), measurements of cardiac function (output, rate, ejection fraction, regurgitation, and so on), and vascular access (location and discrimination between arteries and veins).

Since many ultrasound systems use color (red, blue, or shades of these colors) to indicate blood flow within the lumen of a vascular structure, the clinician *must* be aware of how the transducer is oriented with respect to the target blood vessel for two reasons.



• **Fig. P4.3** The pitch (frequency) of an ultrasound wave will be shifted higher or lower as the sound is reflected off a moving target, in this case, usually erythrocytes or heart valve leaflets. The most effective estimation of velocity is achieved when the transducer is held at a shallow angle relative to the vessel being scanned. (From Cross ME, Plunkett EVE. *Physics, Pharmacology, and Physiology for Anaesthetists: Key Concepts for the FRCA*. Cambridge: Cambridge University Press, 2014.)

The direction of blood flow is *relative*, so that if the transducer is rotated by 180 degrees and reapplied in the same location, what was first colored red as arterial flow would now be colored blue as venous, and vice versa. Second, the most effective estimation of flow is achieved when the transducer is held at a shallow angle relative to the vessel being scanned. Holding the transducer orthogonally over the blood vessel results in loss of a Doppler shifted signal and could lead to an incorrect diagnosis of little or no flow when, in fact, flow is present.

Safety of Ultrasound Imaging

Unlike radiographic imaging, acoustic radiation is nonionizing and has no known cumulative or immediate adverse effects. It can be used on patients with implanted electronic devices or orthopedic implants. It is useful for patients of any sex or age, including fetal scanning. The safety of clinical staff and observers is assured as well.

Key Concepts

Acoustic Impedance: The resistance to the propagation of ultrasound waves through tissues. Each tissue type has a unique acoustic impedance. Acoustic impedance is the product of the density and speed of sound in the tissue.

Attenuation: The loss of energy of transmitted and reflected sound waves owing to scattering, reflection, refraction, and thermal absorption. Attenuation and frequency are directly related (i.e., higher-frequency sound waves attenuate in the body faster than waves of lower frequency). Attenuation limits the maximum depth of penetration and imaging.

Beam Pattern: The 3-dimensional shape and size of the acoustic energy field applied by the ultrasound probe. The beam pattern varies by probe; each pattern is designed for specific imaging goals.

Frequency: The rate, expressed in cycles per second (unit Hertz [Hz]), at which the patterns of compression and rarefaction pass by a certain reference point. Typical frequencies for medical ultrasound are 2 MHz to 20 MHz, depending on the application. Echocardiography uses frequencies of 2.5 to 7.5 MHz.

Piezoelectric Crystals: These crystals can be used to generate or detect ultrasound waves. A voltage applied across the crystals will produce a pressure field (a stress) on the atoms in their lattice with an accompanying overall contraction or expansion (a strain) in 1 or more dimensions of the material, generating ultrasound waves that emanate from the probe.

Probe: Another name for a **transducer** (see definition below).

Resolution: A measure of the ability of an imaging system to resolve and display 2 closely spaced reflecting tissue boundaries.

Snell's Law: A formula describing the relationship between the angle of incidence of a sound wave on a tissue interface and the resultant reflection and refraction of the wave.

Transducer: An array of piezoelectric ceramic crystals and electrical connections with support materials housed in a durable enclosure. The shape, operating frequency, and geometric focus of the transducer are intrinsic and fixed. The transducer emits a pattern of ultrasonic waves and interprets the resultant echoes.

Ultrasound Waves: Regular patterns of mechanical compression and rarefaction traveling in a longitudinal direction in tissue, the frequency of which, by definition, is higher than the human audible range of 20 to 20,000 Hz.

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Neuromuscular Physiology and Pharmacology

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CHAPTER OUTLINE

Overview of Neuromuscular Transmission

Structure and Function of the Neuromuscular Junction
- Presynaptic Structure and Function
- Synaptic Cleft Structure and Function
- Postsynaptic Membrane

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Synaptic Vesicles and Recycling

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  - *Mature and Immature Postjunctional Receptors*
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- Nondepolarizing Agents
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  - *Phase II Block*

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  - *Stroke and Spinal Cord Injury*
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  - *Immobility*

Emerging Developments
- Train-of-Four Fade and Monitoring of Neuromuscular Function
- Muscle Relaxants in Critical Illness

The neuromuscular junction (NMJ) is among the most studied of all synapses and serves as a prototype for understanding communication between neurons and effector cells within the central and peripheral nervous systems. Complete understanding of the development and function of the NMJ in normal and pathologic states continues to evolve. The introduction of new and powerful research techniques has revealed detailed information about the mechanics of neuromuscular transmission.[1] Recent discoveries suggest a more complex signaling system with adaptive receptor physiology and a multifaceted action-response scheme. These discoveries, although adding complexity, help align experimentally derived findings with clinical observations of therapeutic effects and side effects of drugs acting on the cholinergic system.

The physiology and pharmacology of the NMJ is pivotal to many areas of anesthetic practice, including perioperative management and critical care. Despite the central role of the NMJ, in many clinical circumstances our ability to manipulate the NMJ to the patient's advantage is deficient. This is best illustrated by the ongoing problem of residual neuromuscular paralysis recorded after general anesthesia despite the use and availability of intermediate-acting neuromuscular blockers (NMBs), better monitors for assessment of paralysis, and availability of drugs for reversal of paralysis (see Chapter 22).[2,3]

The complexities of normal neuromuscular function are altered by many pathologic states not originally thought to involve the NMJ. For example, an unexpected consequence of improved survival after a critical illness, such as sepsis or acute respiratory distress syndrome (ARDS), is the "unmasking" of profound disease of the nerve, NMJ, and muscle causing substantial morbidity and mortality.[4,5]

Abstract

Neuromuscular transmission in skeletal muscle occurs when acetylcholine released from the nerve ending binds to the endplate nicotinic acetylcholine receptors (AChRs) on the postjunctional muscle membrane. These AChRs respond by opening channels for the influx of sodium ions into the muscle leading to endplate depolarization and muscle contraction. Activation is terminated when acetylcholine is hydrolyzed by acetylcholinesterase.

Neuromuscular transmission is a complex and dynamic process in which the effects of drugs are composites of actions that vary with drug, dose, activity at the junction and muscle, presence of other drugs, age and concomitant disease. The neuromuscular junction undergo constant structural remodeling influenced by multiple factors including endogenous mediators/hormones, age, and genetic and/or pathologic state.

The etiology of neuromuscular disorders can be classified as inherited or acquired, and anatomically as presynaptic, synaptic, or postsynaptic. They are also classified as autoimmune, congenital, pharmacologic, toxic, or pathologic.

The common defect of all disorders of the neuromuscular junction is a decrease in the margin of safety for neuromuscular transmission, which can fail at any point from the motor neuron to nerve terminal to muscle endplate (synapse) or the muscle itself. If the endplate potential fails to reach the threshold for muscle fiber depolarization, an action potential is not generated, the muscle fiber does not contract, and neurotransmission fails.

In some pathologic states such as denervation, burns, immobilization, inflammation, or sepsis, there is upregulation of immature AChRs and α7-AChRs leading to susceptibility to succinylcholine-induced hyperkalemia and also resistance to the effects of nondepolarizing neuromuscular blockers. Use of neuromuscular blockers during critical illness has both beneficial and deleterious effects; guidelines for their use in the perioperative period need consensus and refinement.

Keywords

Acetylcholine
Acetylcholine receptor
Acetylcholinesterase
Congenital neuromuscular diseases
Neuromuscular junction
Postjunctional receptors
Prejunctional receptors
Train-of-four fade

This chapter reviews salient features of the structure and function of the NMJ relevant to understanding the clinical effects of NMBs, neuromuscular monitoring, and the management of disorders of the neuromuscular system in anesthesia and critical care. A detailed discussion of NMB sand drugs that reverse the effects of NMBs is provided in Chapter 22.

Overview of Neuromuscular Transmission

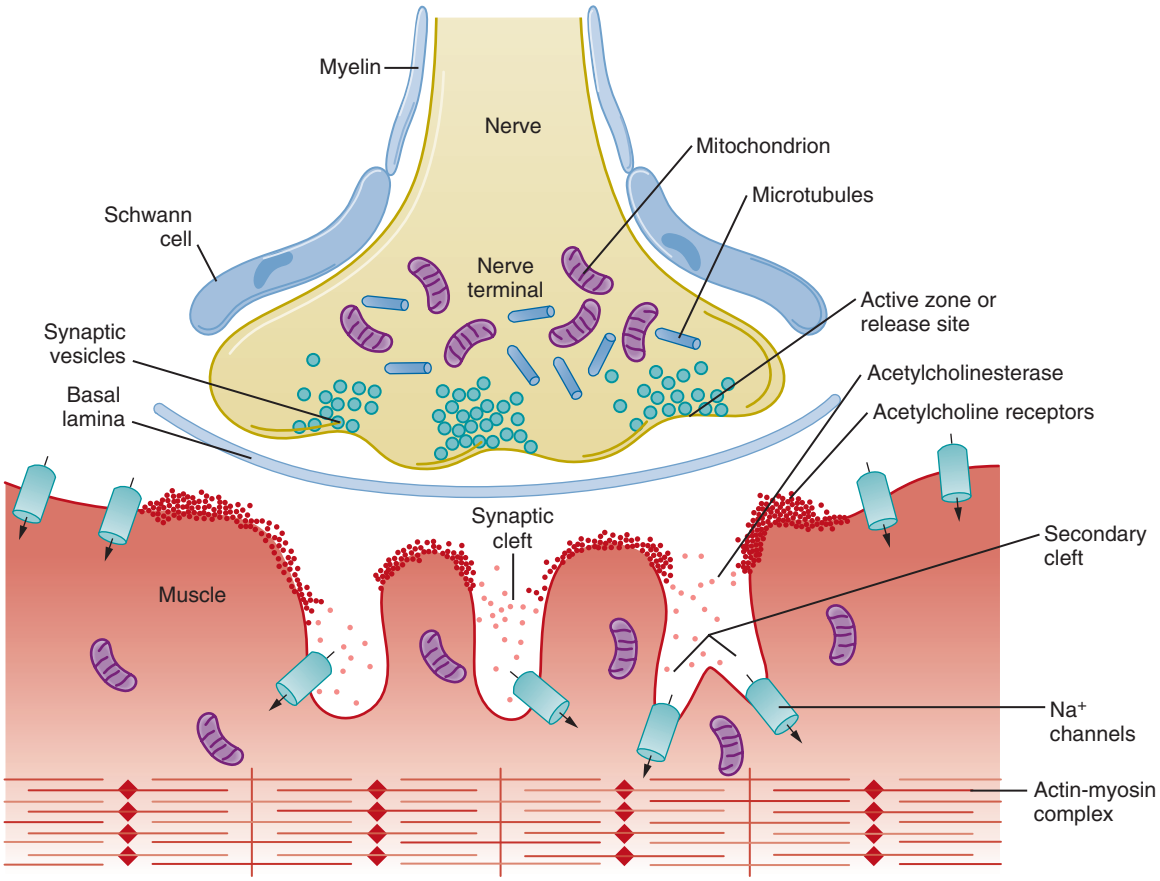
The classic model of neuromuscular transmission is straightforward. The nerve synthesizes acetylcholine (ACh), which is stored in small uniformly sized membrane vesicles called *synaptic vesicles.* When the distal motor nerve is stimulated by an action potential, it causes voltage-gated calcium ion (Ca^{2+}) channels to open, giving rise to an abrupt, rapid, transient increase in nerve terminal Ca^{2+} concentration.[6] The elevated Ca^{2+} concentration triggers fusion of ACh-containing synaptic vesicles to the presynaptic membrane, where they release ACh into the synaptic cleft that separates the nerve from the muscle.[6] ACh released into the cleft binds to nicotinic acetylcholine receptors (AChRs) on the surface of the postjunctional muscle membrane. These heteropentameric ligand-gated ion channels are nonselective caption channels in the postjunctional membrane that allow influx of Na^+, resulting in endplate depolarization and muscle contraction.[6] Much of the released ACh is instantaneously hydrolyzed by synaptic acetylcholinesterase present in the cleft and never reaches its target. The excess release of ACh contributes to a margin of safety that ensures successful neurotransmission.[7]

Structure and Function of the Neuromuscular Junction

The structure and function of the NMJ can be conveniently divided into presynaptic, synaptic cleft, and postsynaptic entities (Fig. 21.1).

Presynaptic Structure and Function

The presynaptic portion of the NMJ is responsible for neurotransmitter (ACh) synthesis, uptake and storage of neurotransmitter into synaptic vesicles, ACh release and reuptake of choline after



• **Fig. 21.1** Structure of the neuromuscular junction, composed of the motor nerve terminal, muscle fiber, and Schwann cell. As the nerve approaches the muscle fibers, it loses its myelin sheath and divides into branches that innervate many individual muscle fibers. The motor nerve without myelin is covered by the Schwann cell. The nerve terminal contains synaptic vesicles clustered about membrane thickenings, the active zones, at the synapse, and also at mitochondria and microtubules which are located further away from the synapse. A synaptic gutter or cleft, made up of a primary and many secondary clefts, separates the nerve from the muscle. The muscle surface is corrugated, and dense areas on the shoulders of each fold contain acetylcholine receptors. Sodium channels are present at the bottom of the clefts and throughout the muscle membrane. Acetylcholinesterase, as well as other proteins and proteoglycans that stabilize the neuromuscular junction, are present in the synaptic clefts.

its hydrolysis, and control of ion flow across the nerve terminal cell membrane. Each motor neuron represents a large myelinated axon that extends from the ventral horn of the spinal cord or medulla to the NMJ. As it approaches the target muscle, the myelinated motor axon divides into 20 to 100 unmyelinated fibers, each of which innervates a single muscle fiber.[8] The functional group of terminal nerve fibers and the muscle fibers they serve is called a *motor unit*. The terminal myelin-free portion of the nerve axon is encapsulated by a Schwann cell. Previously the Schwann cells were thought not to be involved in neuromuscular transmission but were considered to have a support function between nerve and muscle and promote maintenance of the nerve terminal (see Fig. 21.1).[9,10] More recently, however, the terminal Schwann cells, which are glial cells, importantly contribute to presynaptic and postsynaptic maturation. This intricate *dance a trois* (among terminal Schwann cell, nerve terminal, and muscle) is integral to the efficient communication between the highly concentrated postsynaptic AChRs and perfectly aligned presynaptic ACh release sites.

Synaptic Cleft Structure and Function

The junctional or synaptic cleft is the gap (~50 nm) between the nerve terminal ending and the muscle membrane.[11] The cleft contains a basal lamina composed of a variety of cell and other adhesion macromolecules that modulate neuromuscular signaling processes. These molecules include acetylcholinesterase, α- and β-laminin, and collagen.

After release from the nerve terminal, ACh diffuses the short distance across the synaptic cleft to the postsynaptic membrane. The high concentration of ACh in combination with the short distance between the site of release and the postsynaptic membrane ensures rapid transmission. Approximately 50% of the released ACh is either degraded by acetylcholinesterase or diffuses out of the cleft before it reaches its target.[8] Acetylcholinesterase is anchored to the basal lamina, where it degrades ACh into acetate and choline, thereby terminating the activity of the transmitter. Choline is then taken up into the presynaptic terminal by a specific transporter for resynthesis of ACh within the nerve terminal.

Postsynaptic Membrane

The muscle membrane is highly corrugated with deep invaginations representing primary (shallower) and secondary (deeper) clefts such that the total surface area of each endplate is very large (see Fig. 21.1). The depths of these folds vary between muscle types and species. The shoulders of the folds contain high densities of AChRs (~ 5 million in each junction) anchored into the muscle cell membrane by a complex system of cytoskeletal proteins. AChRs are sparse in the depths between the folds, which contain a high density of voltage-gated Na^+ channels for amplification of AChR-induced depolarization.

The perijunctional zone is the area of muscle that lies immediately beyond the junctional area. It serves the critical function of transducing the signal from the junction into deeper regions of the muscle cell. The perijunctional zone contains a high density of Na^+ channels that promote amplification of the transduced signal, culminating in muscle contraction. The density of Na^+ channels in the perijunctional zone is greater than in more distal parts of the muscle membrane.[12] Furthermore, specific isoforms of AChRs and Na^+ channels are expressed in the perijunctional area at different stages of life and during pathologic conditions that decrease nerve activity. Mutations in AChRs and Na^+ and Ca^{2+} channels in this area have been identified.[13,14] For example, in hypokalemic periodic paralysis, characterized by episodes of severe flaccid muscle paralysis, the muscle fiber membrane becomes electrically inexcitable, which can be precipitated by low serum K^+ levels. This pathologic state is the archetypal skeletal muscle channelopathy caused by dysfunction of specific sarcolemmal Na^+ or Ca^{2+} ion channels.[15] These variations in receptors and channels contribute to differences in response to neuromuscular drugs observed in different age groups and pathologic conditions.[16,17]

Quantal Theory of Neuromuscular Transmission

Synaptic vesicles containing neurotransmitter are clustered along thickened, electron-dense patches of membrane in the terminal portion of the nerve referred to as *active zones.* High-resolution scanning microscope imaging reveals small protein particles arranged between vesicles in the active zone that are believed to be voltage-gated Ca^{2+} channels. These channels permit Ca^{2+} to enter the nerve and initiate the process that ultimately triggers vesicle release. The close proximity of voltage-gated Ca^{2+} channels to the vesicle fusion apparatus is believed to contribute to the rapidity with which ACh is released (~200 ns).[6]

The number of quanta of ACh released by a stimulated nerve is strongly influenced by the concentration of extracellular ionized Ca^{2+} and its influx into the nerve. Doubling extracellular Ca^{2+} concentration results in a 16-fold increase in quantal release.[18] The effect of increasing Ca^{2+} in the nerve ending is seen clinically as the phenomenon of posttetanic potentiation. This can occur after the nerve of a patient paralyzed with a nondepolarizing NMBs is stimulated at high tetanic frequencies. With each stimulus, Ca^{2+} enters the nerve, but because it cannot be excreted as quickly as the nerve is stimulated, it accumulates during the tetanic period. The nerve ending contains an elevated amount of Ca^{2+} for some time after the tetanic stimulation, and if another stimulus is applied during this time, it increases the amount of ACh that is released. The increased amount of ACh released antagonizes the nondepolarizing NMBs and results in the characteristic increase in twitch size observed after tetanic stimulation (posttetanic potentiation).

The amount of ACh released by each nerve impulse is large, at least 200 quanta, consisting of about 5000 ACh molecules each, and about 500,000 AChRs are activated.[19] The ions (mainly sodium [Na^+] and some Ca^{2+}) that flow through the AChR channels cause maximal depolarization of the endplate, resulting in an endplate potential that exceeds the threshold for stimulation of the muscle. This produces a biologic advantage. By releasing more molecules of transmitter than actually are needed and evoking a greater response than needed while using only a small fraction of the vesicles and receptors available, neurotransmission has a substantial margin of safety and at the same time has substantial capacity in reserve.[20]

Synaptic Vesicles and Recycling

Two major pools of vesicles are involved in ACh release: a readily releasable pool (sometimes called V2) and a reserve pool (sometimes called V1).[21,22] The readily releasable pool is smaller and is confined to an area very close to the nerve membrane where the vesicles are bound to the active zones. These are the vesicles that are normally available to release neurotransmitter. The reserve pool contains the majority of synaptic vesicles, which are tethered to the cytoskeleton

in a filamentous network composed mainly of actin, synapsin, synaptotagmin, and spectrin.

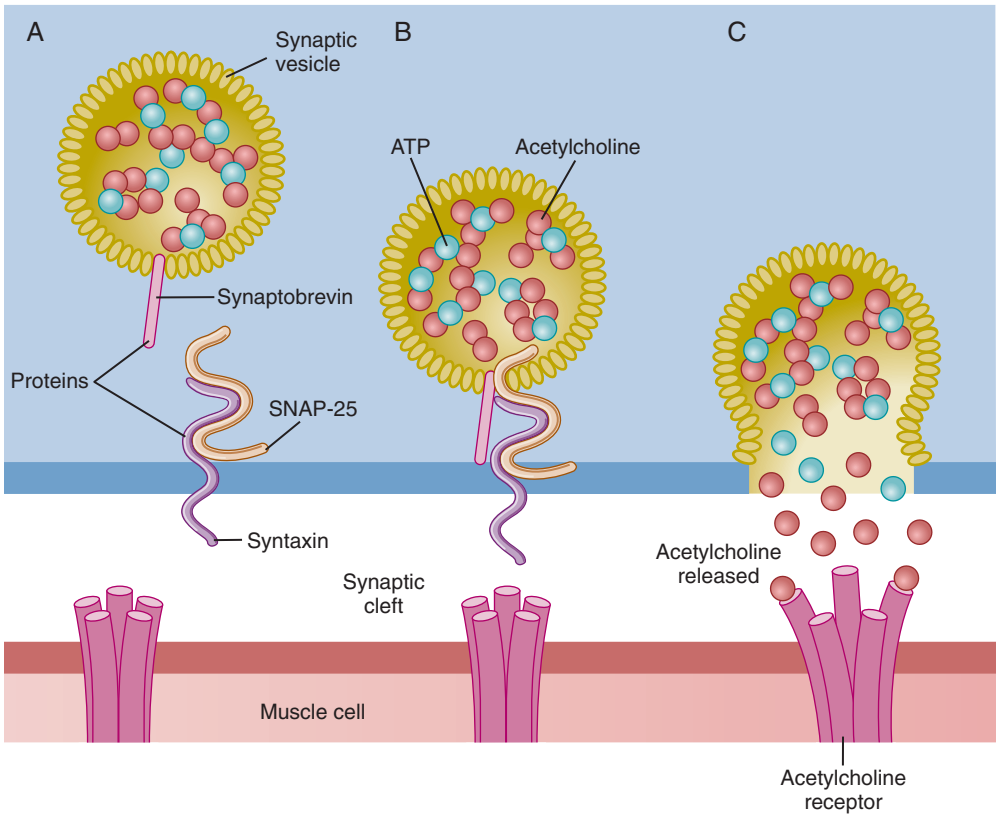
The larger reserve pool (V1) can be mobilized to the readily releasable store when there is increased demand, such as when the nerve is stimulated at high frequencies or for long periods of time. Under such high demand conditions, increases in Ca^{2+} concentration penetrate more deeply than normal into the nerve or might enter via L-type Ca^{2+} channels (see later text). This probably activates Ca^{2+}-dependent enzymes that break the links with synapsin that hold the reserve vesicles to the cytoskeleton, thereby allowing mobilization of vesicles to release sites. Repeated stimulation of the nerve requires replenishment of the nerve ending with synaptic vesicles, a process known as *mobilization*.

The aggregate process is involved in maintaining the capacity of the nerve ending to release neurotransmitter. This process encompasses everything from uptake of choline and synthesis of acetate to the movement of vesicles to release sites. The rate-limiting steps of this process appear to be the uptake of choline and the activity of choline acetyltransferase, the enzyme that synthesizes acetylcholine.[23]

The complex process of docking, fusion, and release of neurotransmitter from synaptic vesicles is called *exocytosis*. Three proteins, synaptobrevin, syntaxin, and synaptosomal-associated protein 25 (SNAP-25), within the group of soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE) proteins have key roles in the process of exocytosis (Fig. 21.2).[24] A complex of syntaxin and SNAP-25 is attached to the plasma membrane. After initial contact, synaptobrevin on the vesicle forms a ternary complex with syntaxin and SNAP-25 that consists of a zippered helical bundle. This complex forces the vesicle close to the nerve terminal membrane at the active zone (release site). Synaptotagmin, a protein on the vesicular membrane that acts as the Ca^{2+} sensor, localizes the vesicles to synaptic zones rich in Ca^{2+} channels and stabilizes the vesicles in the docked state.[25] After fusion and exocytosis, the used vesicle and membrane parts are recycled through an active process into the nerve terminal; there they are reused to form new vesicles (endocytosis), filled with ACh, and then transported to the active sites for release.

Nerve Terminal Action Potential

During the nerve action potential, Na^+ from outside the nerve flows down its electrochemical gradient across the cell membrane and the resulting depolarizing voltage opens voltage-gated Ca^{2+} channels, which permit Ca^{2+} to enter the nerve down its electrochemical gradient, triggering the release of ACh. Of the several



• **Fig. 21.2** Membrane fusion and exocytosis of acetylcholine vesicles from the motor nerve terminal. A, Acetylcholine is stored in synaptic vesicles. Its release is mediated by SNARE proteins. B, During depolarization and calcium ion (Ca^{2+}) entry through voltage-gated Ca^{2+} channels, SNARE proteins on the vesicle (synaptobrevin) and on the membrane (synaptosomal-associated protein 25 [*SNAP-25*] and syntaxin) interact and the vesicle is attached to the membrane. C, Upon depolarization and Ca^{2+} entry, Ca^{2+} binding to the Ca^{2+} sensor synaptotagmin triggers fusion of the vesicle to the nerve membrane at the active zone to release its contents, acetylcholine. *SNARE,* Soluble N-ethylmaleimide-sensitive factor attachment receptor.

subtypes of Ca^{2+} channels, four voltage-gated Ca^{2+} channels are important for spontaneous and evoked release of ACh: P/Q-, N-, L-, and R-type channels. P/Q type channels are found only in nerve terminals immediately adjacent to the active zones and are probably the major type responsible for the normal release of neurotransmitter.[26] They are voltage-gated and open and close in response to changes in the membrane voltage caused by the nerve action potential.

During the nerve action potential, the Ca^{2+} current persists until the channels inactivate and outward fluxes of K^+ from inside the nerve return the membrane potential to normal. As with Ca^{2+} channels on the nerve terminal, there are several forms of K^+ channels, including voltage-gated and Ca^{2+}-activated potassium ion (K^+) channels. These K^+ channels limit the duration of nerve terminal depolarization and thereby Ca^{2+} entry and release of neurotransmitter.[27]

In the absence of an action potential, small spontaneous depolarizing potentials can be recorded at the postsynaptic muscle membrane. These miniature endplate potentials (MEPPs) are the result of the spontaneous release of a small number of ACh-containing vesicles. They have only 1% of the amplitude of the evoked potential produced when the motor nerve is stimulated. Statistical analysis has led to the conclusion that there is a minimum size for MEPPs and that the size of all MEPPs is equal to or a multiple of this minimum size, equivalent to the fusion of a single synaptic vesicle.[28] Consequently, it was deduced that MEPPs are produced by these uniform sized packages or *quanta* of released transmitter in the absence of stimulation. Stimulation-evoked endplate potential depolarization is the additive effect produced by several hundred vesicles synchronously discharging quanta of neurotransmitter. Except for the reduced amplitude, MEPPs resemble the endplate potential in their time course and their sensitivity to drugs.

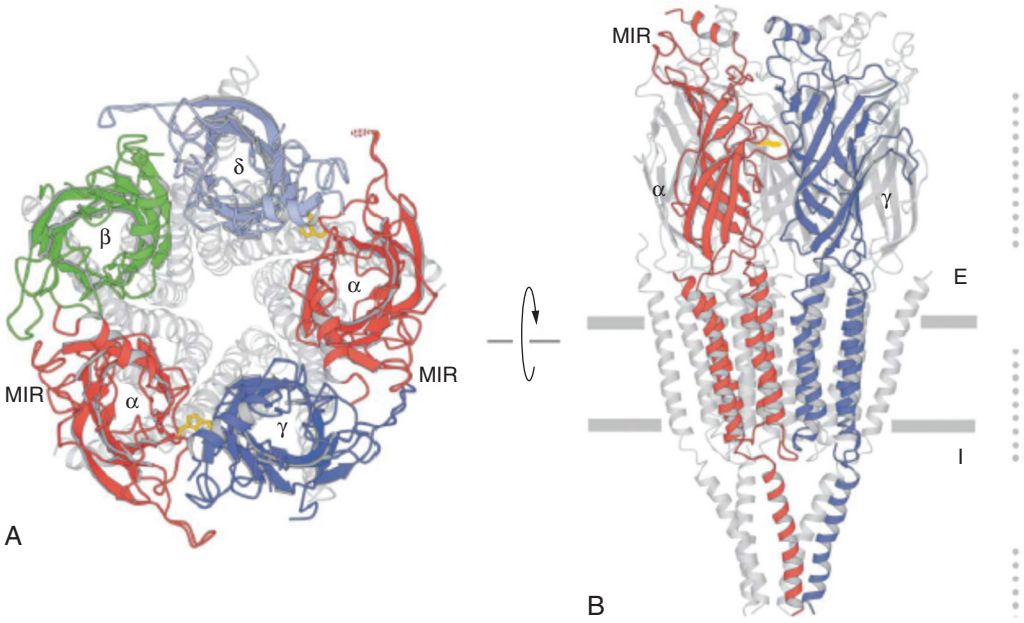
Acetylcholinesterase

Acetylcholinesterase is a type-B carboxylesterase enzyme located primarily in the synaptic cleft with a smaller concentration in the extrajunctional area. Acetylcholinesterase is secreted by the muscle and remains attached to it by collagen fastened to the basal lamina. ACh molecules that do not bind immediately with a receptor or those released after reacting with a receptor are hydrolyzed almost instantly (in less than 1 msec) by acetylcholinesterase. Approximately 50% of the released ACh is hydrolyzed into choline and acetate before reaching the receptor.[6] Choline is taken up by the nerve terminal and reused for synthesis of ACh.

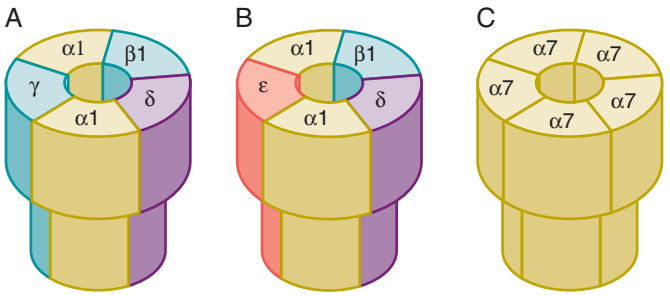
Acetylcholine Receptors

Structure

Nicotinic AChRs belong to the cys-loop superfamily of pentameric ligand-gated ion channels that share a common architecture, with five subunits surrounding a central ion-conducting pore. Each subunit is built on four transmembrane segments with the second transmembrane segment lining the pore (Fig. 21.3).[29] Each subunit is composed of approximately 400 to 500 amino acids. The AChRs are synthesized in muscle cells and anchored to the endplate membrane by the 43-kDa protein rapsyn. Four subtypes of perijunctional AChRs are of clinical importance: the presynaptic $\alpha_3\beta_2$,



• **Fig. 21.3** Ribbon diagrams of the nicotinic acetylcholine receptor, as viewed from above the synaptic cleft (A) and parallel with the plasma membrane plane (B). For clarity, only the ligand-binding domain is highlighted in A and only the front two subunits are highlighted in B (α, *red;* β, *green;* γ, blue; δ, light blue). The main immunogenic region *(MIR),* where antibodies against the receptor in myasthenia gravis patients bind, is very close to the acetylcholine binding site. The membrane is indicated by horizontal bars (*E,* extracellular; *I,* intracellular). The dotted lines on the right denote the three main zones of subunit contacts during folding and formation of the receptor channel. (Reproduced from Unwin N. Refined structure of the nicotinic acetylcholine receptor at 4A resolution. *J Mol Biol*. 2005;346:967–989.)



• **Fig. 21.4** Diagram of postsynaptic nicotinic acetylcholine receptors on the muscle membrane. The immature or fetal pentameric extra-junctional receptor (A) is composed of two α_1 subunits, and one each of β_1, δ, and γ subunits. In the mature receptor (B), which is mostly junctional, the γ subunit is absent and is replaced by the ε-subunit, while all other subunits are the same as the immature receptor. The α_7-acetylcholine receptor (C) is a homopentameric receptor formed of five α_7 subunits.

the postsynaptic $2\alpha_1\beta_1\delta\varepsilon$ or $2\alpha_1\beta_1\delta\gamma$ and the α_7 AChRs located both in terminal Schwann cell and postsynaptically on the muscle (Fig. 21.4). The α subunits contain two adjacent cysteines essential for ACh binding and the non-α subunits contribute to the specificity and stability of each receptor isoform.[30]

Neuronal AChRs include homomeric and heteromeric isoforms, with $\alpha_{7\text{-}9}$ subunits forming homomeric (formed of same subunit) AChRs and heteromeric AChRs formed by a combination of $\alpha_{2\text{-}6}$ and $\beta_{2\text{-}4}$ subunits with a stoichiometry of 2α and 3β. Compared with muscle AChRs, which have two distinct agonist binding sites—one high-affinity site between α_1 and δ and a lower-affinity site between α_1 and δ—neuronal AChR agonist binding sites vary based on the subunit composition. This variation contributes to the pharmacologic specificity of each receptor isoform. Heteromeric neuronal AChRs have two α-subunit binding sites between the α and β subunits, while the homomeric isoforms (e.g., α_7) have five potential binding sites, although the number of bound agonists required for receptor activation is not known.

Although many potential receptors are possible by combining different subunits, only a few have been found to be of biologic importance. In the NMJ, the $\alpha_3\beta2$ (neuronal) subtype is found in the presynaptic nerve ending. The $2\alpha_1\beta_1\delta\gamma$ and α_7 AChRs are found postsynaptically during development and denervation and in other acquired pathologic states (e.g., immobilization and burns).[31] NMBs and their metabolites can block ACh-mediated effects on neuronal AChRs in vitro.[32] The α_7 AChRs are also constitutively expressed in terminal Schwann cells. Small amounts of NMBs do cross the blood-brain barrier, but larger amounts most likely cross in critical illness when the blood-brain barrier is more permeable. The long-term effects of NMBs on AChRs in the central nervous system are unclear, although inadvertent acute direct administration is known to cause seizures. Interestingly, NMBs decrease hypoxic ventilatory response in partially paralyzed humans; the mechanism for this response might be inhibition of neuronal AChRs within the carotid body.[33]

Electrophysiology

The electrophysiologic technique of patch clamping has provided valuable insight into the functioning of prejunctional and postjunctional AChRs. With patch clamping, a glass micropipette is pressed onto the lipid membrane to form a seal. The pipette is filled with an ionic solution and conducts electric current to an amplifier. Depending on the configuration of the patch, the composition of the pipette or external solution can be changed to include drugs such as ACh, an NMB, or other drugs to study the ion channels under different conditions and the current or voltage monitored. Using these methods it is possible to determine how alterations in subunit composition, environment, or drugs change receptor electrophysiology.

Under normal conditions, the ion-conducting pore of the AChR is closed by the approximation of the pore gate. When an agonist such as ACh occupies both binding sites, a conformational change occurs, opening a channel through which ions flow along a concentration gradient. Both α subunits must be occupied simultaneously by agonist; if only one is occupied, the channel remains closed. The NMB binds to one or more of the α subunits, thus preventing ACh from binding and opening the ion channel. This interaction between ACh and NMB is competitive and the outcome—neuromuscular transmission or block—depends on the relative concentration and binding characteristics of the agonist (ACh) and antagonist (NMB).

The AChR ion channel accommodates many cations and electrically neutral molecules but excludes anions. The resulting depolarizing current measured by patch clamp recording through each open channel is minuscule (only a few picoamperes). However, each nerve terminal action potential releases enough ACh to open about 500,000 channels simultaneously, and the total current is more than adequate to depolarize the endplate and produce muscle contraction. This again is part of the increased margin of safety or reserve capacity of neurotransmission.

In addition to open or closed states, receptor channels are capable of a variety of other conformational current-passing states.[29,34] They alter the amount of time that they remain open, open and close more slowly than usual, open briefly and repeatedly, or allow passage of fewer or more ions than they usually do (conductance). Receptor channels are dynamic structures that are influenced by a variety of drugs and changes in external milieu, including membrane fluidity, temperature, electrolyte balance, and chemical and physical factors.[29,34,35] The net effect of these channel influences is ultimately reflected in the strength of neuromuscular transmission and muscle contraction.

Receptor Types

Postsynaptic Receptors

The trophic function of the nerve and the associated electrical activity are vital for the development, maturation, and maintenance of the NMJ.[36] During the late embryonic stage, the motor nerve axons grow into the developing muscle and release growth factors, including agrin and neuregulins ($NR\beta_1$ and $NR\beta_2$) essential to the maturation of myotubules to muscle. Agrin, a nerve- and muscle-derived protein, stimulates postsynaptic differentiation by activating on a muscle-specific tyrosine kinase (MuSK). Agrin, together with neuregulins and other trophic factors, induces the clustering of AChRs and other essential muscle-derived proteins. including MuSK, rapsyn, and Erbβ, all of which are necessary for maturation and stabilization of AChRs at the NMJ.

During development (fetus), the postsynaptic AChRs are composed mainly of $2\alpha_1\beta_1\delta\gamma$ and α_7 AChRs and spread throughout the muscle membrane (see Fig. 21.5). Just before birth and shortly thereafter, the $2\alpha_1\beta_1\delta\gamma$ AChRs (also called *immature AChRs*) are replaced by mature receptors with a subunit composition of $2\alpha_1\beta_1\delta\varepsilon$ and the receptors are clustered around the nerve. The immature

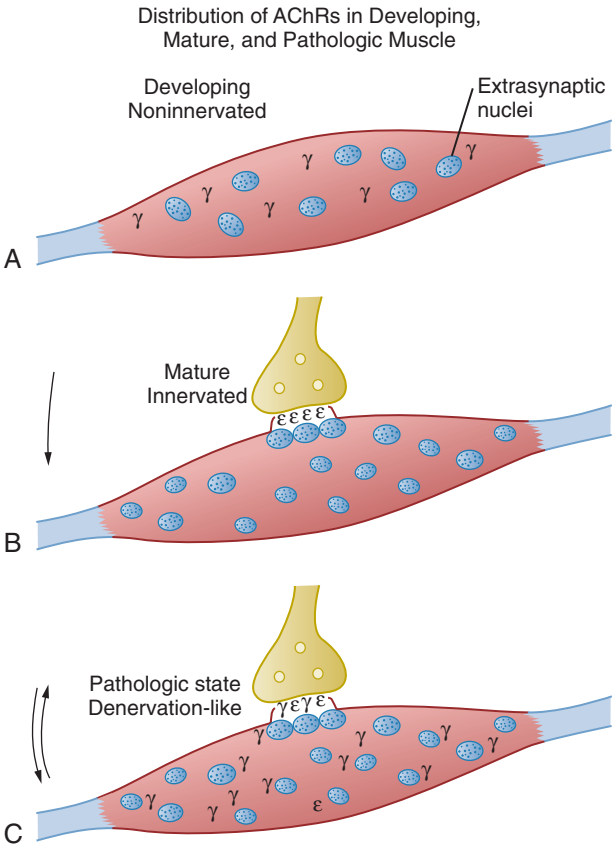
receptors expressed in the fetus are more sensitive to depolarization by ACh, and this increased sensitivity might play a role in directing the nerve bud to muscle. The mechanism of the change from immature to mature receptors is unknown; however, the neuregulin $NR\beta_1$ (also called *ARIA*), which binds to one of the Erbβ receptors, seems to play a role. In the rodent, it takes about 2 weeks for complete conversion of immature to mature AChRs, whereas in humans this process takes longer.[6] The mechanism and time course for disappearance of α_7 AChRs in muscle of the newborn in humans is unknown.

Presynaptic Receptors

Compared with postsynaptic AChRs, the structure and function of presynaptic AChRs are not as well understood. Differences exist between presynaptic and postsynaptic AChRs in their ability to bind toxins, as well as agonists and antagonists. Presynaptic AChRs are autoreceptors responsible for modulating the release of ACh into the synaptic cleft by means of a positive or negative feedback system.[37] The positive feedback system is further regulated by a negative feedback system that senses when the concentration of transmitter in the synaptic cleft has increased to appropriate levels and shuts down further release. Targeted inhibition of presynaptic $\alpha_3\beta_2$ receptors during high-frequency repetitive stimulation results in typical tetanic fade (i.e., the decrease of twitch height during repetitive nerve-stimulated muscle contraction).[39] This tetanic fade during experimental conditions equates to the train-of-four (TOF) fade seen clinically during neuromuscular monitoring after nondepolarizing NMBs and is used as an indicator of the presence of relaxant-induced residual muscle weakness (see Chapter 22).[40] In contrast to block of presynaptic $\alpha_3\beta_2$ receptors produced by clinically used nondepolarizing NMBs, the depolarizing agent succinylcholine (SCh) does not inhibit $\alpha_3\beta_2$ receptors.[40] This explains why TOF fade is absent during SCh-induced block.[41] Recently the terminal Schwann cells have been shown to constitutively express α_7 AChRs. By selective inhibition of the acetylcholine esterase enzymes and α_7 AChRs and the use of α_7 AChRs knockout mice, the authors have demonstrated that α_7 AChRs expressed at the terminal Schwann cells act as sensors for spillover of ACh during neurotransmission. During excessive release of ACh, there is a feedback mechanism via the α_7 AChRs to inhibit the further release of ACh.[42] These new findings on the role of α_7 AChRs in terminal Schwann cell in the control of ACh release needs further study and confirmation. Fade, however, is not always a prejunctional phenomenon, exemplified by the disease myasthenia gravis, a postjunctional disease that shows fade during repetitive stimulation. Fade in myasthenia gravis is due to decrease of postjunctional AChRs, reflecting decreased margin of safety. Thus from a practical point of view, fade observed during repetitive nerve stimulation reflects decreased margin of safety rather than a prejunctional or postjunctional phenomenon.

Mature and Immature Postjunctional Receptors

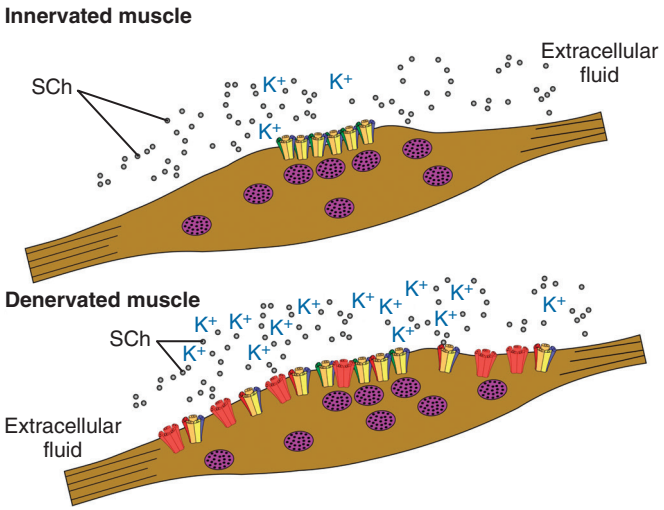
Mature postjunctional AChRs are composed of five subunits consisting of two α_1 subunits and one each of the β_1, δ, and ε subunits (see Fig. 21.4). Although the innervated NMJ only synthesizes the mature form of AChR, expression of other receptor isoforms can be induced with decreased neural influence or activity, as seen, for example, in the fetus before innervation or in adult patients after denervation such as occurs with upper or lower motor neuron injury or after burn injury and immobilization. In these conditions, immature receptors consisting of $2\alpha_1\beta_1\delta\gamma$ AChRs together with α_7 receptors are reexpressed (Fig. 21.5). The immature



• **Fig. 21.5** Distribution of acetylcholine receptors (AChRs) in the fetal or denervated muscle membrane, mature neuromuscular junction, and in acquired pathologic states. A, In the fetus or in denervation, the AChRs are distributed throughout the muscle membrane. These receptors express γ- or α_7-subunit–containing AChRs. B, After birth, with innervation and maturation, AChRs cluster at the junctional area and contain the ε-subunit–containing AChRs. C, In some pathologic states (e.g., burns, immobilization), despite the absence of over anatomic denervation, AChRs spread throughout the muscle membrane and behave as if denervated, expressing γ and α_7 subunits, as well as ε subunits. (The topologic distribution of α_7 AChRs on the muscle membrane in pathologic states is unknown, and therefore not depicted on Fig. 21.5, C.) (See Fig. 21.4 for detailed description of composition of postjunctional AChRs.)

heteromeric AChR is structurally similar to the mature AChR but with a γ subunit replacing the ε subunit. The immature receptors are also referred to as extrajunctional because they are expressed mostly, but not exclusively, in the extrajunctional region of the muscle membrane. The α_7 AChRs are homomeric composed of five α_7 subunits. Expression of α_7 AChRs has been demonstrated in fetal and denervated muscle and seems to be reexpressed in conditions such as immobilization, systemic inflammation, and burn injury and possibly in other pathologic states in which muscle wasting occurs (see later text).

The immature $2\alpha_1\beta_1\delta\gamma$ receptors have a smaller conductance per channel and a longer mean channel open time (2- to 10-fold longer) compared with mature receptors. The difference in subunit composition can alter the sensitivity or affinity of the receptor for certain ligands. For example, ACh and the agonist SCh depolarize this isoform of the immature receptor more easily, requiring only 1% to 10% of the dose necessary to depolarize mature receptors.



• **Fig. 21.6** Response to succinylcholine *(SCh)* in innervated and denervated muscle. In innervated muscle, SCh-induced depolarization occurs only in the junctional area with limited efflux of potassium ions [K^+] from the cell to the extracellular space. In conditions of upregulated and extrajunctional acetylcholine receptors (AChRs), systemically administered SCh comes into contact with all the AChRs throughout the muscle membrane, causing massive efflux of K^+ into the extracellular fluid with potentially lethal hyperkalemia. This occurs because AChRs conduct both sodium ions [Na^+] and K^+, although they are more selective for Na^+.

Notably, α_7 AChRs can be activated not only by ACh and SCh but also by their metabolites, succinylmonocholine and choline. Thus the depolarization of the upregulated immature and α_7 AChRs with SCh or its metabolites has the potential to cause massive efflux of K^+ to the extracellular fluid causing hyperkalemia (Fig. 21.6). Conversely, the potency of the nondepolarizing NMB is decreased with immature receptors as documented by the resistance to these agents in patients with burns, denervation, and immobilization.[17] This resistance might be related to decreased affinity of the $2\alpha_1\beta_1\delta\gamma$ or α_7 AChRs for nondepolarizing NMB and to upregulation of receptors in the perijunctional and extrajunctional areas. The upregulated AChRs can act as a buffer for the diffusion of NMBs to the junctional area.

Upregulation and Downregulation of Receptors

A mechanism for the increased or decreased sensitivity to agonists and antagonist drugs suggests that *decreased* exposure to an agonist results in an increase in the number of receptors (upregulation), while *increased* exposure to an agonist can result in a decrease in the number of receptors (downregulation).[43] Consequently, diseases associated with decreased nerve-mediated contraction (e.g., stroke, spinal cord injury, immobility) result in upregulation of AChRs in skeletal muscle. At the NMJ, this upregulation of AChRs is complicated by the potential for three isoforms of AChRs to coexist. For example, after denervation, there is increased expression of $2\alpha_1\beta_1\delta\gamma$ and α_7 AChRs at the junctional and extrajunctional sites, each of which has its own pharmacologic characteristics. Disease-induced receptor isoform changes and upregulation of AChRs play a role in the resistance to nondepolarizing NMB and hyperkalemia in response to SCh. The classic theory on the interaction of agonists and antagonists on upregulated and downregulated receptors is useful for understanding the responses observed with agonists and competitive antagonists of AChRs. In conditions associated with upregulation of AChRs (e.g., denervation), sensitivity to agonists increases, whereas sensitivity to antagonists decreases. This is observed clinically by increased requirements for nondepolarizing NMBs in patients with upregulation of AChRs (see later text). Conversely, downregulation of AChRs leads to increased requirement for agonists and increased sensitivity to antagonists, as seen in myasthenia gravis.

Reexpression of Immature Receptors After Denervation or Other Pathologic States

After upper or lower motor neuron injury or in certain other pathologic states such as immobilization, burns, infection/inflammation, and critical illness, $2\alpha_1\beta_1\delta\gamma$ and α_7 AChRs are reexpressed, extending beyond the NMJ area (see Fig. 21.5). In other words, AChR expression in the muscle membrane reverts to the form seen in the fetus or following denervation, despite the absence of overt anatomic denervation. In all of these conditions of AChR proliferation, there is also associated insulin resistance and muscle wasting as in denervation. The role of decreased anabolic signaling in the upregulation of AChRs is unclear. Electrical stimulation of denervated muscle can prevent reexpression of immature AChRs. It has been suggested that entry of Ca^{2+} into the muscle during activity prevents reexpression of immature receptors and possibly α_7 AChRs. Synthesis of immature receptors is initiated within hours of inactivity, but it takes several days for full proliferation of receptors on the muscle membrane. With severe and prolonged injury the entire muscle surface, including the perijunctional area, is densely covered with immature receptors. The junctional nuclei also continue to make mature receptors, which results in a mix of mature and immature receptors at the endplates. The change in receptor composition alters electrophysiologic, pharmacologic, and metabolic characteristics of the NMJ.

Plasticity of the Neuromuscular Junction

Classically, transmission of an impulse from the motor nerve to muscle by the mature NMJ was viewed as a "static" relay form of transmission associated with limited plasticity for nerve outgrowth or formation of new synaptic contacts. More recently it has emerged that adult NMJs are constantly undergoing structural remodeling and that the NMJ reflects a dynamic equilibrium between growth and regression.[44] This equilibrium can be influenced by a variety of factors, including drugs, toxins, aging, disuse, and injury. In addition to the continuous remodeling that occurs at the adult NMJ under normal conditions, extended periods of increased or decreased neuromuscular activity stimulate more extensive remodeling. For example, voluntary exercise can significantly alter neuromuscular morphology, resulting in an increase in area measurements of both the presynaptic and postsynaptic components of the NMJ with the effect depending on the muscle type (fast or slow twitch), age, and type of exercise (endurance or resistance training).[44,45]

A reduction in neuromuscular activity also causes structural alterations in the NMJ. Total disuse resulting either from denervation or synaptic blockade by drugs (NMBs) or toxins (botulinum or tetanus-clostridial, or tetrodotoxin [puffer fish] poisoning) prevents impulse conduction between the nerve and muscle and leads to significant degenerative effects, including reduction in endplate area with more shallow primary grooves and a reduced density of secondary folds.[46] Additionally, denervation results in migration of AChRs out of the folds and into the perisynaptic and

extrasynaptic regions, resulting in reduced density of receptors at the endplate.[44] Denervation also affects presynaptic morphology with sprouting extending from the motor nerve terminals. Chronic disuse can also cause the presynaptic terminals to release increased amounts of ACh in response to nerve stimulation and increased spontaneous release of ACh quanta.

Age-Associated Changes in the Neuromuscular Junction

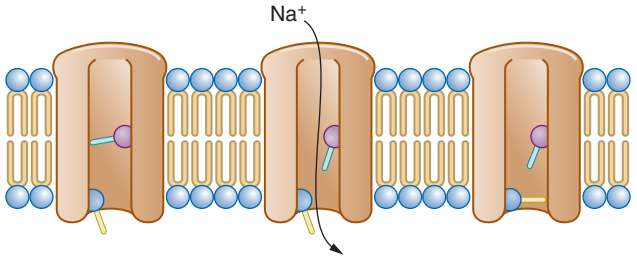
Accumulating evidence points to old age-associated degeneration of the NMJ as a key event leading to functional denervation, muscle wasting, and weakness.[47,48] Anatomic changes involve increased preterminal branching and axonal branching within individual NMJ with or without changes in the total area of the NMJ. The amount of postsynaptic endplate membrane that is *not* in contact with the nerve terminal also increases. The result is a decline in the trophic interaction of nerve and muscle and stimulus transmission. Coupled with the morphologic changes in the NMJ that occur with aging, functional changes in neurotransmission in older adults have been reported, including increased quantal content of neurotransmitter release and more rapid rundown of endplate potential strength during continuous stimulation of the preterminal neuron.[47] In addition, age-related alterations in axonal transport, which could affect the availability of trophic factors, have been reported. Despite these structural and functional changes associated with aging, it appears that an adequate margin of safety for transmission is generally maintained.

Clinical Implications—Actions of Neuromuscular Blocking Drugs

Depolarizing Agents

Depolarizing NMBs act, at least initially, by mimicking the effect of ACh and therefore can be considered agonists, although they block neurotransmission after initial stimulation. SCh, the only clinically used depolarizing NMB, binds to the receptor, thereby opening AChR and allowing ion flow that results in endplate depolarization. In contrast to ACh, which has a brief duration of action (~1 msec or less) as a result of its rapid degradation by acetylcholinesterase, SCh is not susceptible to hydrolysis by acetylcholinesterase. Therefore SCh remains in the synaptic cleft until the plasma concentration of SCh decreases or disappears because of breakdown by plasma pseudocholinesterase (butyrylcholinesterase) or elimination by the kidney. Thus SCh remains available for sustained AChR stimulation causing prolonged channel opening and depolarization of the endplate. SCh exerts a biphasic action on muscle: an initial contraction, observed as fasciculation, followed by relaxation lasting minutes to hours. The time required to hydrolyze or eliminate the drug from the body is the principal determinant of the duration of block (paralysis).

The biphasic action of SCh from initial excitation to eventual block of transmission results from the continuous depolarization of the endplate and inactivation of Na^+ channels located at the edge of the endplate. Sodium channels have three major conformational states and can transition from one state to another (see Chapter 20). When the Na^+ channel is in its resting state, the inactivation gate is open but the voltage-dependent gate is closed and Na^+ cannot pass. When the channel is subjected to a sudden change in voltage by depolarization, the voltage gate opens and Na^+ flows through the channel. However, shortly after the voltage gate opens, the time-dependent inactivation gate closes, stopping the flow of ions. The inactivation gate cannot reopen until the voltage gate closes. When depolarization of the endplate stops, the voltage gate closes, the inactivation gate opens, and the channel returns to the resting state (Fig. 21.7).



• **Fig. 21.7** Diagram of the voltage-gated sodium channel. The bars represent parts of the protein that act as gates. The upper and lower bars represent voltage-dependent and time-dependent (inactivation) gates, respectively. The left side represents the resting state. Once activated by a change in voltage, the sodium ion [Na^+] moves into the cell (*middle figure*). Shortly after, the time-dependent inactivation gate closes with block of further influx of Na^+ despite the voltage gate being open. (See text for further details.)

Depolarization of the endplate by SCh results in opening of voltage gates in adjacent Na^+ channels, causing a wave of depolarization to sweep across the muscle, producing muscle contraction (fasciculation). Shortly after the voltage gates open, the inactivation gates close. Since the depolarizing SCh is not rapidly removed from the cleft, the endplate continues to be depolarized. As a result, the voltage gates of Na^+ channels adjacent to the endplate remain open and the inactivation gates stay closed and Na^+ cannot flow. Because the flow of ions through Na^+ channels in the perijunctional area is stopped, the perijunctional zone does not depolarize and the channels beyond the perijunctional zone are freed from the depolarizing influence. The perijunctional zone, in effect, acts as a buffer that shields the rest of the muscle from the events at the endplate. In other words, the muscle membrane is divided into three zones: the endplate, which is depolarized by SCh (or ACh); the perijunctional muscle membrane, in which the Na^+ channels exist in an inactivated state; and the rest of the muscle membrane, in which the Na^+ channels remain in the resting state. Neuromuscular transmission is blocked because ACh release from the nerve cannot overcome the inactivated Na^+ channels in the perijunctional zone. This phenomenon is called *accommodation*. During accommodation, neuromuscular transmission via ACh release is blocked; however, direct electrical stimulation of muscle can cause muscle contraction because the Na^+ channels beyond the junctional area are in the resting excitable stable.

Nondepolarizing Agents

Nondepolarizing NMBs block neuromuscular transmission predominantly by competitive antagonism of ACh at the postjunctional receptor. The effect of this competitive antagonism depends on the relative concentrations of NMB and ACh and the comparative affinities of each for the AChR. Under normal conditions, acetylcholinesterase rapidly cleaves ACh in the synaptic cleft, thereby improving the competitive advantage of the NMB to bind to the

receptor. If an inhibitor of acetylcholinesterase is added to the mix, the concentration of ACh in the cleft remains high and there is a shift in favor of ACh binding to the receptor. The NMBs compete with ACh at the two binding sites of the AChR. Therefore only one molecule of NMB is needed to prevent activation of the receptor, whereas two ACh molecules are needed for activation. This biases the competition strongly in favor of the antagonist (NMB) drug.

Reversal (Antagonism) of Neuromuscular Blocking Drugs

Because the nondepolarizing NMBs block neuromuscular transmission primarily by competitive antagonism of ACh at the postjunctional receptor, the most straightforward way to overcome the effects of the blockade is to increase the competitive position of ACh by increasing the number of molecules available at the junctional cleft. By doing so, the probability is increased that agonist (ACh) rather than antagonist molecules nondepolarizing (NMBs) will occupy the available receptor sites. Normally, only about 500,000 of the 5 million available receptors are activated by a single nerve impulse. This leaves a large number of unoccupied receptors available to be occupied. Another means of increasing the competitive position of ACh is by increasing the length of time that ACh remains in the cleft. The nondepolarizing NMBs bind to the receptor for slightly less than 1 msec, which is longer than the normal life span of ACh. Under normal conditions, the hydrolysis of ACh by acetylcholinesterase takes place so quickly that most of it is destroyed before a significant number of antagonist molecules can be dissociated from the receptor. Use of an acetylcholinesterase inhibitor prolongs the length of time that ACh remains in the junction and allows the ACh to bind to receptor when the antagonist dissociates. The recently developed γ-cyclodextrin sugammadex can bind directly to steroidal NMBs reversing their action without altering concentrations of ACh at the junction (described further in Chapter 22).

Nonclassic Actions of Drugs Acting at the Neuromuscular Junction

Classic NMBs interfere with neurotransmission directly by interacting with the agonist-binding sites on the AChR, but other drugs such as procaine, ketamine, or inhaled anesthetics can alter the opening and closing characteristics of the AChR ion channel and/or Na^+ channels through other mechanisms, including AChR desensitization and direct channel block.

Desensitization

Under normal conditions, the binding of two agonist molecules (ACH) to the α subunits of the AChR results in a conformational change that opens the channel and allows ions to flow. However, receptors continuously bound by agonists undergo a time-dependent conformational change that results in channel closure, known as desensitization. These receptors are no longer sensitive to the channel opening actions of agonists, analogous to inactivation of voltage-gated channels. Certain antagonists can bind to desensitized receptors, trapping them in the desensitized state. This action of antagonists is not competitive with ACh but can be augmented by ACh if the latter promotes the change to the desensitized state. The mechanism by which desensitization occurs is not fully understood, although some evidence suggests that phosphorylation of a tyrosine unit in the receptor plays a role.[49]

In addition to NMB, a number of commonly used drugs promote the transition of receptors from the sensitized to desensitized state or cause allosteric inhibition, thereby weakening neuromuscular transmission by reducing the margin of safety and by increasing the capacity of NMBs to block transmission (Table 21.1). These actions are independent of the classic competitive inhibition of ACh. The net effect of desensitized receptors is that fewer receptor channels are open to allow passage of the transmembrane current, the efficacy of neuromuscular transmission is decreased, and the system is more susceptible to block by conventional antagonists such as NMB.

Channel Block

Drugs that prevent the flow of ions through channels by blocking the pore are referred to as channel-blocking drugs. Two major types of channel block can occur: open-channel block and closed-channel block.[50] In closed-channel block, certain drugs occupy the mouth of the channel and prevent ions from passing through the channel, thereby preventing depolarization of the endplate. In open-channel block, a drug enters the open channel and binds within it. In both open- and closed-channel block, the normal flow of ions through the channel is prevented, resulting in weaker or blocked neuromuscular transmission. Because the site of action of channel blocking drugs is not at the ACh recognition site, the effect is *not* reversed by increasing the synaptic concentration of ACh and therefore is not relieved by acetylcholinesterase inhibitors. In fact, increasing the concentration of ACh can increase channel blockade

TABLE 21.1 Drugs That Can Promote Desensitization or Allosteric Inhibition of Nicotinic Cholinergic Receptors

- Acetylcholinesterase inhibitors (overdose)
  - Neostigmine
  - Pyridostigmine
  - Difluorophosphate
  - Edrophonium
- Agonists
  - Acetylcholine (high levels)
  - Decamethonium
  - Carbachol
  - Succinylcholine
- Alcohols
  - Ethanol
  - Butanol
  - Octanol
  - Propanol
- Antibiotics
  - Aminoglycosides, polymyxins
- Antiepileptics
  - Carbamazepine (acute)
  - Phenytoin (acute)
- Calcium channel blockers
- Cocaine
- Local anesthetics
- Phencyclidine (ketamine)
- Phenothiazines
  - Chlorpromazine
  - Trifluoperazine
  - Prochlorperazine
- Volatile anesthetics

by causing the channels to be open more often and consequently to be more susceptible to open-channel block. There is evidence that cholinesterase inhibitors such as physostigmine and pyridostigmine can act as channel blocking drugs in this manner.[51] Channel block is believed to play a role in altered neuromuscular function associated with a variety of drugs, including some antibiotics, local anesthetics, tricyclic antidepressants, naloxone, and naltrexone (see Table 21.1). NMBs can not only bind to the ACh recognition site but also occupy the channel in high doses; hence the difficulties in reversing deep neuromuscular block with anticholinesterases.

Phase II Block

Phase II block is a complex phenomenon that results when AChRs are continuously exposed to depolarizing agents (e.g., SCh). The NMJ is depolarized by the initial exposure to the depolarizing agent, but the membrane potential gradually recovers even though the NMJ is still exposed to the agonist. Neuromuscular transmission is prevented during phase II block by several processes. The repeated opening and closing of channels with influx of Na^+ and efflux of K^+ causes an electrolyte imbalance that distorts the function of the junctional membrane. Ca^{2+} entry into the muscle through the open channels causes disruption of receptors and sub-endplate structures.

Neuromuscular Junction in Disease and Injury

Important morphologic and physiologic changes in the NMJ occur in response to injury or disease. The common defect of all disorders of the NMJ is impairment of the margin of safety for neuromuscular transmission. Neurotransmission can fail at any point from the motor neuron to nerve to nerve terminal to the endplate to muscle. If the motor neuron–initiated endplate potential fails to reach the threshold for the muscle fiber, an action potential is not generated, the muscle fiber does not contract, and neuromuscular transmission fails. Failure to generate endplate potentials prevents muscle contraction and produces clinical weakness.

NMJ disorders can be classified as inherited and acquired or anatomically as presynaptic, synaptic, or postsynaptic. The etiology of the dysfunction can also be classified as autoimmune, congenital, pharmacologic, toxic, or traumatic. Most disorders of the NMJ are complex, and multiple mechanisms of failure coexist (Table 21.2).

Neuromuscular Junction in Disease

Congenital Myasthenic Syndromes

Congenital myasthenic syndromes (CMS) are the most diverse group of inherited disorders of NMJ. They arise from mutations in essential presynaptic, synaptic, or postsynaptic proteins of the NMJ.[52,53] The majority are inherited recessively. Presynaptic defects are associated with abnormalities of quantal release of ACh or ACh resynthesis (mutation in choline acetyltransferase). Synaptic defects can be due to mutations in the endplate acetylcholinesterases and result in a deficiency of neurotransmission at the NMJ owing to AChR downregulation as a result of sustained excess in synaptic ACh concentration. Postsynaptic defects, which represent 75% of CMS, are due to mutations in AChR subunits that alter the kinetics of AChR ion channels or reduce channel density at the endplate. The most common mutations are in the ε subunit of the AChR. The immature γ subunit can substitute for the ε subunit but with less efficient neuromuscular transmission. Mutation of the protein rapsyn, which is involved in AChR clustering, represents another frequent cause of CMS. Mutation of Dok-7, another postsynaptic protein involved in AChR clustering, has recently been linked with a limb-girdle pattern of weakness.[54] Many of these disorders present in the perinatal period with hypotonia and weakness, feeding or breathing difficulties, ptosis, ophthalmoplegia, and in some cases, life-threatening episodes of apnea. Some CMS disorders only become evident during adolescence and some even in adult life. Clinical features along with electrophysiologic and molecular criteria are used to distinguish the CMS subtype. Although at least 10 genes have been identified as sites of CMS mutations, others are likely to be identified. For this reason the diagnosis of CMS is sometimes made on the basis of clinical and electrophysiologic features alone.

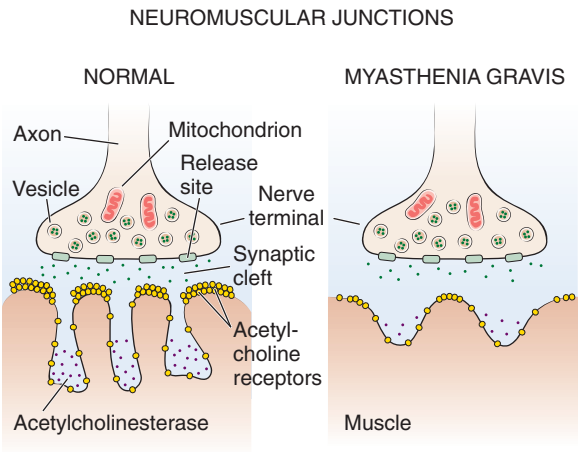
Myasthenia Gravis

Myasthenia gravis, the most common and-well studied postsynaptic neuromuscular transmission disorder, is caused by antibody-mediated reduction in the number of functioning postsynaptic AChRs.[52,53] This complement-mediated destruction is caused by a variety of actions including antibodies directed against the AChRs. The antibody binds to extracellular receptor epitopes, cross-linking adjacent AChRs resulting in enhanced receptor turnover (down-regulation), and even allosteric interference with the ACh-AChR interaction. The morphologic result of this antibody-mediated

TABLE 21.2 Neuromuscular Junction Disorders: Classification by Location of Failure

Location of Dysfunction	Dysfunction	Example
Presynaptic	Choline acetyltransferase deficiency	
	↓ ACh molecules/quanta	CMS-defect in ACh synthesis
	Dysfunction in quantal release mechanism	LEMS, botulism
Synaptic	Dysfunction of endplate acetylcholinesterase	CMS-endplate cholinesterase deficiency
Postsynaptic	Reduced AChR expression	Myasthenia gravis
	AChR mutations	
	AChR kinetic abnormality	CMS-slow channel
	Na^+ channel mutations	CMS-fast channel

Ach, Acetylcholine; *AChR*, acetylcholine receptor; *CMS*, congenital myasthenic syndrome; *LEMS*, Lambert-Eaton myasthenic syndrome.



• **Fig. 21.8** Acetylcholine receptors (AChRs) in the mature neuromuscular junction, and in acquired normal and myasthenia gravis neuromuscular junction. The nerve terminal vesicles are clustered at the release sites. The acetylcholine released crosses the synaptic cleft to reach the acetylcholine receptors (AChRs) located on shoulders of the junctional folds. The myasthenia gravis neuromuscular junction has a reduced number of AChRs owing to antibody-mediated downregulation. Some of the existing non-downregulated AChRs present on the muscle membrane can also be bound by antibodies. In effect, these AChRs are ineffective as they are incapable of responding to acctylcholine because of the bound antibodies. Synaptic folds are shallow and widened and the sodium ion channels on the synaptic clefts are also reduced (not shown in the figure). The nerve terminal is usually unaffected.

destruction is loss of postsynaptic folds and voltage-gated Na^+ channels at the NMJ (Fig. 21.8). Consequently, fewer AChRs are opened by each quantum of ACh release, and the amplitude of the MEPP is reduced. As a result there is marked reduction in the margin of safety and compromised neuromuscular transmission. The NMJ can partially compensate for the loss of AChRs by increasing neurotransmitter release from the nerve terminal.

Clinically, myasthenia gravis is characterized by a fluctuating fatigable weakness of the skeletal muscles. Early in the course of the disease, the weakness can be mild and is often confined to the ocular muscles. In more severe disease, extraocular, bulbar, and proximal muscles are involved. In severe cases, all skeletal muscles, including those involved in ventilation, can be affected. The diagnosis of myasthenia gravis depends on clinical features, the presence of autoantibodies, and electrophysiologic evidence of disordered neuromuscular transmission. Fade can be observed during repetitive nerve stimulation, even in the absence of NMBs, confirming the decreased margin of safety. Up to 20% of patients with clinical and electrodiagnostic evidence of MG do not have detectable levels of AChR antibodies. Of these "seronegative" myasthenic patients, approximately 40% have serologic evidence of antibodies to MuSK, a postsynaptic transmembrane protein at the NMJ.[50,51] MuSK plays a key role during muscular development in the pathway leading to AChR clustering and formation of the NMJ.

Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome (LEMS) is an acquired presynaptic disorder of neuromuscular transmission caused by autoantibodies directed against voltage-gated Ca^{2+} channels in the motor nerve terminal and resulting in downregulation by endocytosis.[52,53] This reduces Ca^{2+} entry into the nerve terminal during an action potential and thus leads to a reduction in the number of quanta (amount of ACh) released. Morphologically, there is a reduction in the number and size of active zones. The disease is characterized by muscle weakness and fatigability of proximal limb muscles during activity. Oropharyngeal and ocular muscles are usually spared but respiratory muscle weakness can occur, giving rise to respiratory failure. Autonomic function is also abnormal in most patients with LEMS. It is associated with a number of malignancies as a paraneoplastic syndrome. This is most commonly seen with small cell lung cancer in which tumor cells express Ca^{2+} channels that resemble those found on the nerve terminal. Autoantibodies produced in response to the tumor cells also bind to the Ca^{2+} channels on the nerve terminal. In contrast to myasthenia gravis, where there is weakness or fade with repetitive stimulation of nerve, in LEMS with sustained muscle activity there is a transient increase in muscle strength from the initial low level. This is likely a consequence of temporary Ca^{2+} buildup in the nerve terminal and results in increased neuromuscular transmission. The diagnosis is based on detection of antibodies directed against voltage-gated Ca^{2+} channels and characteristic electromyographic findings. The majority of patients with LEMS respond to treatment with oral 3,4-diaminopyridine, which blocks voltage-gated K^+ channels, resulting in prolongation of the action potential and increased quantal release.[55] Treatment of the underlying malignancy can also improve the clinical situation. Patients with LEMS not associated with malignancy often respond to immunosuppressive treatment. Patients with LEMS are sensitive to both nondepolarizing and depolarizing NMBs. They are significantly more sensitive to NMBs than patients with myasthenia gravis.

Botulism

A number of naturally occurring toxins act in various ways to inhibit neuromuscular transmission. Botulinum neurotoxin is one of the most potent and lethal substances known and serves as a model for neurotoxic action at the NMJ. Botulism is the clinical syndrome caused by the anaerobic gram-positive organism *Clostridium botulinum*. Seven different serotypes of the organism have been identified, each producing antigenically distinct toxins. The different toxins target different proteins (e.g., toxin types A and E target the SNAP-25 protein of the SNARE complex) at the presynaptic region of the NMJ, resulting in block of release of ACh with ensuing denervation and accompanying muscle paralysis and atrophy.[53,56] Clinically, botulism generally presents with symptoms of fatigability of the bulbar and ocular muscles and in severe cases weakness of neck, extremities, and trunk, producing a generalized paralysis. Botulism can be fatal by causing respiratory failure and cardiac arrest. Long-term neuromuscular changes result from botulinum exposure in a dose-dependent manner.[57] The incidence of *C. botulinum* infection appears to be increasing, especially in patients with traumatic injuries, drug abusers, and tissue allograft recipients.[57] Botulinum toxin targeting the prejunctional SNARE proteins (see Fig. 21.2) is used therapeutically to treat spasticity or spasm in certain neurologic diseases (e.g., torticollis) and cosmetically to treat wrinkles. In effect, botulinum toxin causes a chemical denervation, resulting in the correction of muscle spasm or wrinkles. Local injection for therapeutic purposes generally results in localized paresis, although systemic effects have been reported.[58] Although botulinum toxin causes upregulation of muscle AChRs, increased sensitivity and not resistance to NMBs has been observed. This is possibly related to marked decrease in margin of

safety as the result of decreased ACh release induced by botulinum toxin.[57] SCh-induced hyperkalemia, however, has been reported following botulinum toxin poisoning.[16]

Neuromuscular Junction in Acquired Pathologic States

Stroke and Spinal Cord Injury

Dysfunction of central motor neurons as the result of spinal cord trauma or stroke is associated with muscle weakness or paralysis. This causes a reduction in evoked ACh that leads to upregulation of immature AChRs.[43] Upregulation of immature AChRs results in susceptibility to SCh-induced hyperkalemia (see Fig. 21.6). The onset of vulnerability is not well defined, but on the basis of several case reports it ranges from 1 week to several months after injury and can persist for years or indefinitely depending on the degree of denervation.[16,17] These uncertainties warrant the avoidance of SCh in these patients.

Burns/Trauma/Critical Illness

Thermal injury, direct muscle trauma, and infection are all associated with increased AChR expression, especially at sites proximate to the injury.[59] The concomitant presence of disease-induced immobilization can contribute to increased AChR expression and altered sensitivity to muscle relaxants. Chronic treatment with NMBs commonly used in the intensive care unit to facilitate mechanical ventilation also upregulates AChRs, not only because of immobilization but also as a result of antagonism of the receptor itself. Infections that invariably produce upregulation of AChRs are those by clostridial species that produce toxins that cause paralysis by inhibiting the release of ACh. Infection with other pathogenic microorganisms can also lead to upregulation of AChRs. In all these conditions there is not only an increase in the number of AChRs but also a change in receptor isoforms. The duration of AChR upregulation in critically ill, burn, or trauma patients has not been defined, but eventually it reverts to normal with recovery but may take several months (>1 year).

Immobility

Prolonged immobility is associated with muscle atrophy owing to disuse. Although motor neurons remain intact, immobility results in a relative increase in $2\alpha_1\beta_1\gamma$ and α_7 AChRs. The result is a resistance to nondepolarizing NMBs and increased sensitivity to depolarizing SCh. Resistance to nondepolarizing NMBs has been reported to emerge as early as 4 days after immobilization and hyperkalemic cardiac arrest after the administration of SCh as early as 5 days after immobilization.[43,60] After remobilization, these abnormalities should revert to normal but the duration of the restorative process can take months and depends on the severity of the illness.[4] Based on these findings it is prudent to avoid SCh in patients who have been immobilized for more than 48 to 72 hours.

Emerging Developments

Disruption of signaling at the NMJ is both a planned intention of the anesthesiologist as well as an unintentional consequence of a myriad of drugs, toxins, and concurrent illness. Despite the central role of the NMJ in perioperative care, our understanding of and skill at manipulating the NMJ is deficient. Through the introduction of new and powerful research techniques, a more detailed understanding of neuromuscular transmission is emerging. Several examples of emerging developments in our understanding of neuromuscular physiology, monitoring, and the role of muscle relaxants in critical illness are discussed in the following sections.

Train-of-Four Fade and Monitoring of Neuromuscular Function

A previous study had suggested that during repetitive nerve stimulation, prejunctional AChRs ($\alpha_{3\beta2}$) enhance further mobilization of ACh by a positive feedback mechanism to maintain twitch tension, and that block of prejunctional nicotinic AChRs by nondepolarizing NMB attenuates this enhanced mobilization of ACh, which results in fade.[61] Subsequent studies using specific antagonists indicated that blocking prejunctional ($\alpha_{3\beta2}$) AChRs decreases ACh release by the nerve, but fade was not observed concomitantly. However, fade was manifested when the ($\alpha_{3\beta2}$) blocker was administered together with high Mg^{2+} concentrations in the extracellular fluid.[39] Higher Mg^{2+} levels alone can decrease the margin of safety of neurotransmission, resulting in fade. Botulinum toxin, which also decreases ACh release by a prejunctional mechanism, causes no fade, although it decreases twitch tension.[57] In contrast, the cobra snake venom, α-bungarotoxin, which binds exclusively to postjunctional AChRs, causes TOF fade. Similarly, fade is observed during repetitive nerve stimulation of patients with myasthenia gravis, a disease with decreased functional postjunctional AChRs.[62] More recently in an elegant in vivo study, Petrov and colleagues demonstrated the α_7 AChRs present in nerve terminal Schwann cells act as a sensor for the release. Excess spillover of ACh during inhibition of acetylcholine esterase leads to activation of α_7 AChRs in Schwann cells with decrease of ACh release and depression of nerve-mediated twitch tension.[42] The relative importance of $\alpha_{3\beta2}$ versus α_7 AChRs in the decrease of ACh is unknown. Regardless, fade and/or decrease of twitch tension observed during TOF stimulation and neuromuscular monitoring can be due to prejunctional and/or postjunctional factors, and reflects a decreased margin of safety or efficiency of neurotransmission that requires intervention.

Postoperative residual paralysis, reflected by TOF less than 0.90, is a risk factor for postoperative pulmonary complications.[2,3] However, anesthesiologists in the United States and the European Union do not routinely monitor neuromuscular block using TOF responses despite its utility to prevent postoperative residual curarization. Some authors strongly advocate that perioperative monitoring of evoked neuromuscular responses that assesses reversal from paralysis should be the standard of care.[63,64] Although European and some American experts seem to agree on this statement, there does not seem to be a consensus in the United States. A survey of the current management of neuromuscular block suggests a lack of agreement among anesthesia providers about the best way to monitor neuromuscular function.[65] It is now well established that tactile or visual evaluation of TOF evaluation is prone to error.[64] Muscle function returns to normal when the TOF is more than 0.90 with or without reversal drugs. The accepted gold standard for neuromuscular monitoring is mechanomyography. However, its application and use is almost exclusively for research purposes. There is no consensus, however, whether objective measures using acceleromyography, kinemyography, or electromyography are equally effective. Important limitations of these latter devices for routine monitoring of residual paralysis are that they are cumbersome in the clinical setting and are sometimes unreliable because of external factors. Significant postoperative residual paralysis continues to be a clinical problem (see Chapter 22).

Muscle Relaxants in Critical Illness

Muscle relaxants are used in the intensive care unit to produce effective synchronous mechanical ventilation, decrease energy expenditure, and prevent high intrathoracic or intracranial pressure during coughing and suctioning.[17,66,67] Several reports, however, implicate severe muscle weakness with the use of muscle relaxants in the intensive care unit.[68,69] Muscle relaxants produce a state of complete immobilization leading to disuse atrophy and even a denervation-like state, evidenced by the upregulation of AChRs throughout the muscle membrane.[70,71] Thus immobilization (disuse) alone and profound immobilization produced by muscle relaxants can aggravate systemic disease–induced muscle wasting in critically ill patients.

Despite the reported deleterious effects of muscle relaxants on muscle function, some reports validate the beneficial effects of muscle relaxants on oxygenation, survival, and/or increased time off the ventilator without increasing muscle weakness.[67,72] Synchronous ventilation with the use of small tidal volumes and limitation of end-inspiratory lung stretch with reduced plateau pressure might account for these improved benefits.[73] NMBs have also been shown to have antiinflammatory properties (decrease of cytokine release) in both rodent and in vitro studies,[74,75] although controversy exists as to whether these antiinflammatory properties are mediated by α_1- or α_7-containing AChRs. Thus the use of muscle relaxants in the intensive care unit can have beneficial or deleterious effects; guidelines for the appropriate use of muscle relaxants in perioperative period need consensus and refinement.

Key Points

- Neuromuscular transmission in skeletal muscle occurs when a quantum of acetylcholine from the nerve ending is released and binds to nicotinic acetylcholine receptors (AChRs) on the postjunctional muscle membrane. These AChRs on the endplate respond by opening channels for the influx of sodium ions and subsequent endplate depolarization leads to muscle contraction. Activation is terminated when acetylcholine immediately dissociates from its receptor and is hydrolyzed by acetylcholinesterase.
- Neuromuscular transmission is a complex and dynamic process in which the effects of drugs are composites of actions that vary with drug, dose, activity in the junction and muscle, time after administration, presence of anesthetics or other drugs, and the age and condition of the patient.
- Classically, transmission of an impulse from the motor nerve to muscle by the mature neuromuscular junction (NMJ) was viewed as a "static" relay associated with limited plasticity for nerve growth or formation of new synaptic contacts. Now it is well established that adult NMJs constantly undergo structural remodeling influenced by a variety of factors, including endogenous mediators/hormones, age, disease and/or injury.
- NMJ disorders can be classified as inherited and acquired, or anatomically as presynaptic, synaptic, or postsynaptic. The etiology of the dysfunction can also be classified as autoimmune, congenital, pharmacologic, toxic, or traumatic.
- Age-associated degeneration of the NMJ is a key event leading to functional denervation, muscle wasting, and weakness. Despite these structural and functional changes associated with aging, it appears that an adequate margin of safety for transmission is generally maintained until late in life. Obviously, genetic factors and acquired disease states can influence the maintenance or deterioration of the integrity of the neuromuscular apparatus.
- The common defect of all disorders of the NMJ is a decrease in the margin of safety for neuromuscular transmission, which can fail at any point from the motor neuron to nerve terminal to the muscle endplate (synapse) or muscle itself. If the endplate potential fails to reach the threshold for the muscle fiber, an action potential is not generated, the muscle fiber does not contract, and neuromuscular transmission fails.
- The complexities of normal neuromuscular function are altered by many pathologic states not originally thought to involve the NMJ such as sepsis or acute respiratory distress syndrome, causing substantial morbidity and mortality.
- In some pathologic states such as denervation, burns, immobilization, inflammation, and sepsis, there is upregulation of immature AChRs, resulting in susceptibility to succinylcholine-induced hyperkalemia. In most of these acquired pathologic states encumbered above, there is also resistance to neuromuscular effects of nondepolarizing neuromuscular blockers.

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Neuromuscular Blockers and Reversal Drugs

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Historical Perspective

The nondepolarizing neuromuscular blocking agent (NMBA) d-tubocurarine has been used for 500 years as a paralyzing poison. In the 16th century, Sir Walter Raleigh reported that hunters in South America were using darts and arrows dipped in curare to paralyze their living targets. Curare, the poison of the plant *Strychnos toxifera*, and its active component, d-tubocurarine, were isolated in the 1930s.[1,2] d-Tubocurarine was introduced into clinical practice in 1942 to induce neuromuscular block.[3] It was not widely used until the second half of the 20th century, when maintenance of neuromuscular blockade during surgery became widely accepted.[4] Clinical use of these agents facilitates endotracheal intubation and mechanical ventilation, improving surgical conditions,[4] and recent data suggest that neuromuscular blocking agents have the potential to improve the outcome in patients with respiratory distress syndrome.[5] Since the introduction of d-tubocurarine into clinical practice, the use of NMBAs has become common. In 2010, more than 100 million patients received NMBAs throughout the world, 80% of them nondepolarizing NMBAs.

While the use of NMBAs has allowed the development of modern anesthesia and surgery,[6] their use is not without risk. Shortly after the introduction of NMBAs into clinical practice, Beecher and Todd reported an increased mortality in patients who had received NMBAs as part of their anesthetic.[7] While their conclusions on cause and effect have been criticized,[8] it has now become clear that residual effects of NMBAs can adversely impact patient outcome.[9,10] As reported by Beecher, unrecognized residual paralysis negatively affects ability to breathe and protect the airway. While the introduction of the intermediate-acting NMBAs rocuronium, vecuronium, and cisatracurium into clinical practice in the early 1990s initially decreased the incidence of residual neuromuscular blockade,[11] more recent data indicate that as surgical and anesthetic practices and the definition of inadequate recovery of neuromuscular function have evolved, the incidence of residual neuromuscular block, even with these shorter-acting compounds, remains high.[12,13]

Neuromuscular Blocking Agents

Clinical Utility

Administration of NMBAs for tracheal intubation decreases the incidence of postoperative upper airway trauma-related symptoms[14–16]

Abstract

Nondepolarizing neuromuscular blocking agents were introduced into clinical practice more than 60 years ago. Throughout the world, millions of patients receive neuromuscular blocking agents as part of their general anesthetic each year. With use, increased recognition of complications, pharmacologic advances, the ability to monitor depth of neuromuscular blockade, and changes in surgical practice, a better understanding of neuromuscular blockade and its reversal is developing. Because of this, long-acting neuromuscular blocking agents are rarely, if ever, used in the clinical setting; new neuromuscular blocking agents that can be easily reversed and new reversal agents that can reverse even profound neuromuscular blockade are being developed. The goal of this work is to ensure that neuromuscular blockade can be easily, quickly, and reliably reversed and that the safety of providing neuromuscular blockade intraoperatively will increase.

Keywords

neuromuscular blockade
residual neuromuscular blockade
nondepolarizing neuromuscular blocking agents
reversal agents
sugammadex
neostigmine

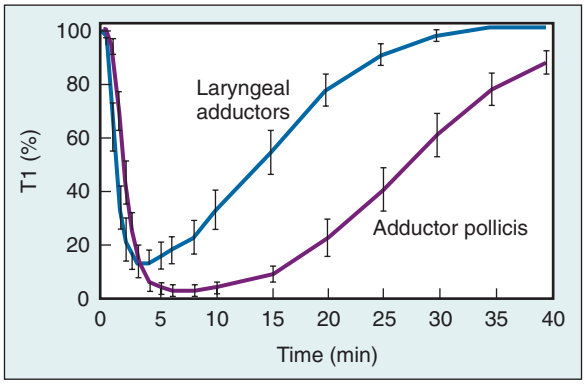
by decreasing the likelihood of tissue trauma, including vocal cord injury and resulting postoperative hoarseness.[15] Administering NMBAs to mechanically ventilated patients with acute respiratory distress syndrome (ARDS) in the intensive care unit for a short period may improve their outcome. Neuromuscular blockade decreases the need to overdose anesthetics in order to decrease reflex movement. It also facilitates surgical exposure and minimizes potentially deleterious complications of intraoperative patient movement.[17] It is not, however, a substitute for an adequate depth of anesthesia. While neuromuscular blockade decreases the likelihood of patient movement, it does not guarantee the absence of pain, recall, and patient movement throughout a surgical procedure; patients can move even when their response to neuromuscular stimulation is significantly reduced (1 or 2 responses to train-of-four [TOF] stimulation).

Since spontaneous recovery of neuromuscular function after administration of a neuromuscular blocking agent does not happen quickly and is not instantaneous even with the administration of an appropriate dose of an anticholinesterase, maintaining a deep level of relaxation throughout a surgical procedure, especially ocular or laparoscopic surgery, might not allow enough time during closure for complete recovery of neuromuscular function. There are a number of possible solutions to ensure adequate recovery of muscle strength at the end of a surgical procedure. First, NMBAs are not always required to optimize surgical conditions.[18] Alternatively, depth of block can be allowed to decrease as the surgical procedure nears completion, allowing for a greater degree of spontaneous recovery before administration of the anticholinesterase. Most recently, it has been possible to use a selective relaxant binding agent rather than an anticholinesterase to facilitate recovery from either rocuronium- or vecuronium-induced neuromuscular block. The "optimal" depth of neuromuscular block to provide the best surgical conditions depends on both the surgical procedure and the anesthetics that are being administered. Administration of volatile anesthetics potentiates NMBAs.[19] Whether profound paralysis (post-tetanic count of 1–3) always improves surgical conditions is currently a matter of debate[19–21]; additional work is necessary to determine whether increased use of deep levels of neuromuscular blockade improves or worsens patient outcomes, such as an increase in the odds of hospital readmission within 30 days after surgery. An association between the intraoperative dose of NMBA and 30-day readmission after abdominal surgery has been demonstrated.[22]

Effects in Different Muscle Groups

The effects of NMBAs are different in different muscles owing to their physiologic differences (Chapter 21). The diaphragm is less susceptible to the effects of NMBAs than either peripheral muscles or pharyngeal upper airway dilator muscles. Additionally, recovery of diaphragmatic function occurs more rapidly than in muscles of the extremity, such as the adductor pollicis, which is the muscle commonly used in clinical practice for monitoring depth of neuromuscular block following administration of an intubating dose of a nondepolarizing NMBA. The resistance of the diaphragm to neuromuscular blockade can be explained by the release of a greater number of acetylcholine-containing vesicles from presynaptic terminals following neural stimulation and the presence of a greater number of postjunctional nicotinic acetylcholine receptor binding sites than exist in peripheral muscles.[23]

In clinical practice, the response of the adductor pollicis muscle to stimulation of the ulnar nerve is recommended for monitoring, as recommendations for dosing of NMBAs are based on the response of this neuromuscular unit to stimulation. When used, its response is assessed by either visual or tactile evaluation. While other superficially located neuromuscular units can be monitored, their response to neuromuscular stimulation will be different than that of the adductor pollicis in the same patient. This occurs because different neuromuscular units have different sensitivities to NMBAs and different time courses for onset of and recovery from neuromuscular block[24,25] (Fig. 22.1). This has been attributed to different blood flow to these different muscles.[26] Typically, when a patient's arms are tucked and not available for monitoring, the posterior tibial nerve that innervates the plantar muscles of the foot, the common peroneal nerve that through the deep peroneal nerve innervates the muscles of the anterior compartment of the leg, or the facial nerve that innervates the muscles used for expression, may be used for monitoring depth of neuromuscular blockade. When dosing of NMBAs based on the results of monitoring at these different sites, the differences in their response to neural stimulation must be considered. The mimetic muscles recover more quickly than those of the periphery and the depth of block in response to a dose of an NMBA is less profound than that in the arm or the leg. While different sites can be monitored, dosing recommendations for NMBAs are based on the response of the adductor pollicis to stimulation of the ulnar nerve.



• **Fig. 22.1** Onset of and recovery from vecuronium-induced neuromuscular block (0.07 mg/kg) at the larynx and the adductor pollicis. The larynx is relatively resistant to neuromuscular blockade. (Adapted from Donati F, Meistelman C, Plaud B. Vecuronium neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis. *Anesthesiology*. 1991;74:833–837.)

Monitoring Neuromuscular Function

The degree of interpatient variability regarding the effects of NMBAs and the potential adverse consequences of their residual effects at the conclusion of an anesthetic are the reasons for the importance of adequately monitoring their effects in clinical practice. Unfortunately, it is not possible to detect reliably residual neuromuscular block with either clinical tests of muscle strength[27] or with commonly used qualitative monitors of neuromuscular function.[28,29]

Reduced strength of contraction during repetitive stimulation of a peripheral nerve is observed with neuromuscular transmission failure, as in myasthenia gravis,[30] and during recovery from NMBAs. Proper muscle function requires different degrees of reserve in terms of neuromuscular transmission depending on the test chosen to assess strength. The ability of a test to measure the effects of an NMBA increases with the force of output required to pass the

test. Assessment of fade during a supramaximal 100 Hz tetanic stimulation can detect subtle effects of NMBAs, whereas twitch height after low-frequency stimulation (e.g., 0.1–1 Hz) decreases only after blockade of 90% of acetylcholine receptors.[31] This is clinically important, as clinicians typically assess neuromuscular function using nontetanic stimulation of peripheral skeletal muscles, usually TOF or double-burst stimulation (DBS). While tetanus will detect more subtle degrees of neuromuscular block, it is not a commonly used monitor of residual neuromuscular block. Tetanic stimulation is exceptionally uncomfortable for the patient who is not deeply anesthetized. In addition, interpretation of the significance of fade in the response to tetanic stimulation is difficult and the degree of fade has not been correlated with the TOF response. Therefore, its utility is of relatively limited clinical value.

Modes of Stimulation

Train-of-Four

The technique of train-of-four monitoring was introduced into clinical practice in 1970.[32] For measurement of the TOF response, muscle contraction is induced by stimulation of the corresponding motor nerve 4 times with a frequency of 2 Hz. Any superficial neuromuscular unit can be monitored in this fashion. In response to TOF stimulation, the TOF ratio (TOFR) is the ratio of the amplitude of the fourth response to the first response.[33] If neuromuscular transmission is intact, TOF stimulation causes 4 twitches with essentially identical amplitudes and a resulting TOFR of 0.9 to 1.0. In contrast, after complete relaxation, TOF stimulation does not result in any muscle contraction and the TOF count (number of responses to TOF stimulation) is zero. Return of the first twitch is described as a TOF count of 1. This is followed by consecutive recovery of the second, third, and fourth twitches (TOF counts of 2, 3, and 4, respectively). Once the fourth response to stimulation has returned, the fade between the first and the fourth twitch responses can be measured as the TOFR. For example, if the amplitude of the fourth twitch is 50% of the amplitude of the first twitch, the TOFR is 0.5. The TOF count can also be used to estimate the recovery of the first twitch in the TOF to baseline values. When the first response in the TOF returns, strength of the first response is approximately 10% of baseline values. Similarly, return of the second, third, and fourth responses corresponds to recovery of the first twitch in the TOF to approximately 20, 35, and 45% of baseline values.

While the TOF will measure residual paralysis, ability to accurately detect degree of fade in the TOF response is not reliable once the TOFR has recovered to 40% or more.[34] In other words, it is impossible to reliably detect fade in the TOFR if there is anything less than 60% fade, and a TOFR of 92% looks and feels the same as a TOFR of 52%.

Double-Burst Stimulation

DBS was developed to improve detection of residual neuromuscular block.[29] Fade in the strength of the second response relative to the first response is used to determine whether residual neuromuscular block is present. Fade in the response to stimulation is equivalent to the fade detected with TOF stimulation; however, the reliability of qualitative monitoring with DBS is improved over that of TOF monitoring. DBS allows detection of fade when the second response is 60% of the first response. This occurs because the presence of the second and third responses to TOF stimulation makes the comparison of the strength of the fourth response to that of the first response more difficult. With DBS, either 2 or 3 short bursts of high-frequency tetanic stimuli are administered, followed by a second series of 2 or 3 short bursts of tetanic stimuli, each resulting in a single muscular contraction. With full recovery from neuromuscular block, 2 equal responses occur with DBS.

Typically, NMBA doses of two times the ED_{95} (the dose required to cause, on average, 95% suppression of muscle response to stimulation) or greater are administered to facilitate tracheal administration in a reasonable time after induction of anesthesia. However, smaller doses of NMBA might be adequate to optimize intubating conditions during deep anesthesia.[14] While recovery is monitored with either TOF or DBS, onset of block is typically determined with the response to single-twitch stimuli. For this pattern of stimulation, supramaximal stimuli are applied at a frequency of 0.1 Hz, or once every 10 seconds. Onset of neuromuscular blockade is defined as the fade in twitch response with each subsequent stimulus. When larger doses of NMBA are administered, onset of 100% neuromuscular block occurs more quickly and is more likely to develop in all patients.[35] Doubling the dose of rocuronium from 0.6 to 1.2 mg/kg shortens the average onset time from 1.5 minutes to just under 1 minute, and decreasing the dose slows onset time.[14]

When monitoring the effect of NMBAs administered to facilitate tracheal intubation, monitoring at the muscles of the face more accurately indicates adequacy of neuromuscular block in the upper airway.[36,37] When lower doses of NMBAs are administered, depth of block at a particular time (60 or 90 seconds after administration) cannot be guaranteed since onset of NMBAs is quite variable.[38] As shown in Fig. 22.2,[14] patients developed 0% to 80% neuromuscular block following administration of 0.1 mg/kg rocuronium. Just as onset of block is variable with small doses of NMBAs, recovery is quite variable following administration of larger doses[39–41] (see Fig. 22.2). This emphasizes the importance of monitoring depth of neuromuscular block throughout surgery to avoid overdosing.

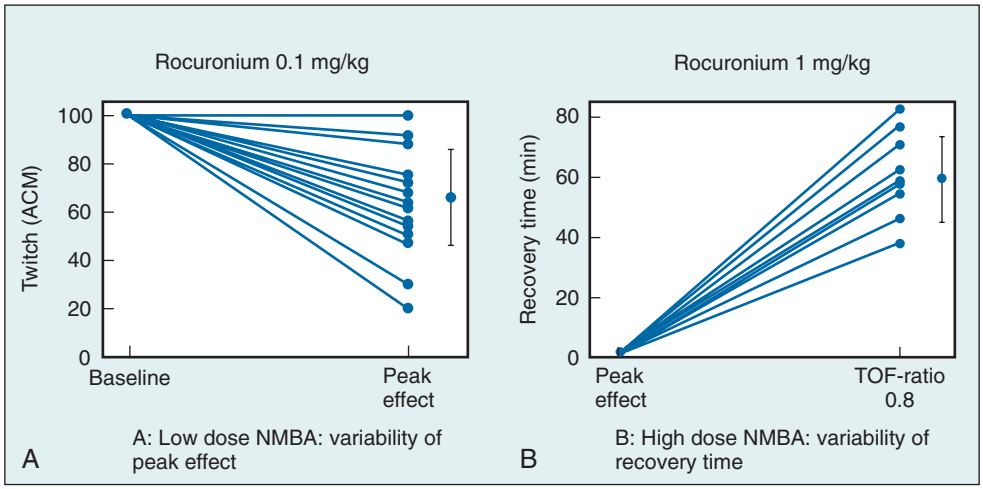
While the most commonly used monitors of depth of neuromuscular block are qualitative monitors,[42] quantitative monitors of depth of block are also available. Without using these quantitative devices, clinicians can reliably detect only severe residual neuromuscular block (TOFR < 0.4),[43] as twitch height at a TOFR between 0.4 and 1.0 is likely to be perceived as 4 responses that are similar.[30,44] Optimally, quantitative methods for measurement of the evoked muscular response should be used. Commercially available techniques include mechanomyography, electromyography, kinemyography, and acceleromyography.[45,46]

Structure–Activity Relationships

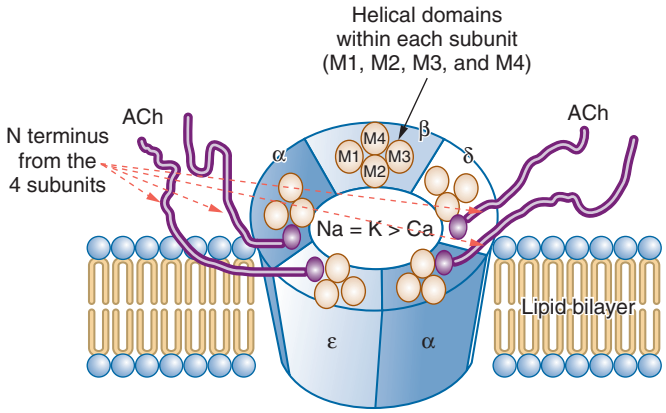
Neuromuscular Blocking Activity

Structure–activity relationships of NMBAs can affect neuromuscular blocking activity, pharmacokinetic properties, and side effect profiles.[47,48] Since the early classification of NMBAs as rigid bulky molecules with amine functions incorporated into ring structures,[49] much has changed in our understanding of the relationships between their structures and function as neuromuscular blockers.

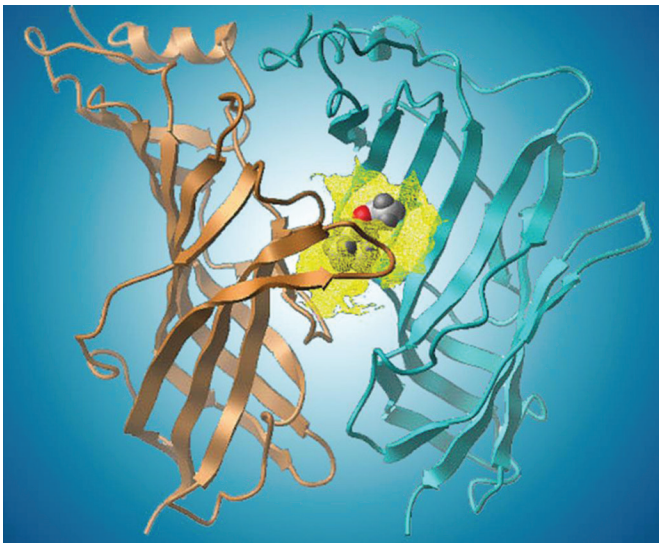
Postjunctional nicotinic acetylcholine receptors are pentameric members of the superfamily of ligand-gated ion channels. The mature form consists of 5 subunits: 2-alpha (α), 1-delta (δ), 1-beta (β) and 1-epsilon (ε); (Fig. 22.3).[144] In the immature (fetal) form of the receptor, the ε subunit is replaced by a gamma (γ) subunit. The N- and C-terminal ends of each subunit are extracellular, with the protein traversing the lipid bilayer membrane 4 times—creating



• **Fig. 22.2** Variability of peak effect and recovery times determined with mechanomyography in response to low-dose (A) or high-dose (B) rocuronium in 20 children aged 2 to 8 years. In one child, rocuronium 0.1 mg/kg did not decrease muscle strength whereas muscle strength was almost completely abolished in another. After rocuronium 1 mg/kg, recovery of a train-of-four ratio to 0.9 varied from 30 to 85 minutes. (Adapted from Eikermann M, Hunkemoller I, Peine L, et al. Optimal rocuronium dose for intubation during inhalation induction with sevoflurane in children. *Br J Anaesth*. 2002;89:277–281.)



• **Fig. 22.3** Schematic representation of the pentameric nicotinic acetylcholine receptor spanning the lipid bilayer. The acetylcholine binding sites are located at the interface of the α-ε and α-δ subunits. Each subunit contains 4 domains (M1–4) that span the lipid bilayer. Influx of Na+ is the same as efflux of K+, which is greater than the influx of Ca+. *Ach,* Acetylcholine; *Ca,* Ca+; *K,* K+; *Na,* Na+. (Adapted from Naguib M, Flood P, McArdle JJ, et al. Advances in neurobiology of the neuromuscular junction: Implications for the anesthesiologist. *Anesthesiology.* 2002;96:202–231.)



• **Fig. 22.4** A structural model of the interface of the acetylcholine binding site in human muscle nicotinic acetylcholine receptor. Each binding site in the acetylcholine receptor has different affinities for neuromuscular blocking agents. (From Dilger PD, James P, Vidal BA, et al. Roles of amino acids and subunits in determining the inhibition of nicotinic acetylcholine receptors by competitive antagonists. *Anesthesiology* 2007;106:1186–1195.)

four transmembrane domains (M1, M2, M3, and M4). The M2 domain of each subunit creates the central ion pore (see Fig. 22.3).

The agonist binding sites of the acetylcholine receptor are located at the interface of the α-δ and α-ε subunits, where the N-terminus of each subunit works with that of the other to form the acetylcholine binding site. In order for the central pore of the receptor to open, allowing for influx of Na^+ and Ca^{2+} and efflux of K^+, two agonist molecules must be bound to the receptor. The two binding sites are not identical (the δ-subunit contributes to one receptor and the ε-subunit contributes to the other). These differences lead to varying affinity at each of the sites for agonists[50,51] and competitive antagonists.[52] The fetal α-γ binding site is generally more sensitive than the mature α-ε one.[52] The α-γ binding site has up to a 500-fold greater affinity for d-tubocurarine than does the α-δ binding site.[53] In mature receptors, the α-δ binding site appears to be more important than the α-ε site in determining receptor affinity for pancuronium, vecuronium, and cisatracurium.[54]

The complexity of fitting large molecules, such as NMBAs, into acetylcholine receptor agonist binding sites (Fig. 22.4) implies that conformational changes in the NMBA are required.[55,56] While these compounds are large, they can bend and fold and will seek a conformation requiring minimal energy. Interaction of the γTyr117 with the 2-N and 13′ positions of d-tubocurarine[57] suggests that allosteric changes in either the antagonist or receptor occur with binding. Several different sites of interaction in the binding site are involved in binding the agonist or antagonist.[57] Different

affinities at each of these sites might account for some of the synergism observed when different NMBAs are administered to the same patient.[58]

In addition to opening the ion channel of postjunctional acetylcholine receptors, neuromuscular transmission is modulated by a population of prejunctional cholinergic receptors. These prejunctional nicotinic and muscarinic receptors on the motor nerve endings are involved in modulating the release of acetylcholine into the neuromuscular junction. Prejunctional nicotinic receptors are activated by acetylcholine and function in a positive feedback control system that serves to maintain the availability of acetylcholine when demand is high. Their activation mobilizes acetylcholine-containing synaptic vesicles toward the release sites in the presynaptic membrane of the motor nerve terminal but not the actual process of acetylcholine release. These presynaptic receptors are morphologically different than those at the postjunctional membrane and consist of 3 α subunits and 2 β subunits. All NMBAs tested—including mivacurium, atracurium, cisatracurium, d-tubocurarine, pancuronium, rocuronium, and vecuronium—inhibit presynaptic nicotinic acetylcholine receptors in a concentration-dependent fashion, with concentrations causing 50% inhibition of response in the micromolar range.[59] Vecuronium and d-tubocurarine are the most potent inhibitors of this receptor subtype; mivacurium is the least potent. Inhibition of this presynaptic receptor by NMBAs is primarily competitive, but d-tubocurarine and vecuronium also produce noncompetitive inhibition. The effect of blockade of these presynaptic receptors during periods of stress, such as TOF or tetanic stimulation, likely accounts for the fade observed in the TOF response with small doses of NMBA, such as those administered prior to succinylcholine to decrease the incidence and severity of fasciculations of NMBAs.[60,61]

Onset of Block

Onset of neuromuscular block is proportional to the dose of NMBA administered and is typically described in terms of multiples of the ED_{95} (the dose causing 95% suppression of twitch response; Table 22.1). The use of larger doses of NMBAs is limited for a number of reasons, including an increase in the duration of action (the time required from administration to recovery of twitch height to 25% of baseline, which increases with increasing dose),[35] more frequent and severe side effects,[62,63] and the limited benefit of increasing the dose beyond a certain point.[64]

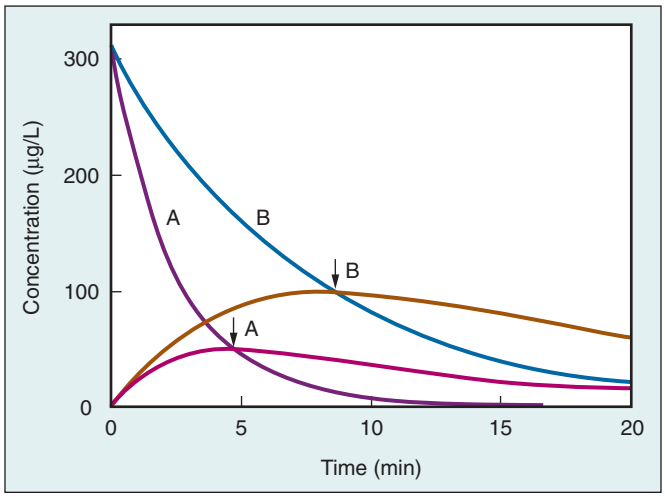
Potency is inversely related to onset of neuromuscular block; the more potent a compound, the slower its onset of effect. Larger doses of NMBAs with a lower potency are administered, increasing the driving force for diffusion of these agents down their concentration gradient to the acetylcholine receptors of the neuromuscular junction. This has been found for the aminosteroid compounds,[65] a series of tetrahydroisoquinolinium chlorofumarates,[66] 3 structurally unrelated compounds with long durations of action[67] and for compounds of different durations of action and structure.[68] Pharmacokinetic modeling with a fixed number of acetylcholine receptors shows that there is a set requirement for the number of antagonist molecules needed to establish block; an ED_{95} greater than 0.1 mg/kg is necessary for a rapid onset of effect.[69]

In order to exert its effect, an NMBA must be able to enter the neuromuscular junction, which is facilitated by its lipophilicity.[70] The speed of onset of neuromuscular block after administration of an NMBA is also related to the speed of recovery of neuromuscular function.[71] This appears to be due to the more rapid equilibration between the plasma and effect compartment with drugs that are metabolized or redistributed more quickly (Fig. 22.5).[70,72–74] Because of this, equipotent doses of mivacurium[75] or succinylcholine[76] have a slower onset of effect in patients who are homozygous for atypical butyrylcholinesterase.

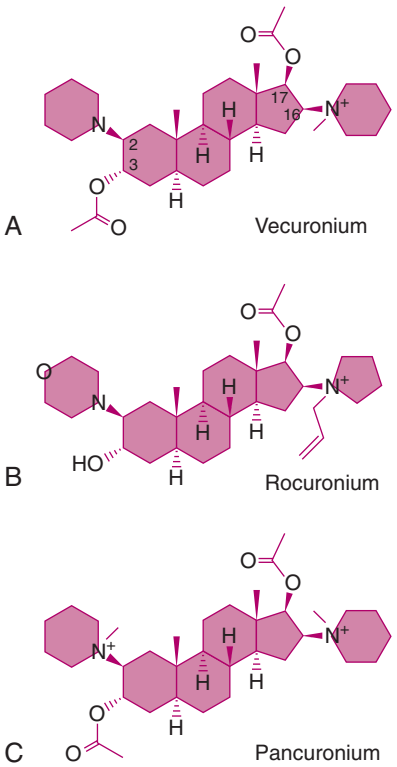
Understanding some of the factors impacting onset of neuromuscular block has led to the development of NMBAs with a faster onset of effect. Structural changes in the steroidal NMBAs have yielded compounds with a rapid onset of effect (Fig. 22.6). In clinical practice, these structural changes provide a real alternative to succinylcholine when intubation within 60 seconds is required. Rocuronium, 1 to 1.2 mg/kg, provides rapid onset of neuromuscular block and can be used effectively in the setting of a rapid sequence induction and intubation.[61,77,78]

TABLE 22.1 Intubating Doses of Neuromuscular Blocking Agents

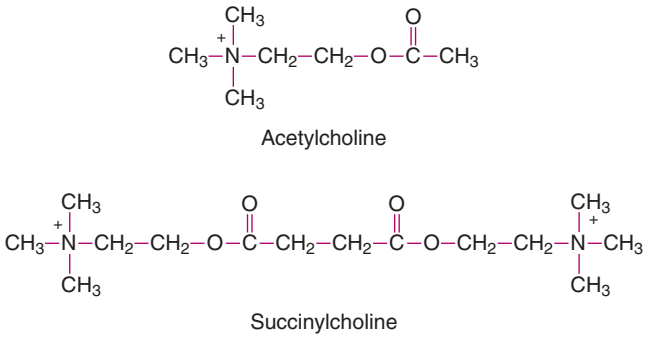
Neuromuscular Blocking Agent	Approximate ED_{95} (mg/kg)	Intubating dose (× ED_{95})
Pancuronium	0.07	1–1.5
Rocuronium	0.30	2–4
Vecuronium	0.05	2–4
Atracurium	0.25	2
Cisatracurium	0.05	3–5



• **Fig. 22.5** Theoretical changes following a bolus dose of neuromuscular blocking agent (NMBA), in its concentration in plasma *(blue and purple lines)* and in the biophase *(orange and pink lines)* over time. The concentration of the NMBA in plasma decreases as a result of its clearance from plasma *(curve A)*. The concentration in the biophase increases because of transfer of NMBA from plasma to the biophase. When the concentrations in plasma and biophase are similar *(arrow A)*, the maximum concentration in the biophase is reached and the peak effect is obtained. The time required for equilibration between plasma and the biophase determines the onset time. If the NMBA is administered in the same dose but has a reduced clearance *(curve B)*, equilibration occurs later *(arrow B)* and at a higher maximum concentration in the biophase. Onset time is prolonged and the peak effect is greater. (Adapted from Beaufort TM, Nigrovic V, Proost JH, et al. Inhibition of the enzymic degradation of suxamethonium and mivacurium increases the onset time of submaximal neuromuscular block. *Anesthesiology*. 1998;89:707–714.)



• **Fig. 22.6** The chemical structures of vecuronium, rocuronium, and pancuronium. The acetyl ester in the steroid nucleus of vecuronium is absent in rocuronium. Changing the substitution at positions 2 and 16 likely contributes to the more rapid onset of block of rocuronium.[68,69] Replacement of the methyl group at the quaternary nitrogen with a larger allyl group contributes to a decrease in potency.[68,70,71].



• **Fig. 22.7** The chemical structure of succinylcholine. It is comprised of 2 molecules of acetylcholine groups bound together at their acetate methyl groups.

Recovery From Neuromuscular Block

As the understanding of the adverse effects of residual neuromuscular blockade is increasingly appreciated, development of NMBAs with a shorter duration of action has become a priority. The two ways to shorten recovery from neuromuscular block involve decreasing the concentration of NMBA at the acetylcholine receptor relative to acetylcholine (Fig. 22.7). This can be done through increasing the metabolism of the NMBA to rapidly remove it from the neuromuscular junction or inhibiting the activity of acetylcholinesterase so that the availability of acetylcholine at the neuromuscular junction is increased. Both mivacurium and succinylcholine have short durations of action and are metabolized by butyrylcholinesterase. Two more recently studied compounds, gantacurium[79–81] and CW002,[81–83] are inactivated through adduction of the amino acid cysteine at the fumarate double bond. Administration of exogenous cysteine shortens the duration of action of CW002 through its rapid inactivation so that acetylcholine available at the neuromuscular junction is more effective. Sugammadex, a selective relaxant binding agent, is a cyclodextrin that encapsulates steroidal NMBAs so that they can no longer bind to the acetylcholine receptor (see the section Antagonism of Residual Neuromuscular Block, to follow). Calabadions provide a broader (increased binding selectivity) and expanded (reversal of benzylisoquinolines) spectrum of indications.[84,85]

Neuromuscular Blocking Agents

Depolarizing Neuromuscular Blocking Agents: Succinylcholine

Structure and Metabolism

Succinylcholine is comprised of 2 molecules of acetylcholine bound at their acetate methyl groups (see Fig. 22.7). This structural similarity to acetylcholine allows it to stimulate acetylcholine receptors as an agonist, causing muscle depolarization. Unlike acetylcholine, it is not a substrate for the acetylcholinesterase found at the neuromuscular junction that terminates normal neuromuscular transmission. Rather, its neuromuscular blocking activity is terminated by diffusion out of the neuromuscular junction into plasma, where it is hydrolyzed by butyrylcholinesterase (also known as plasma cholinesterase) to succinylmonocholine and choline. While succinylmonocholine is also a depolarizing agent, it is less potent than its parent compound succinylcholine. The hydrolysis of succinylcholine by butyrylcholinesterase accounts for its short elimination half-life, which is estimated to be less than 1 minute.[86]

Pharmacodynamics

The ED_{95} of succinylcholine is 0.3 to 0.6 mg/kg.[87,88] Because of its mechanism of action, rapid clearance and relative lack of potency (ED_{95} > 0.1 mg/kg), its onset of effect is faster than that of any other available neuromuscular blocking drug. A dose of 1 mg/kg results in complete block in 1 minute,[89,90] and recovery to a twitch height of 90% in 13 minutes or less.[91] Slightly larger doses may be required to achieve complete neuromuscular block of all muscles during tetanic stimulation.[92]

Recovery of neuromuscular function after administration of succinylcholine is prolonged by reduced concentration or activity of butyrylcholinesterase. Reduced butyrylcholinesterase—whether because of malnutrition, chronic disease, pregnancy, or medications—prolongs the duration of action of succinylcholine.[93–101] Since spontaneous recovery occurs faster than with any available nondepolarizing NMBA, the increased duration of action is not usually appreciated in the clinical setting. Significant decreases in butyrylcholinesterase activity can double the time required for full recovery of 100% twitch response from 10 to 22 minutes.[91] In contrast, patients who are homozygous for atypical butyrylcholinesterase metabolize succinylcholine much more slowly such that the depolarizing NMBA becomes a long-acting neuromuscular blocking agent.

The dibucaine number is used to identify individuals who have an atypical genotype for butyrylcholinesterase. Dibucaine inhibits normal butyrylcholinesterase more than it does the abnormal

enzyme. It will inhibit normal butyrylcholinesterase activity by about 80%; in individuals who are homozygous for the atypical variant, dibucaine inhibits the activity by only 20%. The enzyme activity of individuals who are heterozygous for atypical butyrylcholinesterase is inhibited by approximately 50%.

Clinical management of patients homozygous for atypical butyrylcholinesterase who have received succinylcholine involves conservative management with ventilator support and continued sedation until spontaneous recovery. Prolonged block with succinylcholine, based on monitoring of neuromuscular function, appears similar to that of a nondepolarizing agent with fade in the TOF response. Administration of an anticholinesterase to facilitate recovery of neuromuscular function is unlikely to be effective since it will also inhibit butyrylcholinesterase,[102–104] further slowing hydrolysis of the compound.

Adverse Effects

Adverse effects associated with administration of succinylcholine are numerous (Table 22.2), most of which are due to its depolarizing action. Since it stimulates autonomic nervous system cholinergic receptors, all types of arrhythmias–including tachycardia, bradycardia, junctional rhythms, and ventricular dysrhythmias—may occur (see Chapter 13). To some extent, cardiac dysrhythmias following succinylcholine administration are dose related. Large doses can cause tachycardia[105] and, in adults, administration of a second dose within a few minutes of the first can cause bradycardia or a nodal rhythm.[106] Succinylcholine also lowers the threshold for arrhythmias induced by circulating catecholamines and increases circulating catecholamine levels.[107]

Succinylcholine activates acetylcholine receptors, causing depolarization and activation of perijunctional voltage-gated Na^+ channels, which allows generation of muscle contraction to neural stimulation (see Chapter 21). Opening of muscle acetylcholine receptors and voltage-gated Na^+ channels allows Na^+ influx and K^+ efflux. In healthy patients, this typically results in an increase in plasma K^+ of 0.5 mEq/L. In patients with significant burns,[108] hemiparesis, or any other pathologic process that causes proliferation of extrajunctional nicotinic receptors,[109–114] the response to succinylcholine can be exaggerated due to activation of α-7 receptors, which have a prolonged response to agonists, as well as extrajunctional nicotinic receptors.[115] The resulting hyperkalemia can be great enough to result in dysrhythmias and cardiac arrest. Critically ill patients could be at high risk of hyperkalemia after succinylcholine because one or more factors producing nicotinic receptor upregulation can be present. The risk of hyperkalemia after succinylcholine injection is strongly associated with the length of ICU stay; succinylcholine should not be administered for that reason in patients who stayed in an ICU for longer than 1 to 2 weeks.[116,117]

The mechanisms of increases in intragastric, intracranial, and intraocular pressure are probably less clinically relevant and have not been fully elucidated but include muscular contraction due to activation of acetylcholine receptors and cortical neuronal activation by stretch receptors. The observed increases can be attenuated by prior administration of small doses of nondepolarizing NMBAs, such as 3 mg d-tubocurarine, 1 mg pancuronium, or 1 mg vecuronium, 2 to 3 minutes prior to administration of succinylcholine.[118-120]

When administered with volatile anesthetics to susceptible patients, succinylcholine can trigger malignant hyperthermia, although by itself it is a weak trigger.[121] A recent review article[122] describes the pharmacology of triggering agents in malignant hyperthermia (see Chapter 21).

TABLE 22.2 Adverse Effects of Succinylcholine

Cardiac dysrhythmias
Hyperkalemia
Myalgias
Masseter spasm
Increased intracranial pressure
Increased intragastric pressure
Increased intraocular pressure

Nondepolarizing Neuromuscular Blocking Agents

Benzylisoquinolinium Compounds

There are currently two NMBAs of this class available in the United States: atracurium and cisatracurium. Both are intermediate-acting compounds, with a clinical duration of action of 20 to 50 minutes.

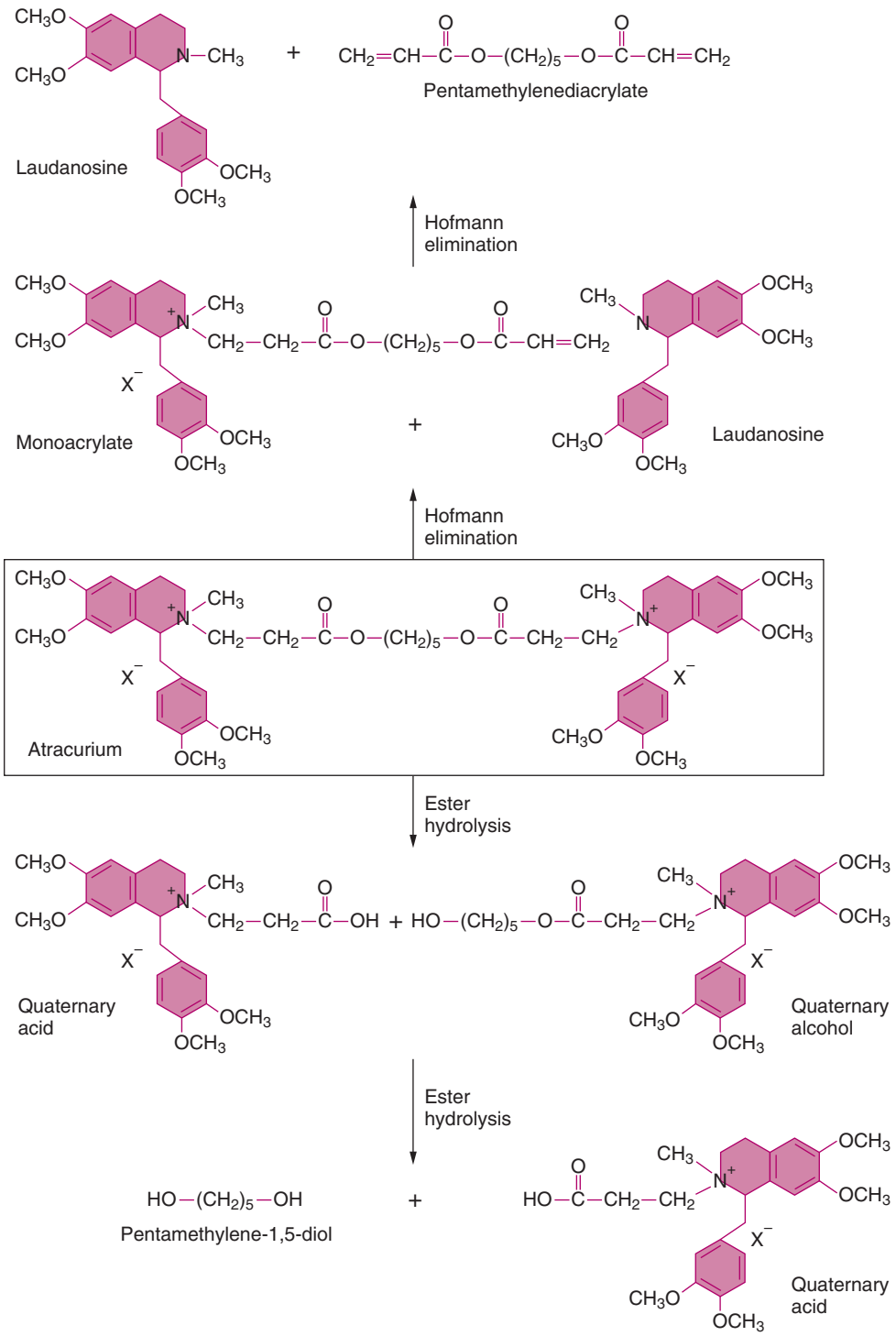
Atracurium

Atracurium (Fig. 22.8), a bisquaternary ammonium benzylisoquinoline compound, is relatively potent with an ED_{95} of 0.2 to 0.25 mg/kg[123] and an intermediate duration of action. Following administration of two times the ED_{95}, maximal block occurs in 2.5 minutes, recovery to 10% of baseline twitch amplitude (approximately 1 twitch in the TOF) occurs in 40 minutes,[124] and complete spontaneous recovery of neuromuscular function in about 60 minutes.[123]

Atracurium was the first NMBA introduced into clinical practice that does not undergo elimination by enzyme-catalyzed hydrolysis or excretion by the kidneys or liver. Chemical degradation to inactive products by Hofmann elimination (see Fig. 22.8) is primarily responsible for its inactivation; enzymatic ester hydrolysis and renal elimination have lesser roles.[125,126] While some studies have found that ester hydrolysis can be responsible for metabolism of as much as 66% of an atracurium dose,[127] and that renal elimination can have a larger role in the pharmacokinetics of atracurium than initially appreciated,[128] its spontaneous degradation is unique and allows for relatively consistent pharmacokinetics and pharmacodynamics even in patients with advanced hepatic and renal disease.

Hofmann elimination is a spontaneous, base-catalyzed, nonenzymatic chemical reaction by which atracurium is cleaved into two molecules.[125,129] Alkalosis increases resistance to atracurium-induced neuromuscular block,[130] while hypothermia slows the temperature-dependent breakdown so that less atracurium is required to maintain a given depth of neuromuscular block.[131,132] The ester hydrolysis involved in atracurium metabolism is catalyzed by a nonspecific esterase distinct from the butyrylcholinesterase hydrolysis for hydrolysis of succinylcholine and mivacurium.

Since recovery from atracurium-induced neuromuscular block occurs by nonsaturable chemical degradation rather than metabolism or redistribution, there is little to no cumulative effect with repeat doses or continuous infusion.[123,133,134] Thus, sequential doses administered at the same point in spontaneous recovery have the same recovery characteristics as the preceding dose. With continuous



• **Fig. 22.8** Degradation and inactivation of atracurium. Atracurium undergoes either Hofmann elimination to yield a monoacrylate and laudanosine or ester hydrolysis to yield a quaternary alcohol and a quaternary acid. Laudanosine, the major product, is excreted in urine and bile. (Adapted from Basta SJ, Ali HH, Savarese JJ, et al. Clinical pharmacology of atracurium besylate [BW 33A]: A new non-depolarizing muscle relaxant. *Anesth Analg.* 1982:61;723–729.)

infusion, no dosing revisions are required to maintain a stable depth of neuromuscular block, even with prolonged infusions.[135,136]

With prolonged infusions of atracurium, the elimination half-life is about 20 minutes[137–140] with a clearance of 4.5 to 10 mL/kg/min, greater than that of long-acting NMBAs. Because of the relative lack of renal or hepatic elimination of atracurium compared to steroidal NMBAs, the pharmacokinetics and duration of action of atracurium are not affected by renal disease.[139,141,142] Similarly, elimination half-life is not prolonged in patients with cirrhosis.[143]

Normal aging is accompanied by a number of physiologic changes, including decreases in hepatic and renal blood flow and

function along with changes in the anatomy and function of the neuromuscular junction.[144] In spite of the changes at the neuromuscular junction, the depth of block at a given plasma concentration of NMBA is the same in young and elderly individuals.[145] It appears that observed differences in the effects of NMBAs associated with aging are due to altered pharmacokinetics. As expected, prolongation of the effect of NMBAs in the elderly is less pronounced or not apparent for compounds that rely less on the kidney and liver for their elimination. For example, the duration of block with atracurium is not increased with advanced age.[146] Subsequent studies have shown that while the clearance of atracurium is similar in elderly and young patients, elimination half-life is prolonged in the elderly.[147,148] Clearance remains constant because, while elimination through the renal pathway is decreased in the elderly, clearance through pathways that are not end organ dependent is increased.

Cisatracurium

Cisatracurium (Fig. 22.9) is the 1 R-cis 1′R-cis stereoisomer of the 10 stereoisomers that comprise atracurium and has been available since 1995. Its development involved isolation and testing of individual stereoisomers from the mixture that are found in atracurium, with selection and further development of the one with fewer side effects. It is approximately 3-fold more potent than atracurium (ED_{95} of 0.05 mg/kg)[147] and, like atracurium, has an intermediate duration of action. Because of its greater potency, however, its onset of effect is considerably slower than that of atracurium.[147] For this reason, doses of 3 to 5 times the ED_{95} are recommended for endotracheal intubation.[148] In contrast to atracurium, administration of these large doses is not associated with histamine release and the resultant hypotension or tachycardia.[149,150]

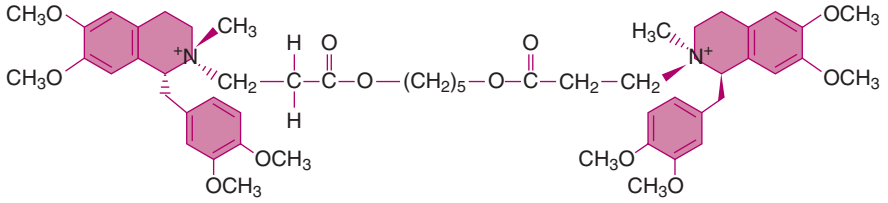
Like atracurium, cisatracurium undergoes Hofmann elimination. Clearance, elimination half-life, and volume of distribution are the same when doses of the ED_{95} or twice the ED_{95} are administered.[151] The clinical duration of action (the time required from administration of a dose to recovery of 25% T1 height) defines the earliest time that reversal of residual neuromuscular block is recommended. The duration of action of 0.1 mg/kg cisatracurium ($2\times ED_{95}$) is 45 minutes. Doubling the dose to $4\times ED_{95}$ increases it to 68 minutes and doubling it again to $8\times ED_{95}$ increase it by another 23 minutes, equivalent to the elimination half-life of the compound.[149]

Hofmann elimination accounts for 77% of total clearance of cisatracurium and renal elimination 16%.[152] The slight dependence on renal elimination likely contributes to the increase in elimination half-life of 14% and decrease in clearance of 13% observed in patients with renal failure.[153] In spite of these pharmacokinetic changes in patients with renal dysfunction, no prolongation of the duration of action is found following a bolus dose.[154] As with atracurium, both volume of distribution and clearance of cisatracurium are increased in patients with hepatic failure.[155] Elimination half-life is unchanged; thus, the clinical duration of action and 25% to 75% recovery interval (the time required to recover from 25% to 75% of baseline muscle strength) is unchanged in patients with liver failure.[155]

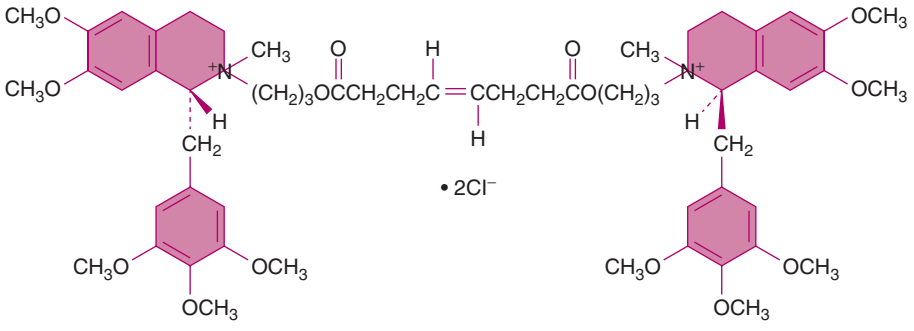
Recovery from cisatracurium-induced neuromuscular block occurs over the same time course in elderly surgical patients as it does in young adults.[156,157] An increase in the volume of distribution and no change in the clearance in the elderly likely account for the prolongation of elimination half-life by up to 28%.[156,157] The decrease in renal function that occurs with normal aging could account for these pharmacokinetic differences. The prolonged elimination half-life of cisatracurium in the geriatric patient does not affect recovery from neuromuscular block induced with a bolus dose of the NMBA.

Mivacurium

Mivacurium (Fig. 22.10) is the only short-acting nondepolarizing neuromuscular blocking agent available. While its availability in the United States has decreased since 2006, it is available throughout Europe.



• **Fig. 22.9** Chemical structure of cisatracurium. Cisatracurium is the 1 R-cis 1′ R-cis stereoisomer that is one of 10 stereoisomers comprising atracurium.



• **Fig. 22.10** Chemical structure of mivacurium. Mivacurium is a bis-benzylisoquinolinium diester compound. Like atracurium, it consists of a series of stereoisomers. The 3 stereoisomers that comprise mivacurium are a *cis-trans*, a *trans-trans*, and a *cis-cis* isomer based on the orientation of the methylated phenolic groups.

The ED_{95} of mivacurium is 0.08 mg/kg and its in vitro elimination half-life is 3.1 minutes.[158] Its short duration is due to metabolism by butyrylcholinesterase[158,159] to quaternary amino alcohols and quaternary monoesters.[97] These metabolites are excreted in the urine with half-lives of 90 minutes.[160] Since they are less than 1/100th as potent as mivacurium, they are unlikely to contribute to neuromuscular block. In a study of the impact of mivacurium in unsedated volunteers, subtle symptoms of weakness persisted after full recovery of muscle strength.[161] Following administration of 0.2 mg/kg mivacurium (2.5× ED_{95} dose) to facilitate intubation, recovery to a TOFR of 0.7 occurred in less than 30 minutes,[162] which is shorter than recovery following administration of comparable doses of any other NMBA.

Mivacurium is comprised of a mixture of 3 stereoisomers, one of which—the *cis-cis* isomer—is less than one-tenth as potent as the *trans-trans* and *cis-trans* isomers. The pharmacodynamics and pharmacokinetics of mivacurium are due largely to the more potent *trans-trans* and *cis-trans* isomers. The half-lives of these isomers are 2 to 3 minutes and their clearances are more than 50 mL/kg/min, with the *cis-trans* isomer having a clearance of 100 mL/kg/min.[163] These rapid clearances are due to extensive metabolism by butyrylcholinesterase. In patients who are homozygous for atypical butyrylcholinesterase, mivacurium behaves as a long-acting neuromuscular blocking agent.[164,165]

Doses of 0.15 to 0.25 mg/kg mivacurium have been used to facilitate endotracheal intubation. Onset of maximal effect of these doses ranges from 2 to 3.3 minutes.[159,166,167] The short duration of action of mivacurium can lead to inadequate intubating conditions following administration of a 2× ED_{95} dose as it is being metabolized while a block is developing. Recommendations have been made to monitor onset of NMBAs at the orbicularis oculi rather than the adductor pollicus since the more centrally located neuromuscular unit of the orbicularis oculi more accurately represents onset of block in the muscles of the airway than response of the adductor pollicis to stimulation.[168] Use of the larger doses of mivacurium, 0.3 mg/kg, administered as a rapid intravenous bolus, can cause hypotension and tachycardia—especially in hemodynamically compromised patients. These hemodynamic changes are due to histamine release that occurs with administration of mivacurium at 0.2 mg/kg or greater.[159] Hemodynamic side effects of large doses of mivacurium can be mitigated by use of divided doses to administer a large dose without histamine release.[169]

Steroidal Compounds

Pancuronium

Pancuronium (see Fig. 22.6) is the only available NMBA with a long duration of action. It was the first of the steroidal agents introduced into clinical practice (1968). While once widely used, its use has become increasingly infrequent since the introduction of shorter-acting compounds. Doses of 0.08 and 0.1 mg/kg used for tracheal intubation have durations of action (the time from administration to 25% recovery of muscle function) of 86 and 100 minutes, respectively.[156,157] Its long duration of action is due to its primary elimination through the kidney.[156] While it undergoes some deacetylation in the liver,[156] it is primarily eliminated through the kidney—resulting in its long duration of action.

Patients with liver disease due to either cholestasis or cirrhosis have an increase in the volume of distribution of pancuronium,[170–172] which contributes to the relative resistance of these patients to pancuronium-induced block.[173] However, clearance of pancuronium in these patients is decreased, and elimination half-life and duration of action are prolonged.[170–172]

As would be predicted, clearance of pancuronium is decreased and elimination half-life is prolonged in patients with renal failure.[174,175] Similarly, clearance is decreased and duration of action of pancuronium is prolonged in patients of advanced age.[176] With an increase in duration of action of about 30 minutes from 44 minutes to 73 minutes,[176] there is an appreciable increase in the interval at which repeat doses are to be administered to maintain a stable depth of block in elderly individuals.

Vecuronium

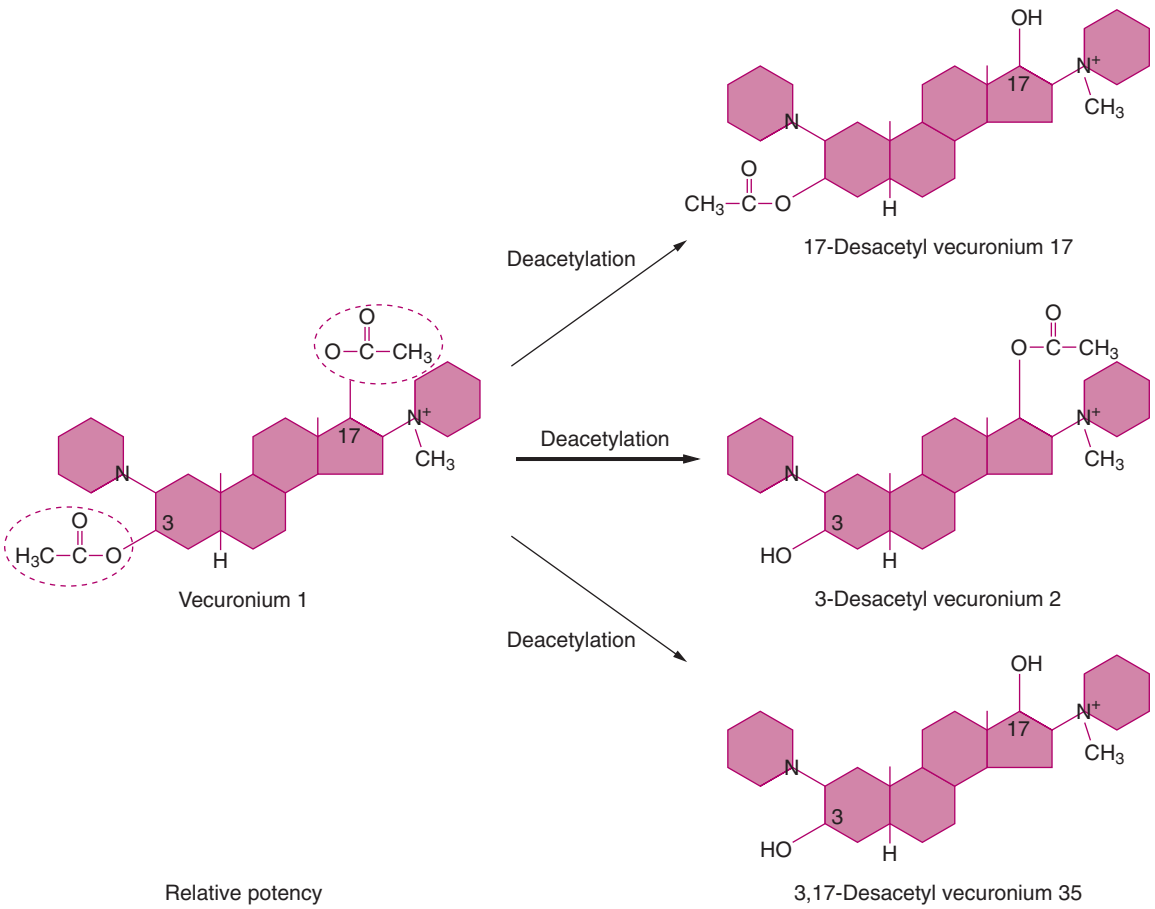
Vecuronium (see Fig. 22.6) was the first nondepolarizing NMBA with an intermediate duration of action to be introduced into clinical practice. With both a shorter duration of action and a lack of hemodynamic side effects, it set a standard against which all subsequent NMBAs were compared. Vecuronium is a potent NMBA (ED_{95} is 0.05 mg/kg) with a duration of action of 40 minutes.[35,177,178] Typically, twice the ED_{95} is administered to facilitate tracheal intubation. Doses of 5 to 6 times the ED_{95} can be administered for more rapid onset of effect [179] without significant hemodynamic side effects.[180]

Vecuronium is the 2-desmethyl derivative of pancuronium. The lack of one methyl group at the quaternary ammonium of the 2 position increases its lipid solubility and significantly alters its degree of metabolism. While it undergoes more hepatic metabolism than pancuronium, it is primarily eliminated unchanged in the urine and bile: up to 40% is cleared through the bile[181,182] and 20% to 30% is eliminated in the urine.[183,184] The remainder of the compound is metabolized by the liver to 3-desacetylvecuronium, 17-desacetylvecuronium and 3,17-desacetylvecuronium[182,185] (Fig. 22.11). The 3-desacetyl metabolite has neuromuscular blocking activity.[185,186] While only 5% is excreted in the urine as the 3-desacetyl metabolite,[187] the prolonged duration of action of vecuronium in critically ill patients with renal failure has been attributed to accumulation of this metabolite.[188]

The elimination half-life of vecuronium is not as reliably prolonged and the clearance not consistently decreased in patients with renal failure as they are with pancuronium. This is likely because the liver is the primary route of clearance of vecuronium. There is a tendency for elimination half-life and duration of action to be increased with renal failure.[184,189–191] Decreased vecuronium infusion rates are required to maintain a stable depth of block[191] and maintenance doses have an increased duration of action[192] in patients with renal failure. Although vecuronium can be used safely in these patients, dose requirements can be unpredictable.[193]

The impact of hepatic failure on the pharmacodynamics of vecuronium is more predictable owing to its dependence on the liver for its elimination. Volume of distribution is increased, clearance is decreased, and elimination half-life prolonged[194,195] in patients with either cholestasis or cirrhosis. Accordingly, the duration of action of vecuronium is increased in this patient population.[183,194,196]

In elderly patients, the clearance of vecuronium is decreased by 30% to 55%[197,198] and elimination half-life is increased by 60%.[197] This results in a 3-fold prolongation of the 25% to 75% recovery interval (the time from recovery from 25% of baseline muscle strength to 75% of muscle strength) of vecuronium[197,199] following either a bolus dose of 0.1 mg/kg or an infusion to maintain 90% suppression of twitch height for 90 minutes. In one study[198] of the dynamics and kinetics of vecuronium in the elderly, after discontinuation of a steady-state infusion of vecuronium to 70% to 80% depression of twitch response, there was no difference in recovery interval between groups. The difference in the results of this study[198] is difficult to explain but might be due to administration



• **Fig. 22.11** Metabolism of vecuronium. Metabolism in the liver leads to the primary metabolite, 3-desacetyl vecuronium, which is almost as potent as vecuronium and is cleared more slowly from the plasma. (From Agoston S, Seyr M, Khuenl-Brady KS, et al. Use of neuromuscular blocking agents in the intensive care unit. *Anesthesiol Clin North Am*. 1993;11:345–359.)

of vecuronium just sufficient to establish neuromuscular block before being allowed to recover.

Rocuronium

Rocuronium (see Fig. 22.6) has an intermediate duration of action[35] and an onset that is more rapid than either vecuronium or atracurium.[200] With an ED_{95} of 0.3 mg/kg,[201–204] it is about six times less potent than vecuronium.[201] A dose of 2 times the ED_{95}, rocuronium has an onset of less than 2 minutes and a clinical duration of less than 40 minutes.[35] Increasing the dose of rocuronium to shorten its onset of effect increases its duration of action.[35]

Rocuronium, like vecuronium, is eliminated primarily through hepatobiliary excretion with < 1% metabolism.[205] Since only 10% is eliminated through the kidneys,[206] it is even less dependent on renal elimination than vecuronium. In patients with renal failure, the clearance of rocuronium is either marginally decreased[207] or unchanged,[208] the volume of distribution is increased, and the elimination half-life is prolonged.[208] The duration of action of single and repeat doses of rocuronium can be prolonged in patients with hepatic failure.[209–211] This is due to a decrease in its clearance and an increase in its volume of distribution.[209,210,212]

Advanced age impacts the pharmacokinetics and duration of action of rocuronium. The duration of effect of repeat doses is prolonged[213] and the clinical duration of 0.6 mg/kg is almost doubled.[214] Clearance of the compound is significantly decreased in this patient population.[214]

Postoperative Residual Neuromuscular Block

Postoperative residual neuromuscular block is not uncommon after an anesthetic during which NMBAs have been administered.[11,40,41] More than 30 years ago, an evaluation of neuromuscular transmission following surgery found residual paralysis (TOFR < 0.7) in 42% of patients who had received gallamine, pancuronium, or d-tubocurarine.[44] Intermediate-acting NMBAs were not yet available when that study was done. More recent studies report that residual block from intermediate-acting NMBAs can be present in one-third to two-thirds of patients following anesthesia.[11,26,215] The frequency of residual neuromuscular blockade depends on the manner in which depth of block is monitored and the approaches used to reverse neuromuscular block at the conclusion of procedures.[33,216–219]

Pulmonary function—as defined by respiratory rate, tidal volume, forced expiratory volume, and forced vital capacity—is usually recovered once the TOFR is greater than or equal to 0.6 at the adductor pollicis muscle. Based on this information, a TOFR of 0.6 was historically felt to be adequate recovery from the effects of NMBAs. Recent data, though, suggest that even lesser degrees of neuromuscular blockade can adversely affect respiratory function, airway patency, and airway protective reflexes (i.e., coughing and swallowing).

Respiratory Effects

A summary of the effects of subtle degrees of residual neuromuscular block on respiratory function and pharyngeal patency is presented in Table 22.3. In volunteers, even slight neuromuscular block, as reflected by a TOFR at the adductor pollicis muscle of 0.8 to 0.9, impairs the hypoxic ventilatory response and increases the risk of upper airway collapse.[42,45,215,220–224] A TOFR of 0.8, and possibly even 0.9, is associated with alterations in upper airway closing pressure (P_{crit}), upper airway dilatory muscle function, and airway volume during inspiration.[219] Of note, tidal volume, vital capacity, and lung volume are typically normal at this low level of residual neuromuscular block. Thus, residual neuromuscular block can be present in the muscles of the upper airway at levels of block at which the respiratory muscles are unaffected.[222,225] These effects are difficult to measure and can go undetected by the clinician.

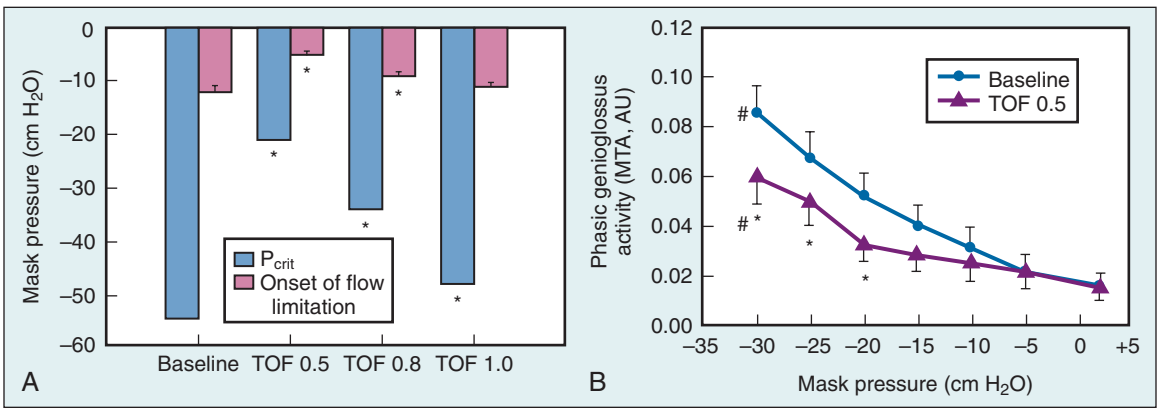
TABLE 22.3 Effects of Partial Neuromuscular Block on Respiration

	MONITORING OF ADDUCTOR POLLICIS MUSCLE		
Ventilatory Function	**TOFR = 0.5**	**TOFR = 0.8**	**TOFR = 1.0**
Tidal volume	Normal	Normal	Normal
Forced vital capacity	↓↓	Normal	Normal
Pharyngeal function (swallowing)	↓↓↓	↓↓	↓
Upper airway patency (closing pressure)	↓↓↓	↓↓	↓
Hypoxic respiratory response	↓↓	↓↓	Normal

TOFR, Train-of-four ratio.
↓↓↓: Consistently impaired
↓↓: Frequently impaired
↓: Usually normal

Risk of Airway Collapse

To maintain upper airway patency during inspiration, the forces generated by the respiratory "pump" muscles, which decrease intraluminal upper airway pressure and therefore tend to collapse the airway, have to be balanced by reflex dilating forces of the pharyngeal musculature. In the absence of neuromuscular block, this stability is maintained in part by the genioglossus muscle, the activity of which almost quadruples at negative pharyngeal pressures. This compensatory increase in the activity of the genioglossus muscle with inspiration is markedly impaired during even minimal neuromuscular block (TOFR = 0.8; see Fig. 22.12). This leads to an increase in airway collapsibility and a decrease in airflow with inspiration.[225,226] Partial paralysis markedly increases P_{crit} to less negative values[219] so that the airway collapses more easily during inspiration. The relationship between the decrease in genioglossus activity caused by neuromuscular block and its effects on P_{crit} and airflow are shown in Fig. 22.12. As a result of the susceptibility of the upper airway to collapse during inspiration with minimal



• **Fig. 22.12** Effects of neuromuscular blockade on upper airway patency. Panel A displays the upper airway critical closing pressure (P_{crit}) and the airway pressure associated with the beginning of flow limitation during inspiration in awake healthy volunteers at baseline before neuromuscular blockade, with impaired neuromuscular transmission at train-of-four (TOF) ratios of 0.5 and 0.8 and after recovery of the TOF ratio to unity. Upper airway closing pressure *(blue bars)* significantly increased during partial neuromuscular blockade and was still abnormal once the TOF ratio recovered to unity. Evidence of flow limitation *(purple bars)* was first observed at an average pressure of –12 cm H_2O. With a TOF ratio of 0.5 or 0.8, flow limitation occurred at significantly less negative values of mask pressure, indicating impairment of airway integrity. $P < 0.05$ versus baseline. Panel B shows genioglossus muscle activity as a function of negative mask pressure without *(circles)* and with *(triangles)* partial neuromuscular blockade at a TOF ratio of 0.5. Genioglossus activity increases markedly as negative pressure is applied, but this effect is attenuated with partial neuromuscular block. $P < 0.05$ versus baseline (same mask pressure); $P < 0.05$ versus mask pressure +5 cm H_2O (same level of neuromuscular function). *AU,* Arbitrary units; *MTA,* moving time average. (Adapted from Eikermann M, Vogt FM, Herbstreit F, et al. The predisposition to inspiratory upper airway collapse during partial neuromuscular blockade. *Am J Respir Crit Care Med*. 2007;175:9–15).

degrees of neuromuscular block, forced inspiratory volume in 1 second (FIV_1) is markedly impaired, while forced expiratory volume is maintained during partial paralysis.

In addition to maintenance of airway patency, the genioglossus muscle has an integral role in swallowing. Genioglossus activity during swallowing and maximum voluntary tongue contraction are impaired during residual neuromuscular block[219,226] (see Table 22.3). An increased incidence of misdirected swallowing and a decreased upper esophageal sphincter resting tone occur with minimal neuromuscular blockade (TOFR = 0.5–1) and persists even with recovery of the TOFR to unity.[225,227,228]

Difficulty swallowing can lead to aspiration.[227,228] Although the pharyngeal constrictor muscle is minimally affected, there is reduced upper esophageal sphincter tone with partial neuromuscular blockade. The greater vulnerability of the upper airway muscles to NMBAs cannot be explained by a higher density of nicotinic acetylcholine receptors,[229] differences in fiber size, or differences in fiber-type composition.[230] Some evidence suggests that the sensitivity of the airway dilator muscles to the effects of NMBAs may be explained at least in part by the rapid firing rate of the motor neurons innervating the muscle. Neuromuscular blocking drugs produce a progressive failure of neuromuscular transmission with increasing rates of stimulation.[231] The TOF stimulation that is typically used to test the strength of the adductor pollicis uses a stimulation rate of 2 Hz. In contrast, the firing frequency of the genioglossus muscle during quiet breathing is significantly greater. It is also greater than that of the diaphragm (8–13 Hz as compared to 15–25 Hz at the genioglossus).[232] This may explain the greater sensitivity of the genioglossus muscle to NMBAs and why the genioglossus muscle is more susceptible to NMBAs than the adductor pollicis, as assessed by stimulation at 2 Hz.

Sensitivity of the Musculature of the Airway to Residual Block

There is a growing body of evidence that postoperative residual block results not only in physiologic impairment but also in increased perioperative risk[226,227,233–235] and health care–related costs.[236] While the symptoms of residual neuromuscular block are difficult to recognize,[31,215,237,238] the subtle effects of NMBAs can result in clinically significant consequences.[239,240] The incidence of critical respiratory events—including hypoxemia, hypoventilation, and upper airway obstruction following anesthesia—increases with both the dose and duration of action of an NMBA.[241] Minimal neuromuscular block, defined by a TOFR of 0.7 or 0.8, is associated with an increased incidence of adverse respiratory events, including airway obstruction, moderate to severe hypoxemia, and the development of atelectasis and pneumonia.[233,242,243] In addition to the effects of propofol and other anesthetics on airway tone,[244] even very low levels of residual block can impair skeletal muscle strength[237] and increase patient discomfort after an anesthetic,[245–247] which can delay readiness for discharge after an ambulatory surgical procedure.

Residual neuromuscular block can also have economic consequences. Length of stay in the postanesthesia care unit is significantly longer in patients with a TOFR less than 0.9 compared to patients with a greater degree of recovery of neuromuscular transmission.[236] This results in delayed discharge and substantially increases the chance that other patients will have to wait to enter the recovery area because of lack of available of space.[236] In addition, large doses of NMBAs have been associated with increased costs of care and an increased risk of readmission to the hospital within 30 days.[22]

Use in Critical Care

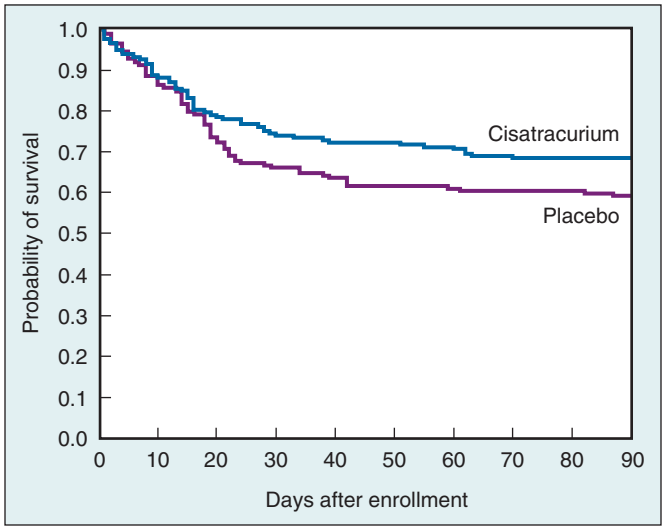
The most common indications for NMBAs in the intensive care unit (ICU) are to facilitate emergent intubation and mechanical ventilation in patients with acute respiratory failure, to reduce oxygen consumption, to prevent shivering, and to control intracranial hypertension.[248] However, the use of NMBAs in critically ill patients is associated with side effects that are summarized in Table 22.4.

The use of NMBAs can be associated with a decrease in procedure-related complications.[249] However, severe complications can occur when insufficiently experienced individuals use NMBAs to facilitate emergent airway management.[250]

In order to control excessive ventilatory drive in patients with severe ARDS, short-term use of NMBAs in the ICU for treatment can be of some benefit[5] (Fig. 22.13). As stated in the Clinical Practice Guidelines for Sustained Neuromuscular Blockade in the Adult Critically Ill Patient, NMBAs can be administered by continuous intravenous infusion early in the course of ARDS for patients with a PaO_2/FIO_2 less than 150.[251] The mechanisms underlying this beneficial effect are unknown, but it is possible that lower

TABLE 22.4 Undesirable Effects of Neuromuscular Blocking Agents in Critically Ill Patients

Effect	Mechanism
Muscle weakness	Persistent failure of neuromuscular transmission Critical illness polyneuropathy Immobilization-induced atrophy of diaphragm
Impairment of ventilation–perfusion distribution Decreased right ventricular end-diastolic volume	Spontaneous breathing abolished
Posttraumatic stress syndrome	Awareness during paralysis



• **Fig. 22.13** Probability of survival through day 90 in patients with acute respiratory distress syndrome receiving cisatracurium to facilitate mechanical ventilation compared to those not receiving a neuromuscular blocking agent. (Adapted from Papazian L, Forel J-M, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363:1107–1116.)

transpulmonary pressures are associated with reduced barotrauma. However, reduction in transpulmonary pressure can also be achieved using sedative agents that lack the adverse effects of NMBAs.[252]

Both the benefits and risks of the use of NMBAs in critically ill patients must be considered when deciding on their use. For example, lack of spontaneous ventilation might decrease the incidence of barotrauma but, in patients with ARDS, breathing spontaneously with ventilator support improves matching of ventilation and perfusion. Additional data suggest that NMBAs exacerbate mechanical ventilation-induced diaphragmatic dysfunction[253] and ICU-acquired muscle weakness.[254] Data suggest that partial neuromuscular blockade facilitates lung-protective ventilation during partial ventilatory support while maintaining diaphragm activity in sedated patients with lung injury.[255] Peripheral nerve stimulation with train-of-four assessment in conjunction with clinical assessment should be used for monitoring the depth of neuromuscular blockade.[254]

Antagonism of Residual Neuromuscular Block

There are several means of enhancing recovery of neuromuscular function. These include increasing acetylcholine concentration at the neuromuscular junction or decreasing plasma concentrations of the NMBA through encapsulation and increased metabolism or increased elimination through the kidneys or liver (Fig. 22.14).[256]

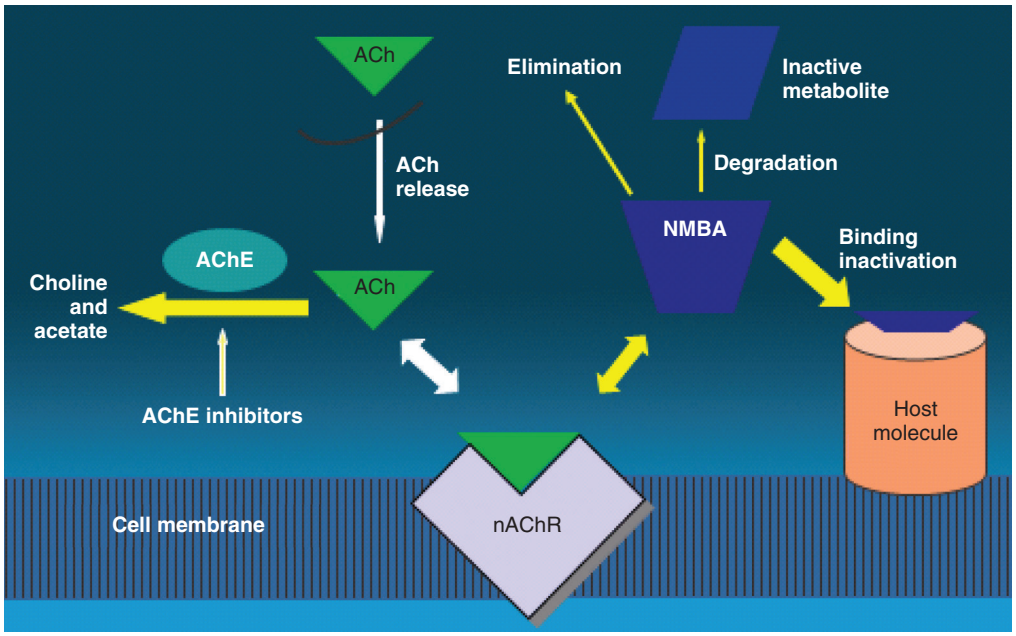
Anticholinesterases

Anticholinesterases used for reversal of neuromuscular blockade inhibit acetylcholinesterases at the neuromuscular junction,[257] which increases the concentration of acetylcholine at the motor endplate to overcome competitive block of nicotinic receptors by NMBAs.[258] Cholinesterase inhibitors are the principal drugs used for reversal of NMBAs and, in some countries, remain the only option.

There is significant variation in antagonism of residual neuromuscular blockade. In contrast to most European countries, where routine antagonism is not the typical practice,[259] the majority of anesthesiologists in the United States antagonize the residual effects of nondepolarizing NMBAs at the end of surgery. This is accomplished through the combined administration of a cholinesterase inhibitor (e.g., neostigmine) and an antimuscarinic agent, such as glycopyrrolate.[27,42] Routine antagonism of neuromuscular block is recommended by some anesthesiologists to ensure complete recovery in all patients regardless of whether depth of block was monitored objectively.[28,260,261] This practice is not without risk, however, as cholinesterase inhibitors can themselves induce muscle weakness when given in the absence of residual of neuromuscular blockade. Additionally, administering an anticholinesterase does not facilitate elimination of the NMBA from the body. Neostigmine blocks acetylcholine receptors, increasing the availability of acetylcholine at the neuromuscular junction. Excessive acetylcholine can cause both a depolarizing and open-channel block.[262]

Determinants of Speed and Adequacy of Recovery

Antagonism of nondepolarizing neuromuscular block with anticholinesterases requires a variable amount of time that depends on several factors. Time from administration to peak effect varies with presynaptic acetylcholine reserve and spontaneous rate of recovery from neuromuscular blockade. The rate of spontaneous recovery depends on the NMBA used, the dose administered, patient temperature, the presence of metabolic abnormalities such as hypokalemia, and concomitant medications. Anticholinesterases



• **Fig. 22.14** Pathways to increase available acetylcholine at the nicotinic acetylcholine receptor and decrease neuromuscular blocking agent (NMBA). Acetylcholine and NMBA compete for the same binding sites in the receptor at the neuromuscular junction. Possible means to increase acetylcholine concentration include inhibiting acetylcholinesterase (AChE) to decrease its metabolism to choline and acetate. To decrease the NMBA at the neuromuscular junction, its plasma concentration has to decrease. This happens through its elimination in the urine or bile, its metabolism to inactive compounds—as occurs with atracurium, cisatracurium, mivacurium, and gantacurium—and its encapsulation by a host molecule such as sugammadex (a selective relaxant binding agent).

should be administered only once spontaneous recovery of neuromuscular function has begun. During anticholinesterase-facilitated antagonism, recovery of neuromuscular transmission is the function of primarily two processes: ongoing spontaneous recovery of neuromuscular function as the NMBA is eliminated from the neuromuscular junction and the increase in acetylcholine at the neuromuscular junction due to the effect of the anticholinesterase.

It takes longer to antagonize profound neuromuscular block than it does moderate or shallow neuromuscular block.[263] Additionally, recovery of muscle strength after administration of anticholinesterase depends on the rate of spontaneous recovery from the NMBA.[264] Anticholinesterase-facilitated recovery from an intermediate-acting NMBA occurs more quickly than that induced with a long-acting compound. Speed of recovery also depends on the anticholinesterase used for reversal. Recovery from a moderate depth of block occurs more quickly following the administration of edrophonium than neostigmine.[265]

If the NMBA is not metabolized more quickly than the anticholinesterase, neuromuscular block can recur (recurarization). Both neostigmine and edrophonium antagonize 90% of d-tubocurarine-induced neuromuscular block for a period of 1 to 2 hours,[266] after which neuromuscular block will recur if the NMBA has not been completely eliminated from the plasma.

There is a limit to what an anticholinesterase can effectively antagonize; profound neuromuscular blockade cannot be reversed. Once the maximum dose of neostigmine (0.07 mg/kg) has been administered, acetylcholinesterase has been maximally inhibited and administration of additional anticholinesterase will not produce greater recovery from residual neuromuscular blockade.[264]

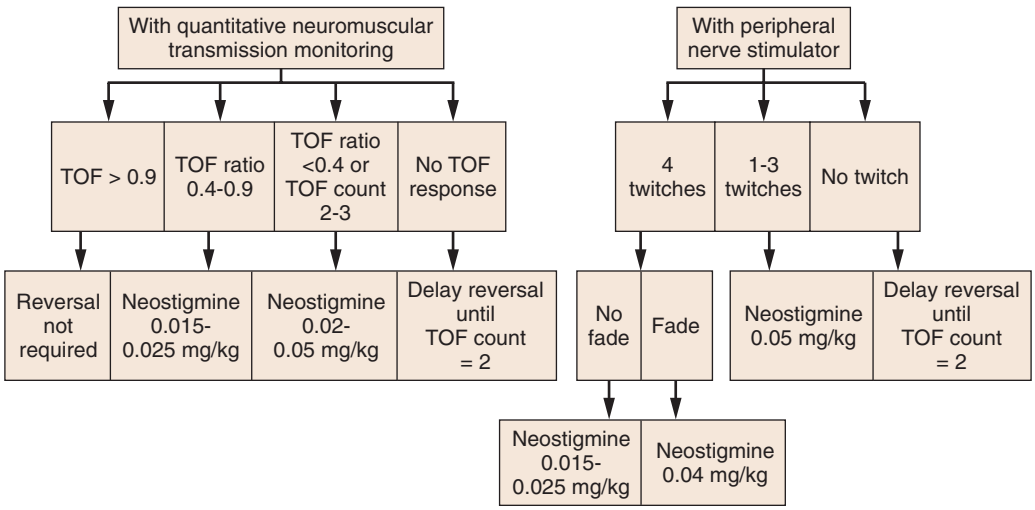
Adverse Effects

The effects of anticholinesterases are not limited to the motor endplate, and administration of these compounds increases acetylcholine concentration at nerve terminals in areas other than the neuromuscular junction.[267] The muscarinic and nicotinic acetylcholine receptors in the parasympathetic system can also be activated,[268,269] causing pronounced vagal effects, such as bradycardia, prolonged QT interval and asystole.[270] Other muscarinic parasympathetic side effects include bronchospasm, increased bronchial and pharyngeal secretions, miosis, and increased intestinal tone. Therefore, anticholinesterases are typically administered in combination with antimuscarinic drugs, such as glycopyrrolate or atropine. These compounds block muscarinic, but not nicotinic, receptors[27] so that neuromuscular block can be antagonized while muscarinic effects are minimized. Antimuscarinic compounds increase the risk of tachyarrhythmias and other effects of antagonism of muscarinic receptor, such as urinary retention, blurred vision, photophobia, mydriasis, xerostomia, dry skin, constipation, nausea, urinary retention, insomnia, and dizziness.

Unnecessary administration of anticholinesterases can itself cause muscle weakness.[39,231] Weakness of the airway dilator muscle genioglossus can lead to upper airway collapse during inspiration. In rats, unnecessary administration of neostigmine (> 0.6 mg/kg) causes diaphragmatic dysfunction.[271] Anticholinesterase administration to healthy volunteers after complete spontaneous recovery from neuromuscular block increased airway collapsibility to the same degree as occurs with a TOFR of 0.5 and reduced compensatory genioglossus activity in response to negative airway pressure.[272]

Dosing

The optimal dose of anticholinesterase depends on the depth of block, duration of action of the NMBA used, timing of the last dose of NMBA relative to administration of the anticholinesterase, and the monitoring technique used. Fig. 22.15 summarizes current recommendations for dosing of anticholinesterases.[27] Ideally, anticholinesterases should be administered only when necessary (i.e., in the presence of residual paralysis). Without objective monitoring of neuromuscular function, it is not possible to discriminate between TOFR values of 0.4 or 0.9. Thus, patients who have completely recovered from NMBAs occasionally receive unwarranted anticholinesterase, putting them at risk of anticholinesterase-induced muscle



• **Fig. 22.15** Neostigmine dosing. The dose of neostigmine depends on both how depth of neuromuscular block is monitored and the degree of recovery. As little as 0.015 to 0.025 mg kg^{-1} of neostigmine is required at a train-of-four (TOF) count of 4 with no fade, whereas 0.04 to 0.05 mg kg^{-1} is needed at a TOF count of 2 or 3. If only a single twitch or none at all can be evoked, neostigmine will not reverse neuromuscular block and antagonism is best delayed until a TOF count of 2 is achieved. (From Kopman AF, Eikermann M. Antagonism of non-depolarising neuromuscular block: current practice. *Anaesthesia*. 2009;64(Suppl 1):22–30).

weakness. The administration of anticholinesterases should optimally be guided by quantitative evaluation of the TOFR. The typical dose of neostigmine for antagonism of profound neuromuscular block (a TOF count of 2) is 0.05 mg/kg and 0.015 to 0.025 mg/kg for antagonism of lesser degrees of neuromuscular block (a TOF count of 4 with no fade).[27,273] Profound block with a TOF count below 2 should not be antagonized with neostigmine because of the risk of inadequate recovery of neuromuscular function.[267,274] No anticholinesterase is required if the TOFR is greater than 0.9 as determined by monitoring with a quantitative monitor of neuromuscular function.

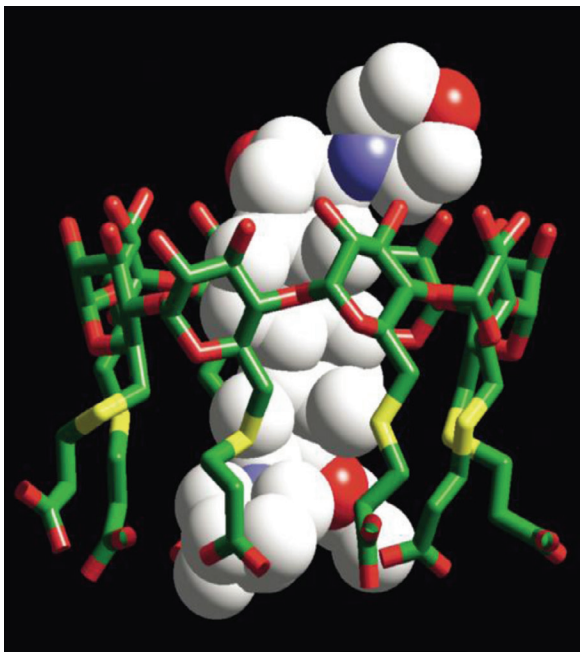
Pharmacokinetics and Pharmacodynamics

Bolus doses of either neostigmine or edrophonium result in peak plasma concentrations within 5 to 10 minutes that decrease rapidly, followed by a slower decline that corresponds to the elimination phase.[266,275] A 2-compartment analysis finds results that are similar for both drugs. The volume of distribution of these anticholinesterases is 0.7 to 1.4 L/kg and their elimination half-lives are 60 to 120 minutes. Clearance is 8 to 16 mL/kg/min, which is greater than the glomerular filtration rate since anticholinesterases are actively secreted. Therefore, in patients with renal failure, in whom the duration of action of NMBAs is likely to be increased, clearance of anticholinesterases is also reduced and elimination half-life increased. This makes dose adjustment of anticholinesterases in patients with renal dysfunction unnecessary.

The anticholinesterases have markedly different onset characteristics, possibly due to the different potency of each agent. Neostigmine is more potent than edrophonium and smaller doses are required to antagonize residual neuromuscular block. During a steady-state infusion of NMBA, the onset of action of edrophonium is 1 to 2 minutes and that of neostigmine is 7 to 11 minutes.[266,275] Similar results have been obtained with neostigmine as an antagonist of either pancuronium or vecuronium or edrophonium as an antagonist of metocurine. Edrophonium has approximately one-twelfth the potency of neostigmine, and its potency increases as spontaneous recovery from neuromuscular block occurs.[252]

Sugammadex

The use of encapsulating agents to reverse neuromuscular blockade is relatively new and offers a unique recovery profile following reversal of rocuronium-induced neuromuscular blockade. Following intravenous administration, molecular containers, such as sugammadex, bind free intravascular guest molecules, resulting in a concentration gradient between the intravascular compartment and the neuromuscular junction. Sugammadex, a selective relaxant binding agent, was specifically designed to bind the steroidal NMBAs rocuronium and vecuronium (Fig. 22.16). As a result of its administration, free NMBA concentration in the plasma decreases, NMBA moves along its diffusion gradient away from the neuromuscular junction, and block of neuromuscular transmission disappears (Fig. 22.17).[276–279] During sugammadex-facilitated recovery, the total concentration of NMBA in the plasma (free and sugammadex bound) increases.[280] Sugammadex significantly reduces time to recovery from rocuronium-induced neuromuscular blockade compared to neostigmine reversal (TOF ≥ 0.9, 107 ± 61 sec vs. 1044 ± 590 sec, respectively).[281] It more rapidly reverses rocuronium-induced neuromuscular blockade than neostigmine antagonizes cisatracurium-induced neuromuscular blockade.[282,283] As a consequence of its rapid reversal of steroidal NMBAs, sugammadex may be an option to reverse neuromuscular blockade in the cannot intubate–cannot ventilate scenario following administration of a large dose of rocuronium.[284,285] Its effective use in this manner, though, requires that it be available in the anesthesiologist's workstation.[286]

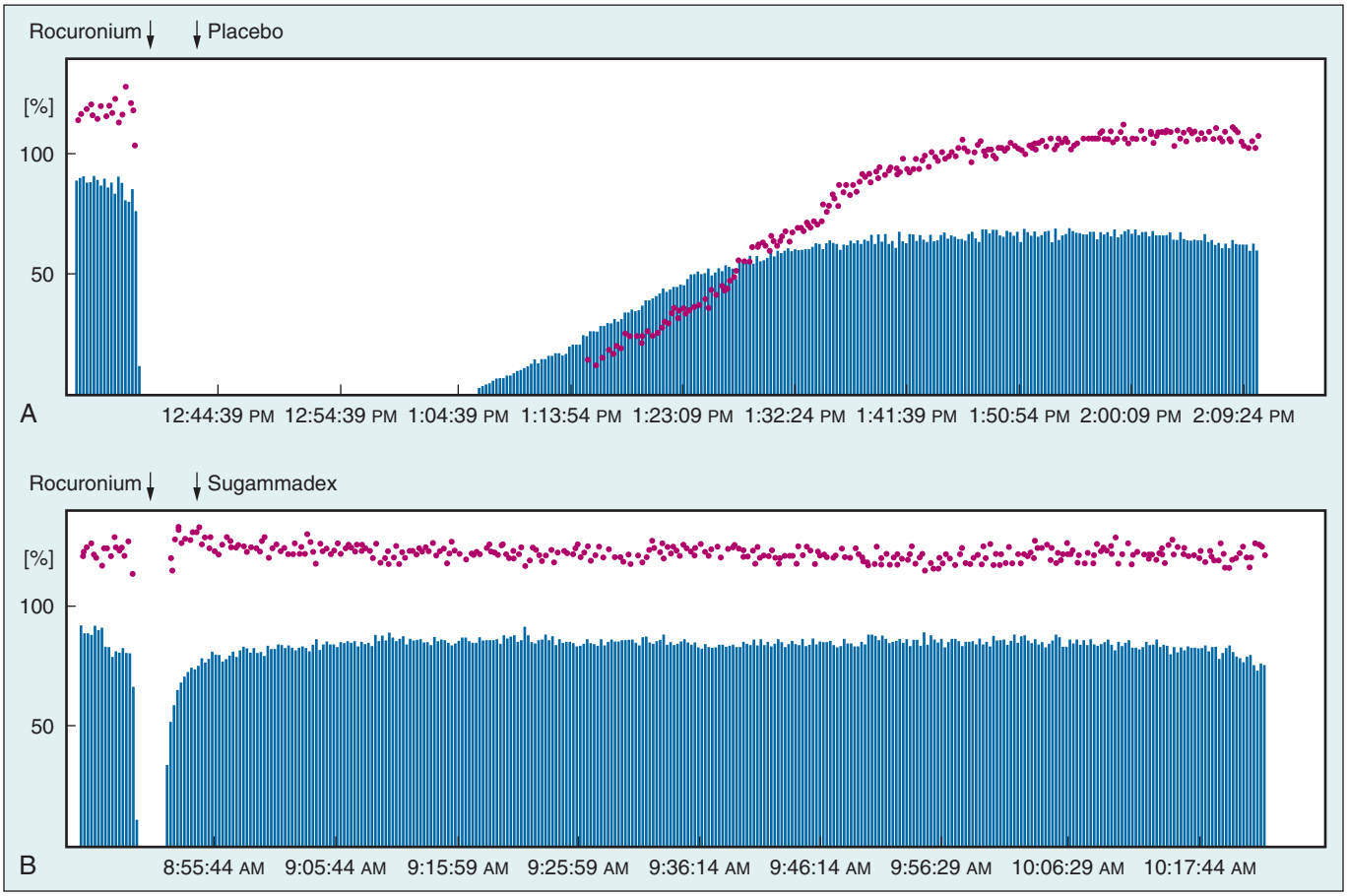


• **Fig. 22.16** Interaction of the cyclodextrin, sugammadex, with the steroidal neuromuscular blocking agent (NMBA) rocuronium. Hydrophobic portions of the NMBA are located within the cyclodextrin ring. Hydrophilic portions remain exposed to plasma.

While sugammadex reversal of neuromuscular blockade can help to eliminate postoperative residual paralysis,[287] its use does not guarantee complete recovery of neuromuscular function.[288,289] Correct dosing of sugammadex requires that depth of the blockade is monitored and that enough sugammadex is administered to reverse the existing blockade. Residual neuromuscular blockade occurs in approximately 5% of patients who receive sugammadex if neuromuscular monitoring is not used.[290] Recurarization, or incomplete reversal after sugammadex, occurs when the number of circulating sugammadex molecules is insufficient to bind a critical number of the rocuronium molecules that are present. One molecule of sugammadex encapsulates one molecule of rocuronium and when a large dose of rocuronium is reversed with an inadequate dose of sugammadex, previously redistributed rocuronium may be mobilized and cause neuromuscular blockade.[291]

Reintroducing neuromuscular blockade after reversal with sugammadex, as may be warranted in laryngospasm or the need to reintubate a patient, presents challenges since any free sugammadex will bind with rocuronium that is administered. In a case series,[292] 0.6 mg/kg rocuronium reestablished neuromuscular blockade in patients who had received sugammadex 3 hours earlier. If, however, that interval was 2 hours or less, more than 0.6 mg/kg (or 2× the ED_{95}) was required. When a small dose (2 mg/kg) of sugammadex has been administered, 0.6 mg/kg rocuronium may be sufficient to reintroduce neuromuscular blockade even shortly after sugammadex administration.[293] Succinylcholine (1 mg/kg) has also been used successfully to reintroduce neuromuscular blockade 3 hours after the administration of sugammadex.[294]

Sugammadex has been used to treat rocuronium-induced anaphylaxis.[295,296] The efficacy, though, of sugammadex is not



• **Fig. 22.17** The speed of antagonism of rocuronium-induced block with sugammadex. In the top panel, a placebo was administered 3 minutes after rocuronium, 0.6 mg/kg. Recovery of twitch height is indicated by the blue lines and the TOFR by the red dots. In the lower panel, sugammadex 8 mg/kg was administered 3 minutes following the same dose of rocuronium. One minute after administration of sugammadex, the TOFR was 0.9. (Adapted from Gijsenbergh F, Ramael S, Houwing N, et al. First human exposure of Org 25969, a novel agent to reverse the action of rocuronium bromide. *Anesthesiology*. 2005;103:695–703.)

consistent.[297–299] Additionally, sugammadex or the sugammadex–rocuronium complex may cause an anaphylactic reaction.[297,300–303]

Administration of sugammadex has been associated with severe bradycardia.[304,305] The risk of this, though, is lower than the risk associated with the use of neostigmine.[306,307]

Other adverse effects of sugammadex are likely related to either displacement of endogenous molecules or to nonspecific binding as occurs in the case of coagulation factor Xa and oral contraceptives.[308,309] Following administration of sugammadex, women of child-bearing potential should use nonhormonal birth control to protect against unwanted pregnancy.[310] This requirement has led to a revision of anesthesia informed consent or additional information being distributed postoperatively to patients who have received sugammadex.[311]

Sugammadex administration has also been reported to have an effect on blood hemostasis. In healthy volunteers, sugammadex induced a dose-dependent, transient prolongation of activated partial thromboplastin time (APTT) and prothrombin time (PT)/international normalized ratio (INR).[312] However, although sugammadex increased the partial thromboplastin time in a randomized, control trial of almost 1200 patients, it did not increase the risk of bleeding when compared to patients who did not receive the selective relaxant binding agent.[313]

In extensive studies of displacement conducted with sugammadex and 300 drugs, only 3 (flucloxacillin, fusidic acid, and toremifene) had the potential for a displacement interaction with sugammadex.[314,315] Therefore, the effects of administration of sugammadex should be carefully considered when either toremifene or fusidic acid have been administered.[316]

Emerging Developments

Fumarates

The fumarates share structural elements with mivacurium. Like mivacurium, they have 3 methyl groups between the quaternary nitrogen and the most proximal oxygen at each end of the carbon chain. This structural feature is different from either atracurium or cisatracurium, each of which has 2 methyl groups in this position, suggesting that Hofmann degradation does not contribute significantly to elimination of mixed-onium chlorofumarates.[317] In contrast to benzylisoquinoliniums, the chlorofumarates have 4 chiral centers, 2 of which are quaternary ammoniums. Additionally, the head groups of these compounds are distinct.[79] Primate studies have shown that onset of these compounds is inversely related to potency. While the chlorofumarates are potent (ED_{95} < 0.2 mg/kg), they

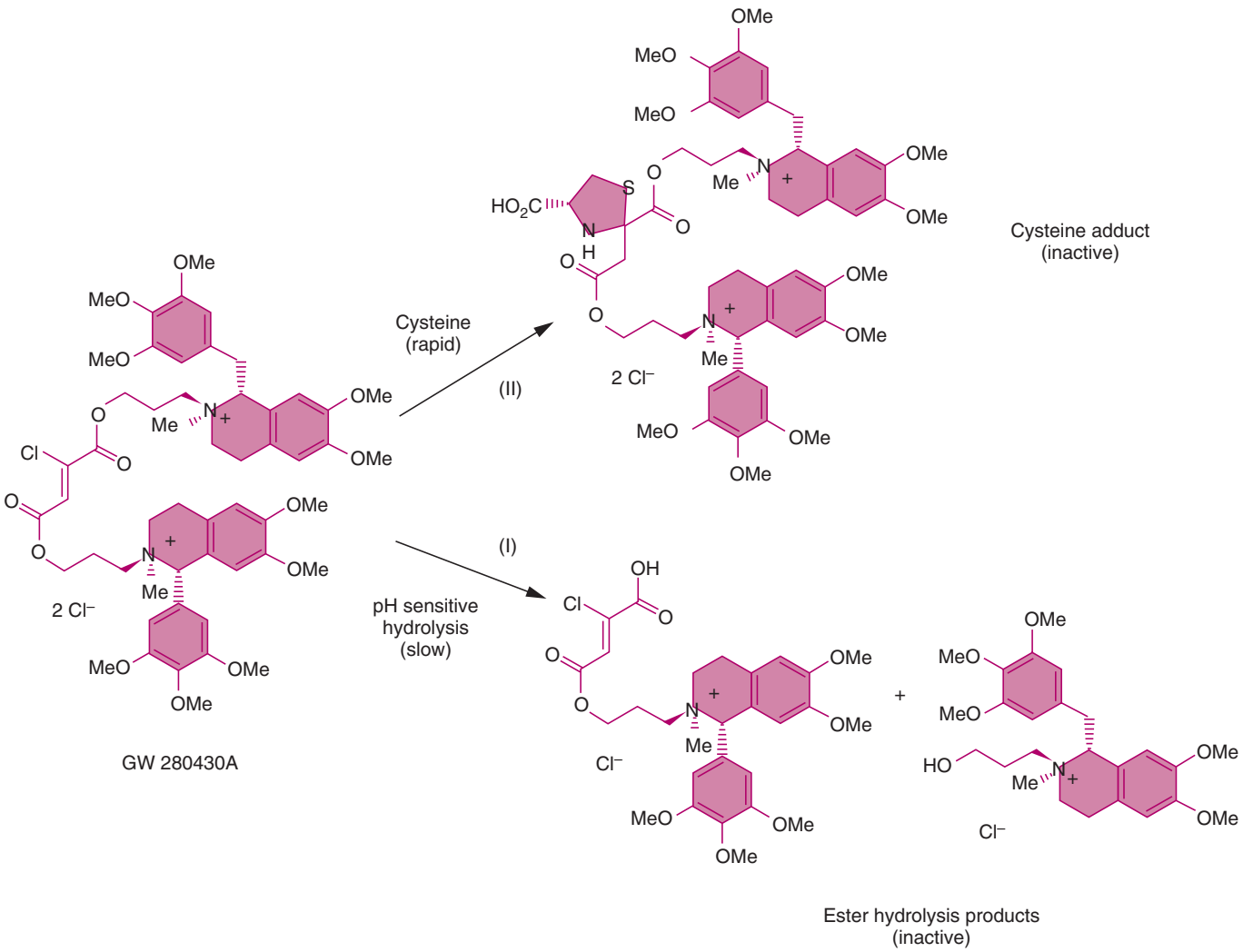
have rapid onsets and very short durations of action.[79] One of the chlorofumarates, gantacurium, has been administered to human volunteers.[63,64] Maximal onset of block at the adductor pollicis and laryngeal adductors following doses approximating 2 and 3 times the ED_{95} were comparable to onset of block following administration of succinylcholine[63] (Table 22.5).

As with atracurium and cisatracurium, the fumarates were chosen for development because of, in addition to their pharmacodynamic profile, their unique means of elimination from plasma.[79–81] Gantacurium is broken down by 2 different pathways; one is a slow, pH-sensitive hydrolysis and the other is adduction of the naturally occurring amino acid cysteine (addition of a cysteine molecule to the NMBA, rendering a new compound; Fig. 22.18). This adduction reaction replaces the chlorine and saturates the fumarate double bond. The resultant product is structurally different than gantacurium and can no longer interact with the acetylcholine receptor. This unique means of inactivation likely accounts for its ultrashort duration of effect.[64] It also provides a novel means of shortening recovery from chlorofumarate-induced neuromuscular block.[82] L-cysteine has an elimination half-life of 1 to 2 hours. Exogenous cysteine administered to dogs during the early phases of spontaneous recovery of neuromuscular function or 1 minute after administration of gantacurium significantly shortens the time required to complete recovery compared to either spontaneous recovery or edrophonium-facilitated recovery. In rhesus monkeys,

TABLE 22.5 Comparison of Onset of Block by Gantacurium and Succinylcholine

Neuromuscular Blocking Agent	Dose (mg/kg)	Minutes to Maximal Block*	
		Laryngeal Adductors	Adductor Pollicis
Gantacurium	0.36	1.1 ± 0.3	1.7 ± 0.2
	0.54	0.9 ± 0.2	1.5 ± 0.3
Succinylcholine	1.0	0.8 ± 0.3	1.5 ± 0.2

*Note that the laryngeal muscles are blocked faster than the thumb.



• **Fig. 22.18** Degradation and inactivation of gantacurium (GW 280430A), an asymmetric chlorofumarate. Gantacurium is inactivated by 2 pathways: rapid adduction of cysteine to yield an inactive cysteine adduct and a slower pH-sensitive hydrolysis to yield ester hydrolysis products. (From Savarese JJ, Belmont MR, Hashim MA, et al. Preclinical pharmacology of GW280430A (AV430A) in the rhesus monkey and in the cat: a comparison with mivacurium. *Anesthesiology*. 2004 Apr;100(4):835–845.)

doses of 8 times the ED_{95} of gantacurium have a duration of action of approximately 14 minutes. Administration of L-cysteine (10 mg/kg) 1 minute after administration of gantacurium results in return of complete neuromuscular function within 1 to 2 minutes. The rapid reversal of fumarate-induced neuromuscular block by administration of L-cysteine has the potential to decrease the frequency of residual neuromuscular block.[318]

Two analogs of the asymmetric fumarate gantacurium, CW002 and CW011, have been synthesized to undergo slower L-cysteine adduction, yielding compounds with intermediate durations of action.[81,82,319] A trial in anesthetized volunteers demonstrated that CW002 was a potent nondepolarizing NMBA with an intermediate duration of action.[320] Its ED_{95} was 0.077 mg/kg, onset of maximal effect occurred in 3.3 minutes, clinical duration of action was 34 minutes, and complete spontaneous recovery occurred in 59 to 86 minutes after a dose of 1.8× ED_{95}. This dose had no cardiopulmonary side effects and did not release histamine. Additional volunteer trials are required to determine whether its recovery and ease of antagonism are improved over that provided by compounds that are currently available.

Calabadion

A new class of reversal agent, the calabadions, provides an expanded (including reversal of benzylisoquinolines) spectrum of possible indications in that they reverse the effects of steroidal and benzylisoquinolinium NMBAs.[84,85] Clinical trials are planned; this reversal agent may provide yet another way to influence our expectations for recovery of neuromuscular function at the conclusion of an anesthetic.

Key Points

- Quantitative monitoring is required to ensure the adequacy of neuromuscular function prior to tracheal extubation at the conclusion of an anesthetic. It should be used to guide dosing of both neuromuscular blocking drugs and their reversal agents.
- A TOFR of less than 0.9 constitutes inadequate recovery of neuromuscular function. Inadequate recovery of neuromuscular function results in postoperative respiratory complications, delayed discharge from the postanesthesia care unit, and decreased patient satisfaction with recovery following an anesthetic.
- In spite of the use of NMBAs with an intermediate duration of action, postoperative residual neuromuscular block is not an infrequent occurrence.
- Upper airway collapse occurs in the presence of subtle degrees of neuromuscular block.
- Anticholinesterases do not guarantee adequate recovery of neuromuscular function and large doses can cause muscle weakness via depolarizing block.
- Availability of newer drugs, such as the selective relaxant binding agent sugammadex, to facilitate recovery of neuromuscular function should decrease the incidence of postoperative residual neuromuscular block.
- The effects of neuromuscular blocking agents that are extensively metabolized can be rapidly antagonized by increasing their metabolism.

Key References

Donati F, Meistelman C, Plaud B. Vecuronium neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis. *Anesthesiology*. 1991;74:833–837. Time to maximal effect of and recovery from vecuronium-induced neuromuscular block (0.4 or 0.7 mg/kg) was determined at the adductor pollicis and the laryngeal adductors in 20 adult patients. While vecuronium had a more rapid effect in the laryngeal adductors, maximal depth of block was less profound than it was at the adductor pollicis. Recovery occurred more quickly in the larynx than at the adductor pollicis. (Ref. 24).

Fuchs-Buder T, Meistelman C, Alla F, et al. Antagonism of low degrees of atracurium-induced neuromuscular blockade: dose-effect relationship for neostigmine. *Anesthesiology*. 2010;112:34–40. Administration of 10, 20, or 30 μg/kg neostigmine at a TOFR of 0.4 or 0.6, when fade is likely not palpable in the TOF response, results in effective antagonism of residual atracurium-induced block. Neostigmine, 20 μg/kg will restore the TOFR to greater than or equal to 0.9 within 10 minutes. Administration of these small doses of neostigmine does not augment existing neuromuscular block. (Ref. 273).

Grosse-Sundrup M, Henneman JP, Sandberg WS, et al. Intermediate acting non-depolarizing neuromuscular blocking agents and risk of postoperative respiratory complications: prospective propensity score matched cohort study. *BMJ*. 2012;345:e6329. This quantitative effectiveness study demonstrated that the use of intermediate-acting nondepolarizing neuromuscular blocking agents during surgery is associated with an increased risk of severe postoperative respiratory complications. Under the conditions studied, reversal of neuromuscular blockade using an acetylcholinesterase inhibitor at the end of surgery did not decrease but rather increased a patient's risk of developing clinically meaningful respiratory complications. (Ref. 9).

Kopman AF, Klewicka MM, Kopman DJ, et al. Molar potency is predictive of the speed of onset of neuromuscular block for agents of intermediate, short, and ultrashort duration. *Anesthesiology*. 1999;90:425–431. Times to peak effect of equipotent doses of five different neuromuscular blocking agents—succinylcholine, mivacurium, cisatracurium, vecuronium, and rocuronium—with different durations of action, structures, and mechanisms of action were studied. The relationship between onset and potency, that less potent compounds have a more rapid onset of effect, that had been demonstrated for long-acting NMBAs was found to also apply to compounds with different durations of action. (Ref. 68).

Koscielniak-Nielsen ZJ, Bevan JC, et al. Onset of maximum neuromuscular block following succinylcholine or vecuronium in 4 age groups. *Anesthesiology*. 1993;79:229–234. Subparalyzing doses of NMBAs were used to determine maximal onset of effect on patients of 4 different age groups: 1 to 3 years, 3 to 10 years, 20 to 40 years, and 60 to 80 years. Older subjects had slower onsets of maximal effect of NMBA. When large doses of NMBAs are administered to facilitate endotracheal intubation, time to onset of maximal effect cannot be distinguished. (Ref. 38).

Martyn JA, Richtsfeld M. Succinylcholine-induced hyperkalemia in acquired pathologic states: Etiologic factors and molecular mechanisms. *Anesthesiology*. 2006;104:158–169. This is a review article describing the molecular mechanisms for hyperkalemia following administration of succinylcholine. The nicotinic α-7 acetylcholine receptor, which is activated by choline, acetylcholine, and succinylcholine, has a prolonged depolarization in the presence of agonist and may have a significant role in the hyperkalemic response to succinylcholine in clinical situations in which there is up-regulation of acetylcholine receptors. (Ref. 115).

Matteo RS, Backus WW, McDaniel DD, et al. Pharmacokinetics and pharmacodynamics of d-tubocurarine and metocurine in the elderly.

Anesth Analg. 1985;64:23–29. This study of the pharmacokinetics and pharmacodynamics of metocurine and d-tubocurarine in elderly patients was the first to document that while clearance was decreased, elimination half-life was prolonged, and recovery was slower in elderly patients, the plasma concentration–response relationships for these two NMBAs were the same in young adults and in the elderly. These findings indicate that in the elderly it is decreased clearance rather than changes in the neuromuscular junction that cause the prolonged duration of effect of NMBAs. (Ref. 143).

Murphy GS, Szokol JW, Marymont JH, et al. Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit. *Anesth Analg*. 2008;107:130–137. An assessment of critical respiratory events in almost 7500 patients who had received general anesthesia. Just under 1% of patients had a critical respiratory event within 15 minutes of admission to the postanesthesia care unit. The majority of patients with a critical respiratory event (74%) had a TOFR of less than 0.7; 17% had a TOFR of less than 0.9 and greater than 0.7. (Ref. 233).

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23

Cardiovascular Physiology: Cellular and Molecular Regulation

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CHAPTER OUTLINE

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Emerging Developments
- Proteomics to Advance Cardiac Physiology

The human heart beats billions of times during the course of a normal life span, with each beat representing the amalgamation of electrical, biochemical, and mechanical events that occur over milliseconds. This chapter reviews the cellular and molecular processes that initiate and maintain blood pressure and blood flow to provide a framework for understanding concepts central to pharmacologic manipulation of the cardiovascular system.

Historical Perspective

Although many aspects of cardiovascular function have been known for thousands of years, it was not until the classic treatise by William Harvey in 1623 that the sequential relationship of the heart and vasculature was systematically characterized. Subsequent observation in both animals and man provided considerable insight into hemodynamics, particularly work by Stephen Hales, who in the 1730s measured blood pressure in horses and man, determined cardiac output, and had such a sophisticated appreciation of anatomy and fluid dynamics that he proposed regulation of vascular resistance by the microcirculation. At the subcellular level, technologic advances over the past 25 years have clearly had a profound effect on modern understanding of the molecular processes involved with cardiovascular function. Nonetheless, beginning in the mid-1800s, and using relatively crude methodologies, scientists developed a remarkably detailed understanding of the cardiac action potential, the central role of the calcium ion (Ca^{2+}) in excitation-contraction coupling and neurohormonal regulation of blood vessels.[1]

Cardiac Excitation

General Concepts

The contraction of the heart follows from the spontaneous generation of an impulse (automaticity) that is routed through the anatomic conduction system, and ultimately to cardiomyocyte shortening. The path and speed of impulse conduction is dictated by the electrical characteristics of different cell types constituting the conduction system, which synchronizes contraction. The heart exhibits three main "electrical" characteristics that are regulated by the autonomic nervous system: *chronotropy* (rhythm of automaticity), *bathmotropy* (cellular excitability), and *dromotropy* (impulse conduction). Pathologic abnormalities (both congenital and acquired), as well as a wide variety of drugs, can alter cellular automaticity, excitability, and the velocity and path of impulse conduction.

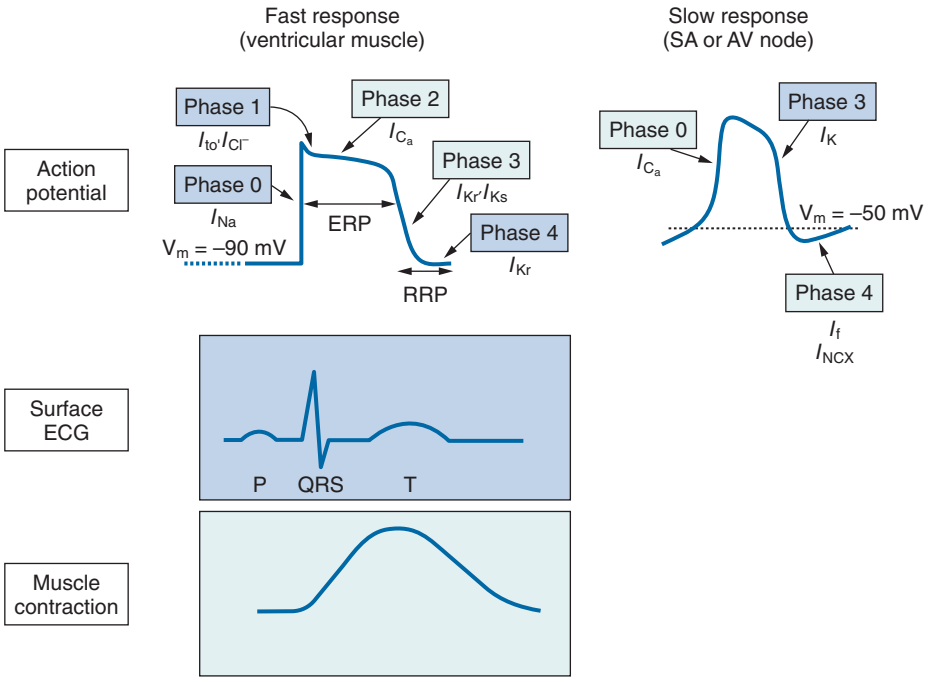
The fundamental process underlying all electrical activity in the heart is the action potential, which is an integrated movement

Abstract

In a normal human life span, the heart beats billions of times. Each beat represents a remarkable combination of events working in harmony over milliseconds to propel blood into the vasculature for distribution to tissues of the body. This chapter first reviews the electrical, biochemical, and mechanical events that constitute a heart beat. Particular emphasis is placed upon intrinsic and extrinsic regulation of these processes in order to highlight how each can be affected by drugs or disease. The chapter then discusses how the pulsatile forces generated by myocardial excitation and contraction move blood into and through the circulation. A wide range of factors influencing how different vessels along the vascular tree contract or relax in order to effectively disperse the pressure and flow generated during systole and diastole are reviewed. Finally, potential implications of recent technological advances in defining subcellular and molecular aspects of cardiovascular physiology are described.

Keywords

Action potential
Myocardial contraction
Vascular tone
Vasoconstriction



• **Fig. 23.1** Representative fast and slow response action potentials along with the corresponding surface electrocardiogram *(ECG)* and the relative timing of cardiomyocyte contraction. Individual phases of the action potentials are depicted along with the predominant ion currents contributing to each phase. *AV,* Atrioventricular; *ERP,* effective refractory period; I_{Na}, inward sodium ion (Na^+) current; I_{to}, transient outward current; I_{Cl}, inward chloride current; I_{Ca}, calcium ion (Ca^{2+}) entry current; I_K, delayed rectifier potassium ion (K^+) current; I_{Kr}, rapid component of delayed rectifier K^+ current; I_{Ks}, slow component of delayed rectifier K^+ current; I_{KI}, inward rectifier potassium current; I_{NCX}, Na^+-Ca^{2+} exchange current; I_f, hyperpolarization activated funny current; *RRP,* relative refractory period; *SA,* sinoatrial; V_m, membrane potential. (Adapted with permission from Balser JR, Thompson A. Cardiac electrophysiology. In: Hemmings H, Hopkins P, eds. *Foundations of Anesthesia: Basic and Clinical Sciences.* 2nd ed. London: Mosby; 2007:485–497.)

of ions back and forth across the cell surface that results in rapid and reproducible changes in the electrical potential of the cell membrane (Fig. 23.1). The characteristics and interactions among the various ion channels contributing to the action potential are complex and are reviewed more extensively in Chapters 8 and 27. For the current discussion, a definition of basic terms and concepts is presented in the following text:

1. *Membrane potential:* Determined by the relative permeability of the cell membrane to specific ions, and forces both *chemical* (concentration gradient) and *electrostatic* (imparted by ion charge) that drive movement of ions across the membrane.
2. *Conductance:* An expression of how easily an ion flows across a membrane either through active pumps located in the membrane or ion channels; when specific ion channels open, conductance *(g)* for that ion increases.
3. *Resting membrane potential:* In cardiac cells, the conductance to the potassium ion (K^+) is high at rest, primarily because of diffusion out of the cells via selective K^+ channels along a concentration gradient; intracellular K^+ ($[K^+]_i$) is ~150 mEq/L, whereas extracellular K^+ ($[K^+]_o$) is ~5 mEq/L. The membrane is relatively impermeable to large anions such as proteins. Because these anions cannot follow K^+ out of the cell, the inside of the cell becomes negatively charged relative to the outside, and the resting membrane potential of myocytes is ~−90 mV. There is some movement of other ions across the cell membrane at rest, but conductance is very low relative to K^+, so the resting membrane potential is close to the equilibrium potential for K^+ (E_K) of approximately −94 mV as calculated using the Nernst equation:

[1]

$$E_K = -61.5 \log([K^+]_i / [K^+]_o)$$

Unlike K^+, myocyte conductance to the sodium ion (Na^+) is low at rest because voltage-gated Na^+ channels that allow Na^+ entry into the cell are closed. Nonetheless, because the concentration of extracellular Na^+ is much higher than intracellular (~145 mM vs. 10 mM) and the cell interior is negatively charged, both chemical and electrostatic forces drive some Na^+ ions across the membrane, which is the basis for secondary active transport of other molecules including Ca^{2+} and hydrogen (H^+) ions. This movement is minimal and only slightly increases the membrane potential above the E_K (i.e., from −94 to −90 mV). However, the slow Na^+ current could eventually depolarize the cell.

Maintenance of the Na^+/K^+ gradient across the cell membrane is therefore critical and is actively achieved by expenditure of energy to move ions against an electrochemical gradient by the sodium-potassium adenosine triphosphatase (Na^+/K^+-ATPase), also known as the "sodium pump". It is composed of α and β subunits and α_1 and α_2 isoforms. The α subunits contain both the Na^+ and K^+

binding sites and the adenosine triphosphate (ATP) catalytic site. The α_1 isoform is homogeneously distributed in the sarcolemma, while the α_2 isoform is localized in the T-tubules and may play a role in the excitation-contraction coupling.[2] This protein extrudes 3 Na^+ ions for every 2 K^+ ions taken in, with ATP serving as the energy source; the pump is electrogenic in that charge movement across the membrane is unbalanced. Because of the central role of the Na^+/K^+-ATPase in maintaining membrane potential and its multiple downstream effects, the protein is the focus of extensive research.[3,4] Myocytes also express Ca^{2+} channels that permit Ca^{2+} to enter the cells along its electrochemical gradient—that is, extracellular $[Ca^{2+}] \gg$ intracellular $[Ca^{2+}]$. The sarcolemmal Na^+/Ca^{2+} exchanger (NCX) catalyzes the countertransport of 3 Na^+ ions and 1 Ca^{2+} ion using the inward gradient for Na^+ to drive the extrusion of Ca^{2+}. Under physiologic conditions, this mechanism contributes to removal of Ca^{2+} from the cardiac cell after each beat, thus facilitating relaxation and the maintenance of Ca^{2+} balance.[5] However, in common pathologic conditions, Ca^{2+} influx via NCX can be enhanced, resulting in intracellular Ca^{2+} accumulation, which can exacerbate cardiac injury and contractile dysfunction and lead to arrhythmias.[5] For example, during reperfusion following ischemia, acidosis provokes Na^+ overload via the Na^+/H^+ exchanger, which can slow or even reverse NCX activity.[5] As with the Na^+/K^+-ATPase, the sarcolemmal NCX remains widely studied in regard to its role in cardiac pathology and as a target for pharmacologic manipulation.[6]

4. *Threshold potential:* The membrane potential at which inward currents exceed outward currents as the result of voltage-gating of Na^+ and Ca^{2+} channels, and depolarization becomes self-sustained. At this point, the action potential is initiated.
5. *Fast versus slow response tissues* (see Fig. 23.1): Fast response tissues depend on the opening of voltage-gated Na^+ channels to initiate depolarization. These tissues include the atria and ventricles, along with the specialized infranodal conducting system (bundle of His, fascicles and bundle branches, terminal Purkinje fibers). In contrast, depolarization in slow response tissues, such as the sinoatrial (SA) and atrioventricular (AV) nodes, is initiated by movement of Ca^{2+} *through long-lasting (L-type)* voltage-gated *Ca^{2+} channels.* Fast and slow response tissues also differ with regard to the magnitude and stability of their resting membrane potential (the basis for automaticity) and the amplitude of the action potential.

The Action Potential

In addition to differences in how depolarization is initiated between fast and slow tissues, there are fundamental differences in the subsequent action potential, underscoring how each tissue can exhibit different sensitivities to disease or drugs. The following comparison starts with the action potential phase during which depolarization begins for each tissue (Table 23.1.)

Fast Response Tissue

Phase 0—Rapid Depolarization

When the membrane potential reaches threshold, *voltage-gated Na^+ channels open,* leading to a rapid Na^+ entry along both a marked concentration gradient (chemical force) and the electrostatic force provided by charge difference across the membrane. The voltage-gated Na^+ channels have a short open time, meaning that most of the channels close within a few milliseconds after the initiation of the action potential. However, a small subgroup of these channels reopens during the latter phases of the action potential, leading to a sustained Na^+ influx called the late current.[2] The Na^+ channels remain in this so-called fast-inactivated state until the membrane potential becomes more negative, at which time they return to their resting (ready-to-go) state. Before this can occur, however, the membrane potential becomes positive for a period of time (overshoot); although there is no longer an electrostatic drive for Na^+ to enter the cell, a concentration gradient still exists to push Na^+ across the membrane. During depolarization, *voltage-gated Ca^{2+} channels (VGCC)* also open but the inward flux is much slower than for Na^+.

Phase 1—Early Repolarization

With termination of the *inward Na^+ current (I_{Na})* resulting from Na^+ channel fast-inactivation and the positive membrane potential, both chemical and electrostatic forces promote K^+ efflux from the

TABLE 23.1 Differences in Action Potential Between Fast and Slow Response Cardiac Tissues

	Fast Response	Slow Response
Tissues	Atria, ventricles, bundle of His, fascicles, bundle branches, and terminal Purkinje fibers	Sinoatrial and atrioventricular nodes
Phase 0—Rapid depolarization	Opening of the voltage-gated Na^+ channels	Increased Ca^{2+} conductance through L-type Ca^{2+} channels
Phase 1— Early repolarization	K^+ efflux and chloride influx	None
Phase 2— Plateau	Slow calcium^{2+} entry Na^+ channels in the closed inactivated state	None
Phase 3—Final repolarization	K^+ efflux exceeds Ca^{2+} influx	Increased K^+ efflux Closure of L-type Ca^{2+} channels
Phase 4—Resting membrane potential	Activation of the NA^+/K^+ -ATPase Na^+ channels in the resting state	–60 mV: Slow inward Na^+ influx –50 mV: Opening of T-type Ca^{2+} channels –40 mV: Opening of voltage gated L-type Ca^{2+} channels Slow K^+ efflux

Na^+, Sodium ion; *K^+*, potassium ion.

cell, described as a *transient outward current* (I_{to}), and a modest inward chloride current (I_{Cl}) to elicit a decline in membrane potential.

Phase 2—Plateau

A continued slow *Ca^{2+} entry current (I_{Ca})* offsets the electrical effect of K^+ loss secondary to opening of voltage-gated K^+ channels. The plateau voltage is sufficient to maintain Na^+ channels in the closed, fast-inactivated state.

Phase 3—Final Repolarization

This phase begins when the efflux of K^+ exceeds the influx of Ca^{2+} and the I_{Ca} current ends. The *delayed rectifier K^+ current (I_K)* in phase 3 has both rapid (I_{Kr}) and slow (I_{Ks}) components that lead to repolarization and return to the resting potential.[7]

Phase 4—Resting Membrane Potential

The Na^+/K^+-ATPase extrudes Na^+ that entered during depolarization and restores the K^+ lost during repolarization. Once the resting potential is stabilized, Na^+ channels return to their resting state and are ready for the next depolarization.

During a single cardiac cycle (i.e., one action potential), the voltage-gated Na^+ channel exists in three different states: (1) resting, (2) active (open) during phase 0 depolarization, and (3) inactive at positive potentials (end of phase 0) and with marked depolarization (phase 2 plateau).[8,9] Even though Na^+ cannot pass through the channel when in the resting or inactivated conformations, these two states are physiologically distinct. In the resting state, achieving the threshold potential opens the channel. In contrast, once the Na^+ channel is inactivated, it cannot be activated again until it cycles back to the resting membrane potential, which brings it into the resting state. Most drugs, including various antiarrhythmic compounds, preferentially bind to the inactivated state of the Na^+ channel. These distinctions can be clinically important.

Slow Response Tissue

Phase 4—Slow Spontaneous Depolarization

When the membrane potential reaches its maximum negative point after repolarization (about −60 mV), slow, inward (depolarizing) Na^+ currents are activated. Referred to as *funny currents* (I_f), because unlike most currents they are activated by hyperpolarization not depolarization, the I_f cause the membrane potential to begin a slow *spontaneous depolarization*.[10] When the membrane potential reaches about −50 mV, transient or *T-type Ca^{2+}* channels open, allowing Ca^{2+} to enter the cell along its electrochemical gradient and further depolarize the membrane. When the potential reaches about −40 mV, VGCC open to further depolarize the cell until an action potential threshold is reached (between −40 and −30 mV). A slow decline in the outward movement of K^+ also occurs during phase 4 as the K^+ channels responsible for repolarization during phase 3 continue to close.

While I_f have come to be known as the "membrane voltage clock" that dictates spontaneous membrane depolarization, recent studies have suggested that automaticity is more complex. Spontaneous, rhythmic release of Ca^{2+} into the cytoplasm from storage sites within the sarcoplasmic reticulum (SR) occurs during phase 4 and leads to activation of another depolarizing ionic current through the NCX (I_{NCX}), known as the "subsarcolemmal calcium clock."[11]

Phase 0—Depolarization

The I_f and T-type Ca^{2+} currents decline as their respective channels close, and depolarization is primarily caused by increased Ca^{2+} conductance through the L-type Ca^{2+} channels that begins toward the end of phase 4. Movement of Ca^{2+} through these channels is not rapid, so the slope of phase 0 (the rate of depolarization) is much slower than found in fast response tissues. However, it is possible for fast response tissues to be converted to slow response tissues by tissue damage and electrolyte imbalance. Under these circumstances, Na^+ channels can become inactivated, with depolarization then dependent on the slow Ca^{2+} channels:

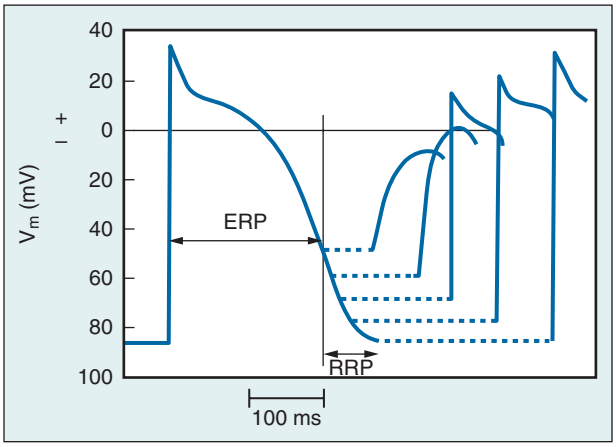
Phase 1—plateau: None for slow response tissue.
Phase 2: None for slow response tissue.
Phase 3: K^+ channels open, thereby increasing outwardly directed, hyperpolarizing K^+ currents. At the same time, there is inactivation and closure of L-type Ca^{2+} channels, decreasing Ca^{2+} conductance and inward depolarizing Ca^{2+} currents.

Impulse Propagation and Conduction

The cardiac muscle fibers are made of many individual cardiac cells connected in series to one another with gap junctions forming a syncytium. When a slow action potential develops in a membrane, current flows from this membrane to adjacent areas. Ions can then flow from one cell to another via low-resistance *gap junctions,* and if the current flow is sufficient, it causes sequential depolarization from cell to cell. The gap junctions are dynamic structures, opening and closing in response to changes in pH, Ca^{2+}, and under some circumstances, voltage.[12,13] Impulse propagation can also be affected by the orientation of myofibers and of the collagen matrix in which the fibers reside.

For an impulse to be conducted from cell to cell, or more globally to be spread throughout the heart, *cells in the path must be excitable (bathmotropy).* The characteristics of excitability for a cell depend on whether it exhibits fast or slow action potentials. Within fast response tissues, the membrane potential is not affected by an electrical impulse from the beginning of phase 0 to a midpoint in the repolarization process in phase 3 (the *effective refractory period;* see Fig. 23.1). When the membrane potential recovers below −50 mV, enough of the fast Na^+ channels have transitioned from the inactivated to resting state to allow for the membrane to again depolarize. However, because not all fast channels have recovered, the slope and amplitude of any resulting action potentials will not be normal until the membrane potential has been allowed to stabilize at its more negative values at the end of phase 3 when the Na^+ channels have entirely recovered from fast inactivation (Fig. 23.2). This represents the *relative refractory period.* In contrast, within slow response tissues the relative refractory period persists even after the membrane has fully repolarized, a characteristic known as *postrepolarization refractoriness*. Importantly, under most circumstances the heart rate—either spontaneous or paced within a physiologic range—provides a cycle length (beat-to-beat duration in milliseconds) that is longer than the refractory period, thus allowing for full recovery of the action potential. However, *duration of the action potential is affected by cycle length.* For example, measurements obtained from canine Purkinje fibers show that at a cycle length of 630 msec (heart rate of 95 beats/min) the action potential duration was 180 msec, whereas at 400 msec (heart rate of 150) action potential duration was shortened to 140 msec, although the amplitude was maintained—that is, the membrane was not in a relative refractory period.[14] This phenomenon appears to primarily reflect changes in K^+ conductance through delayed rectifier K^+ channels.[15]

The velocity at which an impulse is conducted *(dromotropy)* is largely determined by the resting membrane potential, the amplitude



• **Fig. 23.2** Relationship between action potential amplitude and the point at which stimulation occurs within the previous action potential. As stimulation occurs after the end of the effective refractory *period (ERP)* and progressively later in the relative refractory period *(RRP),* action potential amplitude increases. (Adapted with permission from Levy MN, Pappano AJ. Excitation: the cardiac action potential. In: Levy MN, Pappano AJ, eds. *Cardiovascular Physiology*. 9th ed. Philadelphia: Mosby Elsevier; 2007:13–32.)

of the action potential, and the rate of change in membrane potential during phase 0 (dV_m/dt). These characteristics are affected by autonomic nervous system regulation, pathologic or pharmacologic inactivation of Na^+ channels by hyperkalemia or ischemia-induced acidosis, direct damage to cardiomyocytes, or the effect of chemicals, particularly antiarrhythmic drugs. Accordingly, regional variations in conduction velocity can be dynamic and profound. Slow conduction in the AV and SA nodes ranges from 0.02 to 0.1 m/sec, fast conduction in cardiomyocytes range from ~0.3 to 1 m/sec, and those in specialized conducting fibers are even more rapid (~1 to 4 m/sec).

The only normal path for impulse conduction from the atria to the ventricles is through the AV node. Consequently, this region of the heart represents a site for physiologic, pathologic, and pharmacologic alteration of rhythm. Although much of the basic information regarding structure-based electrophysiology of the AV node has come from animal studies, it appears that the AV node and the surrounding "perinodal area" are composed of multiple cell types that are electrophysiologically distinct.[16] Three main types have been described and are localized to regions within or adjacent to the AV node: the atrionodal (AN), nodal (N), and nodal-His (NH) cells. The small, ovoid *N cells* are the primary sites where impulse conduction is slowed and therefore modulated, representing a distinctly slow response tissue with few gap junctions and reduced excitability compared with surrounding cells. The Ca^{2+} current-dependent upstroke of phase 0, a major determinant of conduction velocity, is relatively prolonged in slow response tissue. In contrast, surrounding "transitional cells" have a greater density of Na^+ channels, with an action potential and conduction velocity more like fast response tissue; variations in AV node conduction (i.e., fast and slow pathway conduction) have been described in which impulses are diverted through regions with different conduction velocities.[16,17]

In keeping with a critical regulatory role, the AV node is densely innervated by autonomic nerve fibers and can also be affected by autocoids (adenosine) and local metabolic influences (hypoxia, acidosis). Direct or pharmacologic stimulation of sympathetic or parasympathetic nerves has profound, often counterbalancing, effects on the action potentials, and therefore conduction velocity, of both N and transitional cells. Sympathetic stimulation activates G-protein–coupled β-adrenergic receptors (predominantly β_1) to activate adenylyl cyclase, and via multiple mechanisms increases the L-type calcium current, I_f, and the inward rectifying K^+ current. Ultimately, β_1 agonism enhances automaticity and excitability, along with increasing action potential amplitude and conduction velocity (positive chronotropy, bathmotropy, and dromotropy). *Parasympathetic stimulation* activates G-protein–coupled M_2 muscarinic receptors to decrease adenylyl cyclase activity, and reduces automaticity and excitability, increases refractoriness, and slows AV node conduction (negative chronotropy, bathmotropy, and dromotropy). In addition, AV nodal cells express surface receptors for adenosine (A_1); agonist binding stimulates inhibitory G proteins that inhibit adenylyl cyclase. In addition, pathways downstream to both M_2 and A_1 receptors affect I_f and various K^+ currents.[18] Rate-related hyperpolarization of the N cell membrane also contributes to reduced excitability, increased refractoriness, and AV conduction slowing to the point of even complete block.

Excitation-Contraction Coupling

While the generation and propagation of electrical impulses in the heart provide a stimulus, it is the mechanical response to this stimulus—cardiomyocyte contraction—that generates the pressure actually driving cardiovascular function. Literally hundreds of years of research, using both intact hearts and isolated muscle, have yielded several essential principles for cardiac contraction:

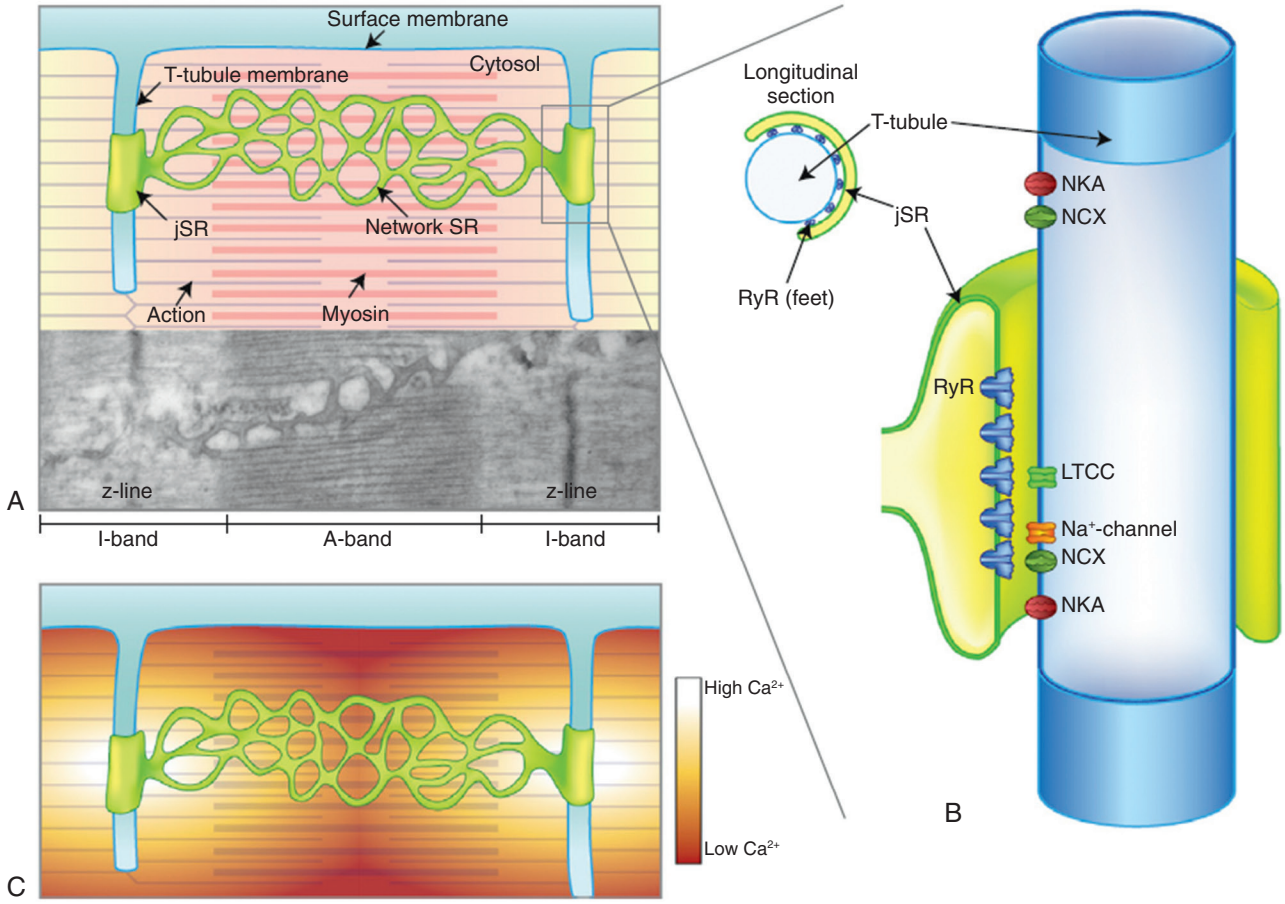
1. Cardiac muscle contraction, unlike that of skeletal muscle, is an all-or-none response.
2. The magnitude and rate of cardiac contractile responses reflect cytoplasmic Ca^{2+} concentration or Ca^{2+} sensitivity of contractile proteins.
3. When stimulated with greater frequency, the heart normally contracts with greater force and relaxes more rapidly.
4. Cardiac muscle contractile force is length-dependent.

Modern experimental techniques involving molecular biology have provided considerable insight into phenomena at the subcellular level and have challenged some traditional fundamental assumptions. Furthermore, increased understanding of cardiac pathophysiology has underscored the importance of molecular regulation of *lusitropy* (relaxation), in addition to that of *inotropy* (contractility).

Membrane Depolarization and Activator Calcium

The T-tubules are invaginations of the myocytes surface cell membrane present at each Z-line that form a complex network within the cells. They constitute specialized regions of the cell membrane that play an integral role in excitation-contraction coupling and in ensuring synchronous Ca^{2+} release and rapid Ca^{2+} extrusion from the myocyte (Fig. 23.3).[2] During phase 2 of the fast tissue action potential, the influx (extracellular to intracellular) of Ca^{2+} via VGCCs and, to a much lesser extent the NCX, functions as "activator Ca^{2+}," which stimulates the SR to release a larger amount of Ca^{2+}, a process known as *Ca^{2+}-induced Ca^{2+} release* (CICR) (Fig. 23.4).

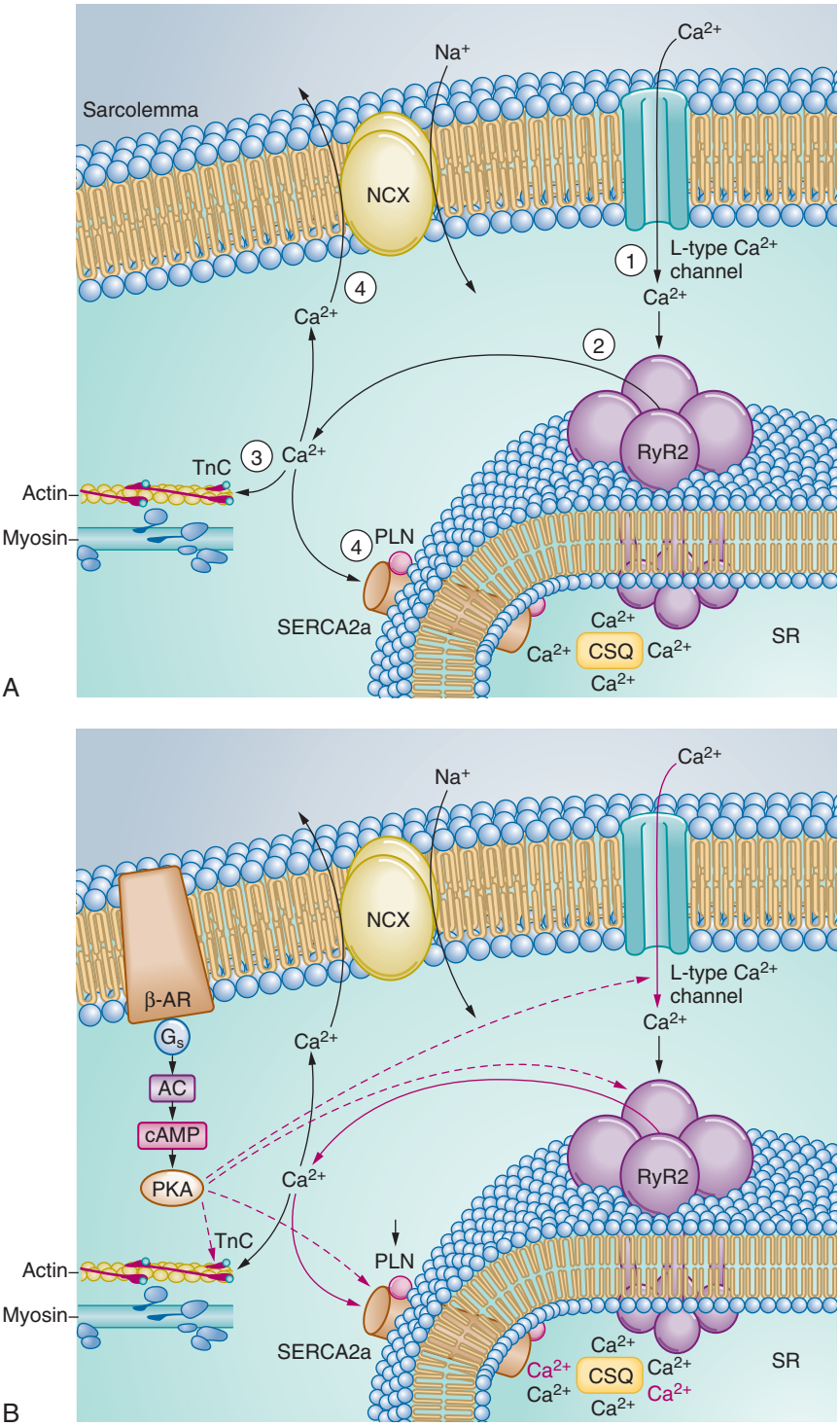
Storage and release of Ca^{2+} by the SR are relatively complex processes modulated by high-capacity Ca^{2+}-binding proteins such as *calsequestrin* and the *ryanodine-sensitive Ca^{2+} release channel,*



• **Fig. 23.3** Structural basis for excitation-contraction (EC) coupling in ventricular cardiomyocytes. A, T-tubules are invaginations of the cell membrane that allow close interaction between the sarcoplasmic reticulum *(SR)* and the sarcolemma. The SR is divided into junctional SR *(jSR)* close to the T-tubules and network SR between two T-tubules. The sarcomere contains regularly organized myofilaments with actin and myosin and is surrounded by the SR. B, The dyadic clefts are close connections between the junctional SR and the T-tubule membrane. L-type calcium ion (Ca^{2+})-channels *(LTCCs)* in the T-tubular membrane are closely apposed to groups of ryanodine receptors *(RyRs),* creating the structural basis for Ca^{2+} sparks during membrane depolarization. C, The concentration gradient of Ca^{2+} in the cytosol is a major regulator of cardiac EC coupling. CICR rapidly increases the local Ca^{2+} concentration in the dyad (*bright color*), leading to Ca^{2+} diffusion out of the dyadic cleft to increase the global Ca^{2+} levels in the cell (*dark color*), which triggers contraction. *CICR,* Ca^{2+} induced Ca^{2+} release; *NCX,* Na^+/Ca^{2+} exchanger; *NKA,* Na^+/K^+ pump; *NKX,* sarcolemmal sodium ion (Na^+)-Ca^{2+} exchanger; *SR,* sarcoplasmic reticulum. (Adapted from Aronsen JM, Swift F, Sejersted OM. Cardiac sodium transport and excitation-contraction coupling. *J Mol Cell Cardiol.* 2013;61:11–19.)

respectively. Calsequestrin is able to bind and store large amounts of Ca^{2+} with low affinity, thus reducing the amount of free Ca^{2+} in the SR and maintaining a low concentration gradient relative to the cytoplasm. Known as the *ryanodine receptor (RyR),* the SR Ca^{2+} release channel exists in multiple isoforms, with type 2 (RyR2) predominantly found in the heart. When activated, RyR2 has a very high conductance for Ca^{2+}; as Ca^{2+} exits the SR, dissociation of Ca^{2+} from calsequestrin provides for continued high conductance, and cytosolic Ca^{2+} concentrations rise rapidly from ~10^{-7} M to 10^{-5} M. Recent evidence indicates that SR Ca^{2+} release is not initially a global event but occurs as bursts or "sparks" in zones where L-type VGCC in T-tubules are in close proximity to the SR and RyR2 proteins.[18] Less well appreciated, and of less physiologic importance, is the fact that SR Ca^{2+} release can also be stimulated by the second messenger *inositol triphosphate* (IP_3) binding to the IP_3 receptor (IP_3R) on the SR membrane.[19,20] This is a relatively slow-onset process that has been linked to stimulation of α-adrenergic receptors on cardiomyocytes and to muscle remodeling.[21,22]

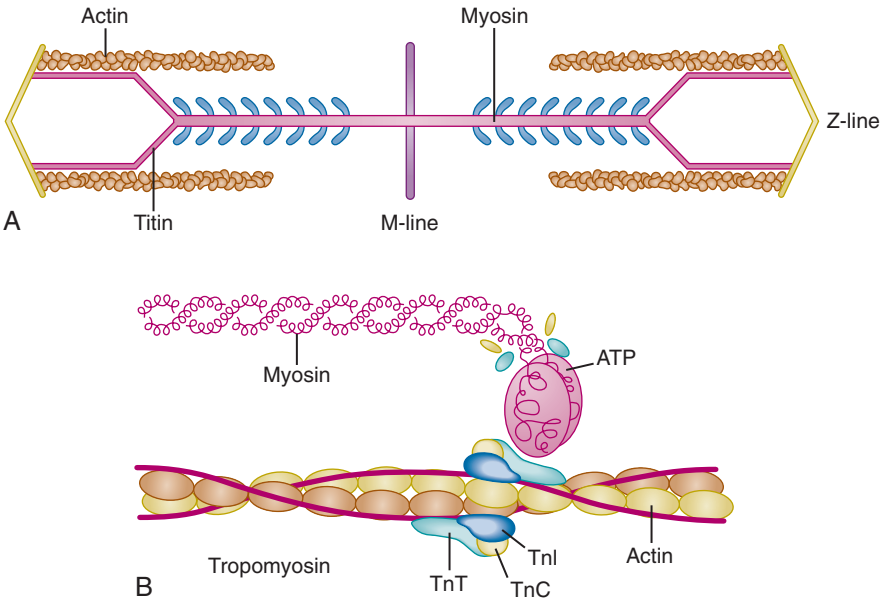
As with all muscles, the molecular stimulus for contraction of the cardiomyocyte is Ca^{2+} binding with contractile proteins (Fig. 23.5). Within the sarcomere, the *troponin complex containing the subunits TnI (binds to actin), TnC (the Ca^{2+} binding component), and TnT (binds troponin to tropomyosin)* dictates the interaction between actin and myosin. In the relaxed state, tropomyosin blocks formation of myosin cross-bridges. When cytoplasmic Ca^{2+} reaches ~10^{-6} M, binding to TnC results in a conformational change in troponin, leading to changes in tropomyosin that facilitate formation of actin-myosin cross-bridges. The number of cross-bridges formed, the rate at which this process occurs, and the duration of cross-bridge



• **Fig. 23.4** A, The sequence of events involved with excitation-contraction (EC) coupling in the cardiomyocyte. *1,* Membrane depolarization leads to an influx of "activator calcium ion (Ca^{2+})" via voltage-gated L-type Ca^{+} channels. *2,* The relatively small amount of activator Ca^{2+} binds to the adjacent Ca^{2+} release channel, the ryanodine receptor subtype 2 *(RyR2)*, on the sarcoplasmic reticulum *(SR)* and induces release of a large amount of Ca^{+} stored within the SR on the binding protein calsequestrin *(CSQ). 3,* Once in the cytoplasm, the released Ca^{+} binds with troponin C *(TnC)* to produce muscle contraction. *4,* Cytoplasmic Ca^{+} is then extruded from the cell via the sarcolemmal sodium ion (Na^{+})-Ca^{2+} exchanger *(NCX)* or taken back into the SR via the sarcoplasmic endoreticular Ca^{2+} ATPase subtype 2a *(SERCA2a)*, activity of which is regulated by the phosphorylation state of the attendant protein phospholamban *(PLN).* B, Regulation of EC coupling by stimulation of β-adrenergic receptors (β-AR) on the cardiomyocyte (in *red*). Activation of adenylyl cyclase *(AC)* and ultimately of protein kinase A *(PKA)* leads to phosphorylation of L-type voltage-gated Ca^{+} channel, RyR2, contractile proteins, and SERCA2a, resulting in increased Ca^{+} influx, augmented Ca^{+} release from the SR, altered TnC affinity for Ca^{+}, and increased Ca^{+} reuptake into the SR by SERCA2a, respectively. *cAMP,* Cyclic adenosine monophosphate. (Adapted with permission from Vittone L, Mundina-Weilenmann C, Mattiazzi A. Phospholamban phosphorylation by CaMKII under pathophysiological conditions. *Front Biosci.* 2008;13:5988–6005.)

attachment determine the resulting force. Each cross-bridge cycle consumes one molecule of adenosine triphosphate (ATP). A simplified two-stage model involving "on-time" and "off-time" for actin-myosin cross-bridges has been proposed as a means to help characterize inotropic regulation.[23] Within this model, during each cross-bridge cycle (and there are many during each cardiac contraction), the myosin head attaches to actin and rotates to produce a unitary force for that interaction that is maintained during the on-time. Dissociation of myosin results in a non–force-producing state during the off-time. It is then the combination of on-time and the unitary force that determines the force-time integral for each cross-bridge, and ultimately the number of cross bridges attached per unit time, that determines overall contractile force.

As soon as the stimulus to release Ca^{2+} is terminated, active reuptake into the SR, and, to a lesser extent, extrusion from the cell via the NCX, leads to a rapid decline in intracellular Ca^{2+}, thus facilitating dissociation of Ca^{2+} from TnC and to relaxation. The reuptake of Ca^{2+} into the SR is a fast (time constant of



• **Fig. 23.5** Schematic representation of the cardiac sarcomere (A) showing orientation of the structural elements (titin, M-line, Z-line) and contractile elements (actin and myosin). B, An expanded view of the site for actin-myosin interaction. In the absence of calcium ions (Ca^{2+}), tropomyosin prevents the interaction between the myosin head and actin. Binding of Ca^{2+} to the troponin C *(TnC)* component of a complex also containing troponin T *(TnT)* and troponin I *(TnI)* removes the inhibitory effect of tropomyosin allowing for actin-myosin interaction, adenosine triphosphate *(ATP)* hydrolysis, and cross-bridge formation. (Adapted with permission from: Nyhan D, Blanck TJJ. Cardiac physiology. In: Hemmings H, Hopkins P, eds. *Foundations of Anesthesia: Basic and Clinical Sciences.* 2nd ed. London: Mosby; 2007:473–484.)

~100 msec), energy-dependent process involving the *sarcoplasmic endoreticular calcium ATPase* (SERCA) and its regulatory protein *phospholamban (PLN).* As with RyR, SERCA is found throughout the body in different isoforms; the type 2a isoform (SERCA2a) predominates in the heart. Under resting conditions, SERCA2a does not function at maximal capacity owing to an inhibitory influence of PLN. However, the inhibitory effect of PLN is lost when the protein is phosphorylated at one of two sites, each sensitive to different kinases (protein kinase A [PKA] and calmodulin-dependent kinase II [CaMKII]).[24]

Modulation of Excitation-Contraction Coupling

The interaction of Ca^{2+} with a variety of proteins plays a role in a wide range of cellular processes, in addition to muscle contraction and relaxation. Most proteins functioning as Ca^{2+} signaling targets or sensors share a specific Ca^{2+} binding motif referred to as *EF hand.* Calmodulin (CaM) represents the prototypical Ca^{2+} sensor with four EF hands; proteins such as TnC and myosin light chain kinase in vascular smooth muscle originated from a prokaryotic CaM precursor via gene duplications and fusions.[23] Today, related proteins comprise one of the largest protein superfamilies known. Within the myocardium, the direct role of TnC is clear, but less apparent is the incorporation of CaM structure within both the L-type VGCC and RyR2. More recently, the S100 protein family has been linked to a wide range of Ca^{2+}-based intracellular functions.[25] These are calcium-binding proteins that use Ca^{2+} influx to control several cellular processes such as contraction, apoptosis, and gene expression. In the heart, the S100A1 is abundantly present in the left ventricle. When activated, S100A1 interacts with SERCA2 and phospholambin in a calcium-dependent manner. Through its colocalization with the RyR2 receptors, S100A1 enhances CICR-mediated modulation of systolic function. S100A1 also increases the activity of the L-type Ca^{2+} channels and NCX.[26]

Because of the central role of Ca^{2+} in excitation-contraction coupling, changes in Ca^{2+} movement or binding can affect both inotropy and lusitropy (see Fig. 23.4). For example, augmentation or inhibition of Ca^{2+} influx via L-type VGCC alters the activator Ca^{2+} entry and produces a positive or negative inotropic response, respectively. Similarly, physiologic, pathologic (i.e., dilated myopathy), or pharmacologic alterations in function of the RyR2 alter Ca^{2+} release from the SR and the subsequent contractile response.[19,27,28] In addition, physiologic, pathologic, or pharmacologic alterations in activity of SERCA2a, both directly and via PLN phosphorylation, affect the rapidity of Ca^{2+} reuptake into the SR. This influences both lusitropy and inotropy in that the amount of Ca^{2+} taken up during diastole influences how much can be released during the subsequent systole.[19,28,29] Changes in the Ca^{2+} sensitivity of TnC, and perhaps other regulatory proteins, represent a mechanism by which the cardiomyocyte can respond differently to the same amount of Ca^{2+}.[19]

The most prominent physiologic mechanism regulating cardiac Ca^{2+} dynamics and thus mechanical function (both inotropic and lusitropic) is the sympathetic nervous system.[30] Increased sympathetic stimulation acts largely via β-receptors, adenylyl cyclase, and PKA to alter a number of processes, including (1) phosphorylation of L-type VGCC to increase channel open time and enhance RyR2 stimulation; (2) phosphorylation of PLN with subsequent "disinhibition" of SERCA2a and acceleration of SR Ca^{2+} uptake in diastole; (3) phosphorylation of TnI, which in turn leads to a reduction in the affinity of TnC for Ca^{2+}, allowing for more rapid dissociation and relaxation; (4) phosphorylation of RyR2 to augment SR Ca^{2+} release. In addition, secondary effects on a range of ion channels and regulatory proteins have been proposed.[31]

Autoregulation of Mechanical Function: Frequency and Length Dependence

Frequency Dependence

In 1871 Bowditch observed that when an isolated frog heart was stimulated with greater frequency, it contracted with greater force. This "Bowditch effect," now more widely referred to as the *force-frequency relationship (FFR),* has been extensively studied in both isolated and intact muscle preparations. Modern experimental techniques have clearly established that the FFR is modulated by rapid adaptive alterations in intracellular Ca^{2+} cycling and as such

represents true changes in both inotropy and lusitropy of the cardiomyocyte.[32] Because FFR is a fundamental property of cardiac muscle and an index of contractile reserve, it is widely used in assessing the response to conventional and emerging treatments for heart failure.[28,33] The FFR of human ventricular myocardium, and most other mammals, is normally positive—that is, increased stimulation frequency over a physiologic range augments contractile force, which occurs in association with an increase in the amplitude of Ca^{2+} transients. The FFR reflects an acute change in the integrated balance of the intracellular Ca^{2+} concentration, which is modulated primarily by increased SR Ca^{2+} load, and augmented Ca^{2+} flux through the sarcolemma via L-type VGCC and the Na^{+}-Ca^{2+} exchanger.[32] A key feature of the FFR appears to be activation of SERCA2a, at least in part due to PLN phosphorylation via activation of CaMKII.[24] Recent data also suggest a role for CaMKII phosphorylation of RyR2.[34]

In the setting of systolic heart failure, the FFR becomes negative—force declines with increasing stimulation rate—reflecting a pathologic loss of both inotropic and lusitropic reserve. Under these circumstances, Ca^{2+} cycling is impaired at multiple levels related to release from the SR, extrusion from the cell, and, most prominently, impaired SR reuptake by SERCA2a. Investigation has now established that activation (either pharmacologic or by mechanical unloading of the failing myocardium) and/or overexpression of SERCA2a can normalize the FFR.[19,28,33]

Length Dependence

As discussed in Chapter 24, adaptation of the intact heart to increasing volume (preload) plays a critical role in maintaining cardiovascular homeostasis. Fundamentally, a progressive increase in muscle stretch results in a rapid progressive increase in contractile force *(Frank-Starling mechanism).* This has been termed *heterometric autoregulation* and does not reflect a change in Ca^{2+} cycling. Instead, there is formation of an increased number of acto-myosin cross-bridges as the sarcomere lengthens, with maximal tension achieved when the sarcomere length is ~2.2 μm. Work with single myocytes has confirmed that the length-tension relationship is indeed an intrinsic property of individual cells, not the product of a "network effect" produced by the interaction of multiple linked myocytes.[35] Although increasing length augments *contractile force,* it does not augment *contractility,* which by definition is independent of load. Using the concepts of on-time, off-time, and force-time integral as described earlier, an increase in myocyte length increases the number of cross-bridges, each with a unitary force, but not necessarily the on-/off-time and force-time integral for each cross-bridge. As described in Chapter 24, a change in contractility is defined as change in myocardial shortening at any given preload. Accordingly, if a muscle is progressively stretched in the presence of a β-adrenergic agonist, the force produced at any length will be greater than that measured in the absence of the β-agonist.

In 1960 Sarnoff observed in isolated dog hearts that, in addition to the rapid response, there is a slow, secondary response to muscle stretch, whereby contractile force continues to rise despite maintenance of a relatively fixed preload, a process he termed *homeometric autoregulation.*[36] Subsequent investigation by other investigators has established that this "second slow phase" (now commonly known as the *slow force response*) is modulated by a progressive rise in the peak Ca^{2+} transient.[35] Ultimately, the Frank-Starling relationship seems to have at least two cellular/molecular mechanisms: an acute change in myofilament cross-bridging and a secondary, late change in Ca^{2+} cycling. Recent work has focused on autocrine/paracrine mechanisms and downstream signaling processes associated with the slow force response, not necessarily for the mechanical response, but as a component in the maladaptive myocardial remodeling.[37]

Vascular Regulation

Although the function of the heart is to provide a pulsatile, hydromotive source for moving blood into and through the circulation, it is the role of vessels to effectively disperse the pressure and flow generated both during systole and diastole. As such, blood vessels are structurally and functionally adapted to both facilitate global hemodynamics—that is, the elastic recoil of the aorta providing diastolic flow—and meet the differing needs of the various tissues. Central to vascular physiology is dynamic regulation of wall tension and cross-sectional area by vascular smooth muscle (VSM).

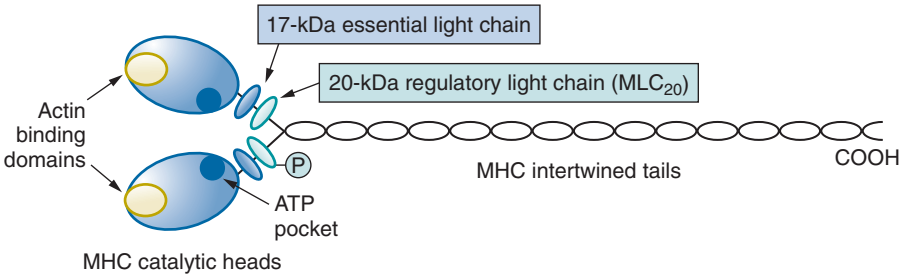
Principles and Caveats

As with the myocardium, regulation of VSM can be simplified as reflecting changes in intracellular free Ca^{2+} concentration ($[Ca^{2+}]i$) and/or myofilament Ca^{2+} sensitivity. These processes are subject to a wide array of local, neural, and humoral mechanisms. Among the local mechanisms are metabolically linked factors that match blood flow to the prevailing metabolic demand. These factors predominate in the myocardium, which requires a continuous delivery of oxygen to support its considerable workload (see Chapter 24). Modern advances in molecular and analytical techniques have permitted elucidation of the downstream subcellular signaling pathways underlying adjustments of vascular tone. The highly complex, multilayered nature of these pathways helps explain why VSM responses can vary with vessel size and location.

In light of the critical importance of vasoregulation in the maintenance of blood pressure and flow, it is not surprising that considerable redundancy exists among signaling pathways and that pathways promoting vasorelaxation are closely intertwined with those promoting vasoconstriction to provide a system of checks and balances. It is important to keep in mind that pharmacologic interventions that raise or lower blood pressure initiate secondary compensatory events, such as the arterial baroreceptor reflex, that are not the direct result of a drug's primary effect on vascular tone. Most clinicians are aware that the integrated action of autonomic nervous tone, circulating chemicals, and local release of substances from the vascular endothelium is important in maintaining "stable" blood pressure. Less well appreciated, however, is the intrinsic *myogenic response* central to regional autoregulation, and the intriguing processes of *vasomotion,* a rhythmic, spontaneous variation in VSM tone within certain vascular beds.[38,39] Myogenic vasoconstriction protects the downstream vasculature from structural damage due to large, acute elevations in blood pressure. Furthermore, it is becoming increasingly apparent that changes in VSM tone induced at one level of the circulation can be electrically propagated to others in what has been termed *conducted responses* modulated by gap junctions.[40] Gap junctions between endothelial cells and VSM cells facilitate direct, nonchemical interactions based on propagated effects on resting membrane potential.[41,42]

Vascular Smooth Muscle Structure

The structure of VSM (smooth muscle) is distinctly different than that of cardiac muscle (striated muscle); although VSM also contains actin and myosin, the filaments are not organized into distinct



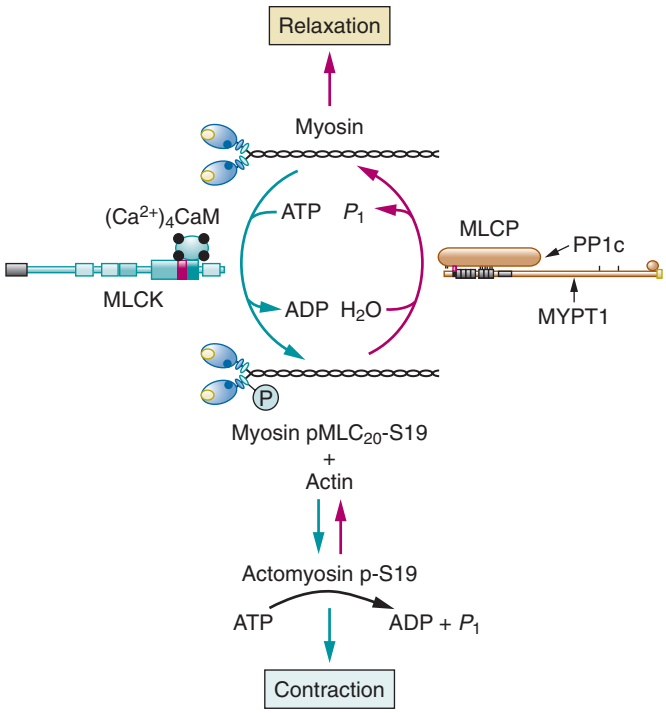
• **Fig. 23.6** Vascular smooth muscle myosin composed of intertwined myosin heavy chain *(MHC)* tails, the 17-kDa and 20-kDa light chains (with the 20-kDa unit representing the 20-kDa regulatory myosin light chain *(MLC_{20})*, and the catalytic heads that bind actin. *ATP,* Adenosine triphosphate. (Adapted with permission from Cole WC, Welsh DG. Role of myosin light chain kinase and myosin light chain phosphatase in the resistance arterial myogenic response to intravascular pressure. *Arch Biochem Biophys.* 2011;510: 160–173.)

bands to transmit force as in cardiac muscle.[43] Instead there is a network of intermediate filaments, dense bodies in the myoplasm, and dense areas along the sarcolemma. In addition, VSM does not have troponin on the actin filaments (Fig. 23.6), reflecting a profound, fundamental difference in how muscle activity is regulated (see later text). *Relative to cardiac muscle, VSM is more dependent on extracellular Ca^{2+}, contracts more slowly, develops greater force, and can function over a wider range of length.* In addition, once at full tension, this effect can be maintained with relatively little energy expenditure despite a reduction in activation (the "latch phenomenon").[44] Finally, in contrast to cardiac muscle, relaxation can be actively initiated and maintained (i.e., vasodilation).

Modulation of Vascular Smooth Muscle Tone

The sequence of events involved with contraction of VSM is shown in Fig. 23.7. In brief, increased $[Ca^{2+}]i$ from either an increased flux of Ca^{2+} into the cell (primarily via L-type VGCCs) or by release of Ca^{2+} from the SR binds CaM at its four EF hand Ca^{2+}-binding sites. Calcium-CaM then activates *myosin light chain kinase* (MLCK), an enzyme that phosphorylates a serine at position 19 of the 20-kDa regulatory *myosin light chain* (MLC_{20}). Located at the junction between the myosin heavy chain "tails" and the globular "heads" containing the actin-binding domains and ATP binding sites (see Fig. 23.6), MLC_{20} regulates the interaction between actin and myosin; when dephosphorylated, MLC_{20} prevents actin-myosin interaction. Alternatively, with phosphorylation of MLC_{20}, cross-bridge formation between the myosin heads and actin filaments ensues and the VSM contracts. Relaxation is produced when $[Ca^{2+}]i$ declines, inactivating MLCK and inducing dephosphorylation of MLC_{20} by *myosin light-chain phosphatase* (MLCP). Besides MLC_{20} phosphorylation, thin filament-associated proteins such as *caldesmon* and *calponin* also control actin-myosin interactions; when dephosphorylated, these proteins block myosin binding and/or inhibit acto-myosin ATPase activity.[45] *Despite the complexity of vasoregulation, VSM tone is ultimately dictated by the phosphorylation state of MLC_{20} and, to a lesser extent, regulatory proteins such as caldesmon and calponin.* A third process involving structural changes in the cytoskeleton that facilitate force transmission appears most relevant in vascular remodeling.[45]

The balance between VSM contraction and relaxation or "tone" is determined by factors that can be broadly classified as (1) purely mechanical, reflecting an autoregulatory myogenic effect; (2) electrical, modulated by cellular depolarization or hyperpolarization; and (3) chemical, modulated by receptors on VSM cells and adjacent



• **Fig. 23.7** Events involved with contraction/relaxation of vascular smooth muscle. Calcium binds calmodulin *(CaM)* at its four EF hand calcium ion (Ca^{2+})-binding sites, and then activates myosin light chain kinase *(MLCK),* which in turn phosphorylates the 20-kDa regulatory myosin light chain *(MLC_{20}).* The interaction between actin and myosin is regulated by the phosphorylation state of MLC_{20}; with phosphorylation of MLC_{20} at serine 19 *($pMLC_{20}$-S19),* cross-bridge formation between the myosin heads and actin filaments ensues with adenosine triphosphate (ATP) hydrolysis and the vascular smooth muscle contracts. When $pMLC_{20}$-S19 is dephosphorylated by myosin light chain phosphatase *(MLCP),* relaxation results. The MLCP complex has both protein phosphatase catalytic substrate subunit 1c *(PP1c)* and regulatory components (myosin phosphatase target subunit 1 *[MYPT1]),* and the dynamic interaction between Ca^{2+}-CaM, MLCK, and MLCP is influenced by a wide range of processes. *ADP,* Adenosine diphosphate; *MLCP,* myosin light chain phosphatase; *P_1,* ———————. (Adapted with permission from Cole WC, Welsh DG. Role of myosin light chain kinase and myosin light chain phosphatase in the resistance arterial myogenic response to intravascular pressure. *Arch Biochem Biophys.* 2011;510:160–173.)

System	Stimulus	VSM transducer	Signal pathway	Response	Primary Effect
Neurohumoral	Angiotensin II	GPCR (All)	Primary: PLC activation Secondary: rho-kinase activation	Increase intracellular Ca^{2+}	Vasoconstriction
	Vasopressin	GPCR (V_1)			
	Histamine	GPCR (H_1)	Primary: AC activation Secondary: Endothelial H_1 stimulation, NO release	Decrease Ca^{2+} sensitivity Decrease intracellular Ca^{2+}	Vasodilation
	Epinephrine	GPCR (β_2)	AC activation		
Endothelial	Endothelin	GPCR (ET_A, ET_B)	PLC activation	Increase intracellular Ca^{2+}	Vasoconstriction
	Thromboxane A_2	GPCR (TXA_2)	PLC activation		
	PGH_2	GPCR (TXA_2/PGH_2)	PLC activation		
	Nitric oxide	Diffusion →	GC activation	Decrease Ca^{2+} sensitivity Decrease intracellular Ca^{2+}	Vasodilation
	Prostacyclin (PGI_2)	GPCR (IP_1)	AC activation		
	EDHF	? Diffusion	?	Hyperpolarize – decrease Ca^{2+} entry	
	Hydrogen sulfide	Diffusion	S-sulfhydration of K_{ATP} channel		
Local	Adenosine	GPCR (A_{2a})	Primary: AC activation Secondary: GC activation	Decrease Ca^{2+} sensitivity Hyperpolarization – decrease Ca^{2+} entry	Vasodilation
Mechanical	Decrease vessel wall tension	Membrane depolarization	Opening VGCC	Increase intracellular Ca^{2+}	Vasoconstriction
	Increase vessel wall tension	Membrane hyperpolarization	K^+ channels	Decrease Ca^{2+} entry	Vasodilation
Autonomic	Norepinephrine	GPCR (α_1)	Primary: PLC activation Secondary: rho-kinase activation	Increase intracellular Ca^{2+}	Vasoconstriction
	Acetylcholine	GPCR (muscarinic subtypes)			

• **Fig. 23.8** AC, Adenylyl cyclase; *Ca^{2+},* calcium ion; *EDHF,* endothelium-derived hyperpolarizing factor; *GC*, guanylyl cyclase; *GPCR,* G protein–coupled receptor; *NO,* nitric oxide; *PGH_2,* prostaglandin H_2; *PLC,* phospholipase C; *TXA_2,* thromboxane A_2; *VGCC,* voltage-gated calcium channel; *VSM,* vascular smooth muscle.

endothelium. A brief summary of endogenous modulators of vasomotor tone and the signaling pathways that evoke an effect on $[Ca^{2+}]_i$ and/or the sensitivity of contractile proteins is shown in Fig. 23.8. It is important to recognize that, even though VSM cells are commonly lumped together as a singular entity, there is marked phenotypic diversity reflecting tissue differences in the response to specific stimuli.[46] For example, the vascular response to local hypoxia in the lung (vasoconstriction) is opposite that in the brain (vasodilation).

Mechanisms of Vasoconstriction

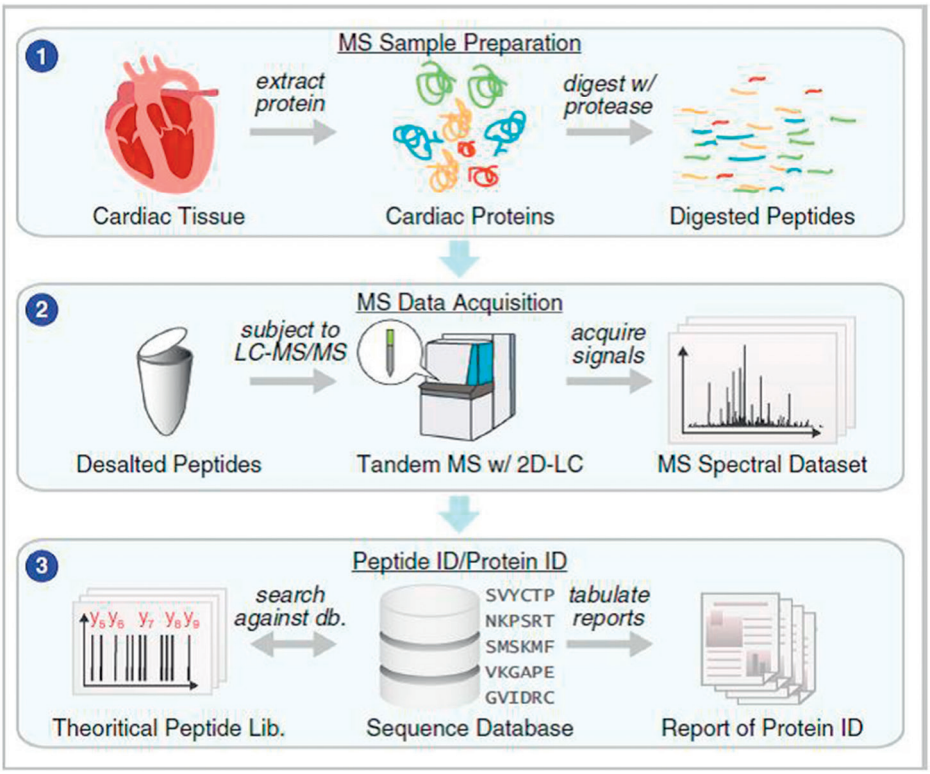
Unlike cardiac muscle, depolarization is not required for contraction of VSM; Ca^{2+} entry into the cytoplasm alone can produce a response. However, membrane depolarization does play a role in the response to some stimuli and in the maintenance of tone.

Increasing $[Ca^{2+}]_i$ by increased trans-sarcolemmal influx:

- Voltage-gated (or operated) calcium channels (VGCC). These include both L- and T-type VGCCs, with L-type representing the primary path for activating Ca^{2+} influx.
- Receptor-operated calcium channels (ROCC). These represent Ca^{2+}-permeable channels gated by binding of an agonist to G-protein–coupled receptors (GPCRs) or tyrosine kinase–coupled receptors. Subsequent Ca^{2+} entry into VSM produces contraction.
- Store-operated calcium channels (SOCC). When intracellular Ca^{2+} stores become depleted, the process of "capacitative Ca^{2+} entry" via these channels is activated. It has been postulated that there is release of a diffusible messenger by the depleted intracellular Ca^{2+} store that affects sarcolemmal Ca^{2+} channels.[47]

Increasing $[Ca^{2+}]_i$ by SR Ca^{2+} release:

- Inositol triphosphate receptors (IP_3R). With agonist activation of a variety of GPCRs (see Fig. 23.8), phospholipase C (PLC) is activated which, in turn, leads to the hydrolysis of phosphatidylinositol bisphosphate (PIP_2) and formation of 1,2-diacylglycerol (DAG) and IP_3. Ca^{2+} release from the SR is then stimulated by IP_3 binding to the IP_3R, a tetrameric polypeptide with a central aqueous channel that permits Ca^{2+} movement into the cytosol. This receptor has binding domains for both IP_3 and Ca^{2+}, and release of Ca^{2+} from the SR following binding to the IP_3R is biphasic (fast then slow).[45] As an example of integrative feedback, the IP_3R is regulated both by kinases involved with vasodilator pathways (i.e., PKA and protein kinase G [PKG]; see later), which inhibit Ca^{2+} release, and by high $[Ca^{2+}]_i$ (negative feedback).
- The RyR. Although less important in VSM than cardiomyocytes, "calcium-induced calcium release" involving an RyR can provide rapid amplification of the Ca^{2+} signal induced by transsarcolemmal Ca^{2+} entry. Primary RyR isoforms in VSM are RyR2 and RyR3.



• **Fig. 23.9** A summary of a typical sequence of analytical and computational methods in proteomic studies. *1,* Cardiac samples are processed to extract the proteomes or subproteomes of interest, which may then be proteolyzed to obtain peptide digests. *2,* The resulting peptides are desalted and subjected to analytical chemistry analysis (LC-MS/MS) to build the spectral database relating to protein structure. *3,* The peptide sequences present in the spectral database can then be identified using a sequence database search or a spectral library search. *LC-MS/MS,* Liquid chromatography-tandem mass spectrometry; *MS,* mass spectrometry. (Modified with permission from Lam MP, Lau E, Ng DC, et al. Cardiovascular proteomics in the era of big data: experimental and computational advances. *Clin Proteomics.* 2016;13:23.)

Increased myofilament sensitivity to $[Ca^{2+}]_i$:

- Inhibition of MLCP prevents dephosphorylation of MLC_{20} phosphorylation to augment the force developed by VSM at a fixed $[Ca^{2+}]_i$. MLCP is a holoenzyme (see Fig. 23.7) composed of a type 1 protein phosphatase (PP1c) catalytic subunit, a large regulatory subunit (MYPT1), and a small subunit of unknown function. The MYPT1 subunit dictates activation of PP1c, and in targets myosin. Accordingly, inhibition of MLCP is accomplished by phosphorylation of MYPT1.[38]
- Regulation of thin filament–associated proteins. Caldesmon is an actin-binding protein located on actin filaments that blocks myosin binding. This effect is prevented by phosphorylation, primarily via mitogen-activated protein kinase (MAPK) and PKC. Calponin, another actin- and calmodulin-binding protein that is relatively specific for VSM, is also located on actin filaments and inhibits acto-myosin ATPase and actin filament motility. Phosphorylation of calponin by PKC and CaMKII markedly decreases affinity for actin, which reduces its ability to inhibit acto-myosin ATPase.[45]
- Following an increase in intracellular Ca^{2+}, the high cytosolic concentration of Ca^{2+} forms a complex with calmodulin. This complex activates a kinase that phosphorylates the regulatory light chain of myosin. This phosphorylation results in activation of myosin adenosine triphosphatase (ATPase) by actin and the cycling of myosin cross-bridges along the actin filaments leading to muscle contraction (see Fig. 23.9).[48]
- Alteration in intracellular pH. Myofibrillar acto-myosin ATPase activity is pH-dependent and is increased by alkalinization. Intracellular pH can be rapidly increased by agonist-modulated activation of the Na^+/H^+ exchanger, an electroneutral transporter that mediates the 1:1 exchange of extracellular Na^+ for intracellular H^+, and is generally not activated in the basal state.[49] Activation of the Na^+/H^+ exchanger can be accomplished by phosphorylation through PKC- and Ca^{2+}-dependent pathways.

Mechanisms of Vasodilation

Decreasing $[Ca^{2+}]_i$ by decreasing entry:

- K^+ channels. These channels are critical to the establishment and regulation of membrane potential in VSM cells and thus a key regulator of inward Ca^{2+} via the VGCC. At least four different classes of K^+ channel exist, the most prominent being the (1) ATP-sensitive (K_{ATP}); (2) large-conductance Ca^{2+}-activated (BK_{Ca}); (3) voltage-activated (K_v); and (4) inward rectifier (K_{IR}). Opening of K^+ channels results in outward conductance, membrane hyperpolarization, reduced flux through VGCCs, and vasodilation. Again, as an example of integrative control, processes that induce *closure* of K^+ channels promote vasoconstriction.[50]

Decreasing $[Ca^{2+}]_i$ by increasing transsarcolemmal Ca^{2+} efflux:

- Plasma membrane Ca^{2+} ATPase (PMCA). The primary process for Ca^{2+} extrusion from the cell is active (energy-dependent)

removal by PMCA. Activated by CaM, PMCA produces Ca^{2+} efflux from the cell in exchange for influx of $2H^+$. PMCA is regulated by multiple protein kinases in vasodilator pathways (PKA and PKG along with CaMKII all enhance PMCA affinity of Ca^{2+} and augment Ca^{2+} uptake).[51] In addition, the activity of PMCA is enhanced by some hormones and reduced by IP_3, another example of integrative control.

- The Na^+/Ca^{2+} exchanger. Unlike the PMCA that uses energy derived from ATP, the Na^+/Ca^{2+} exchanger uses energy from the electrochemical gradient for Na^+, transporting Na^+ into the cell while removing Ca^{2+} in a 3:1 ratio.

Decreasing $[Ca^{2+}]_i$ by enhanced SR Ca^{2+} reuptake:

- SERCA activity. As with cardiomyocytes, cytosolic Ca^{2+} is reduced by active SERCA reuptake into the SR using ATP as the energy source. This Ca^{2+} is then bound within the SR lumen, primarily by calreticulin and calsequestrin, to keep the free Ca^{2+} concentration relatively low, thus reducing the energy required to pump Ca^{2+} against a concentration gradient. Also, similar to the myocardium, VSM SERCA pumps are regulated by the phosphorylation state of PLB; when not phosphorylated, PLB inhibits SERCA activity (promoting VSM contraction). In contrast, when phosphorylated, SERCA inhibition by PLB is relieved, promoting Ca^{2+} reuptake and VSM relaxation.[52]

Modulators of decreased myofilament sensitivity to $[Ca^{2+}]_i$:

- Phosphorylation of MLCK. This is the main process by which desensitization of VSM occurs. Several kinases involved with vasodilatory pathways can phosphorylate MLCK to *reduce affinity for the Ca^{2+}-CaM complex,* resulting in decreased Ca^{2+} sensitivity of MLC_{20} for phosphorylation.

Vasoregulation Signaling Pathways

The processes described for regulating $[Ca^{2+}]_i$ or Ca^{2+} sensitivity are generally subject to upstream influences that activate, enhance, impede, or inhibit the response. Consistent with the wide range of local, neural, and humoral influences necessary for maintaining vascular homeostasis, the signaling pathways involved are complex and interconnected.

Regulation of $[Ca^{2+}]_i$

Three mechanisms are most prominent, with two being primarily associated with vasodilation (decreased $[Ca^{2+}]_i$), and the other with vasoconstriction (increased $[Ca^{2+}]_i$). However, inhibition of vasodilatory pathways promotes vasoconstriction, and vice versa.

Vasodilation: The G-Protein–cAMP Pathway

Formation of cyclic adenosine monophosphate (cAMP) following activation of adenylyl cyclase leads to *activation of PKA* and subsequent inhibition of Ca^{2+} mobilization at multiple levels, including inhibition of SR Ca^{2+} release, augmentation of SR Ca^{2+} reuptake, and inhibition of Ca^{2+} entry via VGCCs. In addition, PKA phosphorylation of MLCK results in decreased myofilament Ca^{2+} sensitivity. *Adenylyl cyclase activity is stimulated via G_s protein activation (promoting VSM relaxation) or inhibited via G_i protein activation (promoting vasoconstriction).*

Vasodilation: Nitric Oxide–cGMP Pathway

NO activates guanylyl cyclase to increase *formation of cyclic guanosine monophosphate (cGMP), which in turn activates PKG.* Vasorelaxation is then produced by multiple mechanisms, including phosphorylation of PLN and activation of SERCA, stimulation of the PMCA and Na^+/Ca^{2+} exchanger, inhibition of Ca^{2+} release from the SR by phosphorylation of the IP_3R, activation of K^+ channels, resulting in membrane hyperpolarization and decreased Ca^{2+} entry via VGCCs.

Vasoconstriction: PLC-Phosphatidylinositol Pathway

Multiple endogenous modulators of vascular tone (norepinephrine, angiotensin II, endothelin-I [ET-I]) bind to GPCRs that activate PLC to produce DAG and IP_3 (see Fig. 23.8). As noted earlier, IP_3 binds to the IP_3R to evoke SR Ca^{2+} release, and DAG activates PKC, ultimately leading to phosphorylation of VGCCs and increased Ca^{2+} influx.

Regulation of Myofilament Ca^{2+} Sensitivity

Increased myofilament sensitivity to Ca^{2+}, with resultant augmentation of vasomotor tone, can be accomplished by phosphorylation of multiple proteins via three principal pathways:

1. rho Kinase. Agonist-induced Ca^{2+} sensitization is largely mediated by activation of the small GTPase (rho) via GPCRs. Activated (rho) then interacts with rho kinase, leading to its activation, which, in turn, *can increase myofilament Ca^{2+} sensitivity* and promote contraction by both inhibition of MLCP and direct MLC_{20} phosphorylation.[53]
2. Protein kinase C. Activation of PKC via multiple mechanisms leads to *Ca^{2+} sensitization.* A variety of PKC-mediated mechanisms have been proposed: (1) PKC-dependent phosphorylation of caldesmon and calponin; (2) phosphorylation of myosin phosphatase target subunit 1 (MYPT-1) with resultant inhibition of MLCP; (3) phosphorylation of MLC_{20}; (4) activation of the Na^+/H^+ exchanger.
3. Tyrosine kinases. Although they have a number of independent functions, tyrosine kinases are also involved in the activation of rho and PKC, providing the basis for cross-talk among different kinase pathways involved in the *Ca^{2+} sensitization.* Both tyrosine kinases and phosphatases are present in large amounts in VSM, and they influence other processes such as ion channel gating in addition to Ca^{2+} sensitization of the contractile process by phosphorylation of MLC_{20}.[54]

Regulation of Vascular Smooth Muscle by the Endothelium

The vascular endothelium is a single layer of thin cells lining the intimal surface of blood vessels. The past 20 years have seen a profound increase in the understanding of how VSM tone is regulated on a second-to-second basis by the vascular endothelium. With this understanding has come an appreciation of the critical role of the vascular endothelium in health and disease, which has made it an important target for drug development.[42,55]

Endothelial cells modulate VSM tone via synthesis and release of endothelium-derived relaxing factors and endothelium-derived contracting factors (see Fig. 23.8). The relative balance is determined by anatomic location (i.e., relaxing factors predominate in most areas, but in peripheral veins and large cerebral arteries contracting factors are more prominent) and physiologic or pathologic stress.

Endothelium-Derived Relaxing Factors

Nitric Oxide

Synthesized by endothelial nitric oxide synthase (eNOS), a Ca^{2+}-calmodulin-dependent enzyme, NO is the result of oxidation of L-arginine. *An increase in cytosolic Ca^{2+} in response to mechanical shear stress and/or a wide range of agonists with endothelial receptors (acetylcholine, bradykinin, serotonin, substance P, thrombin, vasoactive intestinal peptide) stimulates NO formation and release.* The molecule

then diffuses into adjacent VSM cells and produces vasodilation via the cGMP pathway.

Prostacyclin

Produced via the cyclooxygenase pathway for arachidonic acid metabolism, prostacyclin (prostaglandin I_2 [PGI_2]) produces vasodilation via the cAMP pathway. As with NO, endogenous agonists (bradykinin, thrombin, serotonin, adenine nucleotides) induce *PGI_2 synthesis by triggering an increase in cytosolic Ca^{2+}*. PGI_2 also inhibits platelet adhesion to the vascular endothelium.

Endothelium-Derived Hyperpolarizing Factor

Initially described as a factor derived from endothelium that promotes vasodilation independent of NO and PGI_2, the precise molecular biology of endothelium-derived hyperpolarizing factor (EDHF) remains unclear; cellular effects of EDHF appear to reflect activation of K_{ATP} channels. Studies indicate that VSM can produce the gas hydrogen sulfide (H_2S) by metabolism of the amino acid L-cysteine and that H_2S promotes vasodilation. Recent data indicate that H_2S directly activates K_{ATP} channels, possibly by S-sulfhydration of cysteine residues, to produce membrane hyperpolarization and closure of VGCCs.[56] Ultimately, existing data suggest that H_2S is at least one of the EDHFs elaborated by the endothelium.

Another mechanism for endothelial hyperpolarization was recently shown through the role of endothelial Ca^{2+}-calmodulin–gated K^+ channels of intermediate and small conductance (KCa3.1 and KCa2.3, respectively). Following an increase in $[Ca^{2+}]_i$ via release from the SR or entry through VGCC, these K^+ channels hyperpolarize the endothelial cell membrane from a resting potential of −20 to −40 mV toward more negative values (−50 to −89 mV). This hyperpolarization reduces the opening of VGCC, leading to a drop in $[Ca^{2+}]_i$ and VSM relaxation.[57]

Endothelium-Derived Contracting Factors

Endothelin I

Although a family of endothelin isoforms exists (ET-1, ET-2, ET-3), the only one synthesized by endothelial cells is ET-1. Stimulated by angiotensin II, platelet-derived factors, thrombin, cytokines, reactive oxygen species, and local shear forces, an endothelin-converting enzyme cleaves a precursor protein to yield ET-1. Vasoconstriction by ET-1 is produced by binding to ETA and ETB receptors on VSM; these GPCRs lead to IP_3 formation. ET-1 also binds to ETB receptors on endothelial cells to produce NO. The end result of vasoconstriction versus vasodilation then reflects tissue type and receptor density.

Cyclooxygenase Products

Direct physical effects such as stretch along with local factors (i.e., hypoxia) and circulating hormones initiate formation of prostaglandin H_2 (PGH_2), thromboxane A_2 (TXA_2), and superoxide anions via the cyclooxygenase pathway. In the synthetic pathway, PGH_2 is upstream from TXA_2 but nonetheless retains biologic activity, with both substances producing vasoconstriction via the PLC-phosphatidylinositol pathway. In contrast, superoxide anions inactivate NO, thus removing a counterbalancing vasodilator effect.

Examples of Local, Autonomic, and Humoral Regulation of Vascular Smooth Muscle

Local Regulation

The *myogenic* response of small arteries and arterioles is characterized by intrinsic vasoconstriction after an increase of transmural pressure and by vasodilation following a decrease. It plays a critical role in the autoregulation of flow in different vascular beds and does not require the presence of an intact endothelium, although the factors released from the endothelium can modulate the response as can autonomic tone. As transmural pressure rises, membrane depolarization occurs with a subsequent rise in $[Ca^{2+}]_i$, largely via VGCC opening. However, the mechanism of this depolarization, as well as the role of intracellular Ca^{2+} release in the myogenic response, remains controversial, and the contribution of various second-messenger systems, along with the role of pulsatility and signals for adjacent vascular segments, remains unclear.[38,58]

Metabolites (e.g., carbon dioxide, adenosine, K^+) released locally and a decline in tissue oxygen tension will relax VSM. With increased metabolic rate (i.e., exercise), there is greater formation and release of metabolites, providing a mechanism to match tissue oxygen supply to an increased oxygen demand. These effects are amplified by increased body temperature and decreased tissue pH.

Although low oxygen tension has a direct vasodilating effect in systemic vascular beds, it causes vasoconstriction in the pulmonary circulation. Hypoxic pulmonary vasoconstriction (HPV) is an important protective mechanism promoting ventilation-perfusion matching. The molecular mechanism underlying HPV is uncertain, although several theories have been proposed.[59] One theory involves a closure of K^+ channels by hypoxia, resulting in vascular smooth muscle depolarization, Ca^{2+} entry, and contraction. A second theory proposes that oxygen tension regulates the production of reactive oxygen species, which control transmembrane Ca^{2+} flux via a direct action on sulfhydryl groups in the Ca^{2+} channel protein of the vascular smooth muscle cell.[59]

Autonomic Regulation

Adrenergic

Both α- and β-adrenoceptors are present on VSM and endothelial cells. Norepinephrine release from sympathetic nerve terminals acts predominantly on postjunctional VSM α_1-adrenergic receptors to produce contraction. However, stimulation of α_2 receptors on endothelial cells induces NO release and vasodilation. In contrast, epinephrine is humoral and affects both α_1 and β_2 receptors that mediate relaxation; the net result can vary among vascular beds, reflecting the distribution and affinity of different receptor subtypes.

Cholinergic

Muscarinic cholinergic receptors are also present on VSM and endothelial cells. Although it is less prominent than sympathetic tone in vasoregulation, parasympathetic stimulation of muscarinic receptors evokes VSM contraction, primarily in the venous circulation. In the arterial circulation, stimulation of muscarinic receptors is primarily vasorelaxant via stimulation of endothelial cells to release NO.

Humoral

Vasopressin is formed in the hypothalamus and secreted by the posterior pituitary gland. In VSM, two main subtypes of GPCRs for vasopressin are found (V1 and V2), with V1 agonism producing vasoconstriction and V2 stimulation producing vasodilation. The end response depends on the regional circulation being studied. In addition to direct VSM effects, vasopressin also interacts with prejunctional and postjunctional adrenergic receptors to facilitate the effects of adrenergic agonists.

Angiotensin II is formed when the liver-derived precursor angiotensinogen is cleaved by renin (released by the kidney in

response to decreased blood pressure or delivery of Na^+ and Cl^-), to produce angiotensin I, which is further cleaved by angiotensin-converting enzyme to yield biologically active angiotensin II, a potent vasoconstrictor. Effects of angiotensin II are modulated by stimulation of a GPCR and activation of PLC.

Serotonin is derived from tryptophan and found primarily in the gastrointestinal tract and central nervous system. It is also found in platelets and contributes to both aggregation and local vasoconstriction via activation of 5-HT receptors. However, the vascular response to serotonin is complex, with the molecule producing vasodilation in some vascular beds. This effect appears to be influenced by both serotonin concentration and the relative density of receptor subtypes that modulate vasoconstriction or dilation.[60]

Primarily generated by mast cells and to a lesser extent basophils, when released into the circulation *histamine* causes local, and if intense enough systemic, vasodilation that can be profound. Multiple histamine GPCR subtypes exist, but smooth muscle responses appear to be more affected by which signaling pathways are linked to the receptor.[61] For example, in VSM, H_1 receptors are primarily linked to the adenylate cyclase pathway to directly produce vasodilation, and this effect can be amplified by stimulation of H_1 receptors on endothelial cells to release NO. In contrast, in bronchial smooth muscle, H_1 receptors are linked to the DAG/IP_3 pathway and produce constriction.

Emerging Developments

Proteomics to Advance Cardiac Physiology

Proteomics, the large-scale study of proteins, has emerged as an important, maturing method in the study of cardiac physiology and pathophysiology over the past two decades. Molecular biologists focused on cardiac physiology and disease have recognized the shortcomings of genomics and transcriptomics. The knowledge provided by massive databases of DNA sequences and RNA transcripts cannot fully elucidate the physiology.[62] To move from genotype to phenotype, it is necessary to understand what proteins are actually expressed and how those proteins interact with other proteins; this is the focus of proteomics.

The mammalian heart expresses thousands of genes; more than 8000 human proteins relevant to cardiac physiology have been described.[63] Considering alternative splicing, posttrancriptional changes, and posttranslational modifications, the cardiac proteome is immensely complex; it is clear that cardiac proteins, as with other organs, interact in a complex way. This high dimensionality necessitates analysis of the proteins (i.e., the "proteome") using complex statistical methods and computational approaches. Fig. 23.9 summarizes the general line of attack in proteomic studies (see legend for explanation).

The science of proteomics applied to cardiovascular medicine is poised to advance the field in important and likely unanticipated ways.[64] The identification of biomarkers for cardiomyocyte necrosis (e.g., troponin) and subsequently the development of more sensitive troponin assays are apropos examples of the power of proteomics in cardiovascular medicine.

Key Points

- Action potentials vary within the heart and can be classified as fast or slow in nature. Characteristics of action potentials determine or contribute to cardiac automaticity, bathmotropy (cellular excitability), and dromotropy (impulse conduction).
- The normal heartbeat begins with spontaneous depolarization of cells within the sinoatrial node and is the result of both a slow, inward Na^+ current (also known as a "funny" current) and spontaneous, rhythmic release of Ca^{2+} from the sarcoplasmic reticulum.
- Within the myocardium proper, fast action potentials occur and are initiated by rapid entry of Na^+ into the cell via voltage-gated Na^+ channels. These channels represent an important site for pharmacologic intervention.
- During phase 2 of the action potential, voltage-gated Ca^{2+} channels open and Ca^{2+} enters the cardiomyocyte. This small amount of activator Ca^{2+} induces release of a larger amount from the sarcoplasmic reticulum in what has been termed *calcium-stimulated calcium release*. As intracellular Ca^{2+} rises, binding to troponin C occurs, allowing interaction between actin and myosin and resulting in cardiomyocyte contraction. The amount of Ca^{2+} released during each beat along with the sensitivity of contractile proteins dictates myocardial inotropy (active relaxation).
- Relaxation ensues when Ca^{2+} is taken back into the sarcoplasmic reticulum or extruded from the cell. The rate at which Ca^{2+} is removed from the cytoplasm, in addition to how quickly it dissociates from the contractile proteins, dictates myocardial lusitropy.
- When the myocardium is stimulated more frequently, adaptations occur within the cardiomyocyte, causing Ca^{2+} to be cleared more quickly during diastole and released in larger amounts during systole. As a result, the myocardium exhibits increased inotropy (contractility) and lusitropy in what has been termed the *force-frequency relationship*.
- When the myocardium is stretched, the number of actin-myosin cross-bridges increases and the overall force of contraction increases. This represents the length-tension relationship, or Frank-Starling mechanism. Importantly, this effect initially does not involve an increase in Ca^{2+} release from the sarcoplasmic reticulum or a change in Ca^{2+} sensitivity of the contractile proteins, so although the force of contraction increases, myocardial inotropy does not. By definition, increased inotropy means an augmented ability to do work independent of muscle stretch.
- In contrast to the myocardium, Ca^{2+} entering vascular smooth muscle binds with calmodulin rather than troponin. The

Ca^{2+}-calmodulin complex then activates myosin light chain kinase, which phosphorylates the 20-kDa regulatory myosin light chain, releasing inhibition of the actin-myosin interaction. Relaxation then ensues when the regulatory myosin light chain is dephosphorylated by myosin light chain phosphatase.

- Vascular smooth muscle tone is critical for maintaining blood pressure and proper distribution of tissue blood flow, and multiple levels of regulation exist. These encompass autonomic, humoral, and local processes as well as intrinsic myogenic responses to stretch that affect either the phosphorylation state of the regulatory myosin light chain or the sensitivity of contractile proteins.

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24

Cardiovascular Physiology: Integrative Function

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CHAPTER OUTLINE

Cardiac Physiology
- Basic Cardiac Anatomy
- Determinants and Control of Cardiac Output
  - *Heart Rate*
  - *Stroke Volume*
  - *Preload*
  - *Contractility*
  - *Afterload*
- The Cardiac Cycle
- Indices of Cardiac Function
  - *Calculation of Cardiac Output Using the Thermodilution Method*
  - *Cardiac Function Curves With the Pulmonary Artery Catheter*
  - *Cardiac Function Using the Transpulmonary Thermodilution Method*
  - *Isovolumic Contraction Index*
  - *Ejection Phase Index*
- Ventricular Pressure-Volume Loop: End-Systolic Pressure-Volume Relations

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- Pressure Changes in Systemic and Pulmonary Circulations
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- Oxygen Transport in the Blood
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- Diffusion of Oxygen to Tissues: Capillary to Cell Oxygen Delivery
- Measurement of Oxygen Consumption
- Critical Oxygen Delivery

Determinants of Myocardial Oxygen Supply and Demand
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- Coronary Flow Reserve
- Myocardial Oxygen Demand
- Impaired Myocardial Oxygen Balance: Mechanisms of Myocardial Ischemia

Emerging Developments
- Noninvasive Perioperative Monitoring

A thorough understanding of the basic principles of cardiovascular physiology is essential for effective and safe patient management in the perioperative period. This information provides a theoretical rationale for the use of drugs, intravenous infusions, and other therapeutic measures to maintain and optimize vital organ function.

The primary role of the circulation is to provide sufficient blood flow to satisfy the metabolic demands of body tissues. However, the circulation has additional functions, not considered here, including return of carbon dioxide to the lungs and other metabolic end products to the kidneys, supply of nutrients absorbed from the gastrointestinal tract to the tissues, regulation of body temperature, and distribution of hormones and other agents that regulate cellular function.

Tissue blood flow depends on activity of both the heart and blood vessels (Fig. 24.1); arterial pressure, a major determinant of tissue blood flow, is the product of cardiac output and total peripheral resistance, while local vascular resistance, the other major determinant of tissue blood flow, is a function of local vasomotor tone.[1] The complex interplay of the relationships summarized in Fig. 24.1 is the primary focus of this chapter.

Cardiac Physiology

Basic Cardiac Anatomy

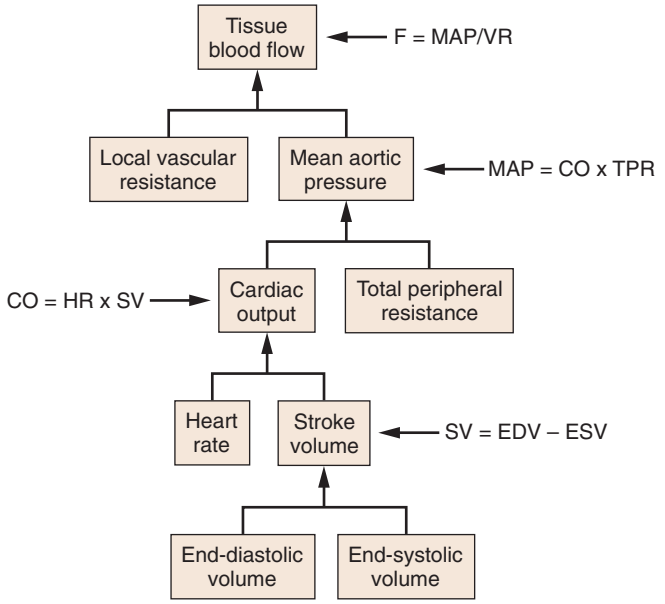
The atria are thin-walled structures that are similar in size and dimension on the right and left sides of the heart. However, the

Abstract

A thorough understanding of cardiovascular physiology is a cornerstone of patient management in the perioperative period. The primary role of the cardiovascular system is to provide sufficient blood flow to satisfy the metabolic demands of the body tissues. This chapter presents the primary determinants of tissue blood flow (arterial pressure and local vascular resistance) and the factors that alter them. Because of its critical pumping role, the physiology of the heart is given particular emphasis. The major determinants of stroke volume, i.e., preload, contractility, and afterload, are discussed. Indices of cardiac function are reviewed, including cardiac output using thermodilution, ejection fraction from image-based measurements, and myocardial contractility assessed by cardiac function curves using a pulmonary artery catheter, and by end-systolic pressure-volume relations from pressure-volume loops. The determinants of coronary blood flow and myocardial oxygen demand are described, as well as how an imbalance between these variables may produce myocardial ischemia. Other topics covered include: 1) the principles of hemodynamics, and the mechanisms regulating function of the various vessel types, including the large arteries, arterioles, capillaries, and veins; 2) the transport of oxygen by blood and its delivery to the body tissues; 3) methods to measure tissue oxygen consumption, along with their advantages and limitations; 4) the role of the capillaries in tissue oxygen delivery, and in fluid filtration and absorption; 5) the responses elicited by activation of the major circulatory reflexes (the arterial baroreceptor, Bezold-Jarisch, and Bainbridge reflexes); 6) emerging developments in noninvasive perioperative cardiovascular monitoring.

Keywords

cardiac function
hemodynamics
oxygen transport
capillary function
tissure edema
myocardial ischemia



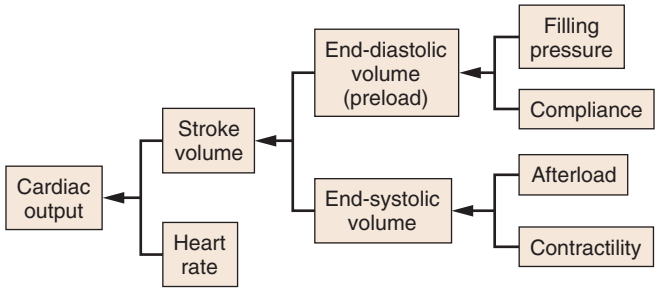
• **Fig. 24.1** The cardiac and peripheral vascular factors (and their interrelationships) determining tissue blood flow. *CO,* Cardiac output; *EDV,* end-diastolic volume; *ESV,* end-systolic volume; *F,* flow; *HR,* heart rate; *MAP,* mean arterial pressure; *SV,* stroke volume; *TPR,* total peripheral resistance; *VR,* vascular resistance. (Modified from Rothe CF. Cardiodynamics. In: Selkurt EE, ed. *Physiology*. Boston: Little, Brown and Company; 1971:321.)

left and right ventricles (LV and RV) are quite different; the LV has an ellipsoidal shape and is thick-walled, whereas the RV has a thin wall and is crescent-shaped (owing to the concave free wall opposite the convex interventricular septum) approximating a pyramid with a triangular base longitudinally.[2] The mass of the LV is approximately six times that of the RV, which reflects their respective pressure loads (systemic vascular resistance is 10 times the pulmonary vascular resistance) and hence, the RV performs ¼ stroke work compared with the LV. Because of its thin wall, acute increases in afterload are poorly tolerated by the RV. A high degree of interaction and interdependence exists between the ventricles because of their shared interventricular septum and the restraining influence of the surrounding pericardium (except after cardiac surgery).[3] The shift of the interventricular septum secondary to an increase in volume or pressure load of one ventricle impairs the filling of the other ventricle by reducing chamber compliance and diastolic filling.[4]

At the cellular level, the heart consists primarily of cells that contract (myocytes) or conduct impulses (Purkinje fibers). The myocardium proper is composed of individual myocytes linked by specialized gap junctions to form a functional syncytium that allows rapid conduction of electrical charge, and intercalated discs that modulate force transmission during contraction. Cardiac cells display five basic characteristics: excitability (bathmotropy), conductivity (dromotropy), rhythmicity (chronotropy), contractility (inotropy), and relaxation (lusitropy).

Determinants and Control of Cardiac Output

Cardiac output is the volume of blood pumped to body tissues per minute; it is equal to the product of heart rate and stroke volume (Fig. 24.2). Normal values for cardiac output are 5 to 6 L/min in a 70-kg man, with a heart rate of 80 beats/min and a stroke



• **Fig. 24.2** Determinants of cardiac output.

volume of 60 to 90 mL/beat. Cardiac index is a normalized value for cardiac output based on body surface area, normally 2.5 to 3.5 L/min/m^2. Cardiac output varies in proportion to work requirement and oxygen demand.

Heart Rate

Heart rate is normally determined by rhythmic spontaneous depolarizations of pacemaker cells in the sinoatrial (SA) node. The rate of these depolarizations is modulated by the autonomic nervous system. Sympathetic stimulation increases activity, whereas parasympathetic stimulation (vagus nerve) decreases activity of the SA node.

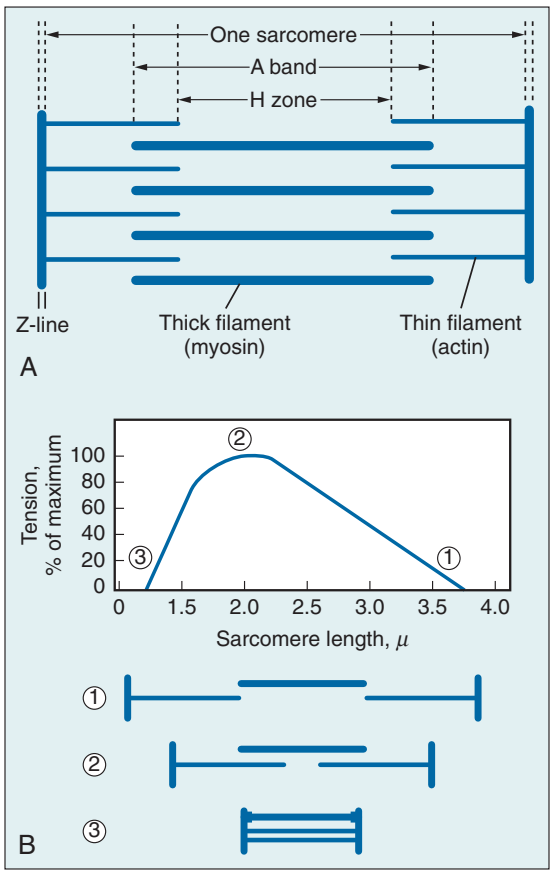
Stroke Volume

Stroke volume is the difference between end-diastolic volume and end-systolic volume (see Fig. 24.2). It can be influenced by changes in end-diastolic volume (Starling's law), myocardial contractility, and afterload (see later text). The sarcomere is the basic functional unit of the myocardium (Fig. 24.3A).[5] The ultrastructural arrangement of the thick (myosin) and thin (actin) myofilaments within the sarcomere and their interaction explain much of the mechanical behavior of cardiac muscle. Cardiac muscle contraction is initiated by an increase in intracellular calcium ions (Ca^{2+}), which results in the formation of cross-bridges between adjacent actin and myosin filaments. This process draws thin myofilaments and the Z-lines toward the center of the sarcomere and is the fundamental mechanism for myocardial contraction.

The relation between resting sarcomere length and developed tension was originally defined in isolated skeletal muscle fibers (see Fig. 24.3B).[5] Developed tension is a direct function of the number of cross-bridges pulling in parallel, and thus on the amount of overlap between thin and thick filaments prior to activation. Subsequent work extended this behavior to cardiac muscle. The length-tension relation provides the basis for Starling's law of the heart: the strength of contraction of the intact heart is proportional to the initial length of the cardiac muscle fiber—that is, end-diastolic volume (preload). This can be demonstrated using a cardiac function curve, which is a plot of ventricular performance (i.e., stroke volume) as a function of ventricular end-diastolic volume or an index thereof, such as ventricular end-diastolic pressure (Fig. 24.4A).[5]

Preload

In vivo cardiac muscle fibers are stretched by venous filling pressure. Normally, the volume in the ventricle before contraction (preload) sets the sarcomere to a suboptimal length; thus the active tension that can be developed is not maximal. Increases in end-diastolic volume owing to enhanced venous return cause increases in sarcomere length, resulting in a proportional rise in force development and ventricular stroke work. Active tension development levels off



• **Fig. 24.3** A, Contractile machinery and ultrastructure of the cardiac cell. B, Tension development as a function of sarcomere length. Myofilament overlap at three points in the length-tension curve is depicted below. (Modified from Braunwald E, Ross J Jr, Sonnenblick EH. *Mechanisms of Contraction of the Normal and Failing Heart*. Boston: Little, Brown; 1968:77.)

as the sarcomere is increased to the optimal length. Beyond this point, overstretching of the sarcomere is accompanied by a decline in tension development. Clinicians traditionally have equated filling pressure with preload, which assumes that the relationship between end-diastolic pressure and end-diastolic volume (i.e., the compliance or distensibility) is constant. However, a fibrotic heart, hypertrophied heart, or aging heart has reduced compliance.

Venous return, and thus cardiac filling, is augmented by conditions associated with reduced systemic vascular resistance. These include the opening of arteriovenous fistulae or conditions that mimic it, such as fever (marked dilation of cutaneous beds), pregnancy, and exercise (see Fig. 24.4A).

Rapid, large reductions in total blood volume reduce venous return. At any given total blood volume, venous return is a function of the distribution of blood between the intrathoracic and extrathoracic compartments. For example, assumption of an upright posture, because of gravity, tends to increase extrathoracic volume at the expense of intrathoracic volume, thus reducing venous return. Elevation of intrathoracic pressure, as occurs during positive-pressure ventilation or pneumothorax, has a similar effect.

Sympathetic nerve stimulation produces systemic venoconstriction, which augments cardiac filling, whereas drugs that interfere with adrenergic nerve function, such as ganglionic blockers or drugs that act directly to relax venous smooth muscle such as nitrates, have the opposite effect. Extravascular compression of veins by contracting muscle increases venous return during exercise.

Atrial contraction normally contributes less than 20% to LV diastolic filling in young healthy adults. It becomes more important at rapid heart rates "where the time available for passive ventricular filling is limited" and in patients with decreased LV compliance "where the atrial contraction contribution approaches 50% of the LV diastolic filling."[6]

Increases in pericardial pressure, as in cardiac tamponade, limit ventricular filling and stroke volume.

Contractility

Contractility relates to the ability of the myocardium to perform mechanical work (i.e., to generate force and shorten), independently of changes in preload or afterload with heart rate fixed. Contractility can be illustrated graphically using a family of cardiac function curves (see Fig. 24.4B).[5] Changes in contractility can augment cardiac performance (positive inotropic effect) or depress it (negative inotropic effect). Movement of an entire curve upward (more work for a given preload) or downward (less work for a given preload) signifies a positive or negative inotropic effect, respectively. Positive inotropic factors include circulating catecholamines and the cardiac sympathetic nerves, whereas negative inotropic factors include severe anoxia, acidosis, and the volatile anesthetics

Afterload

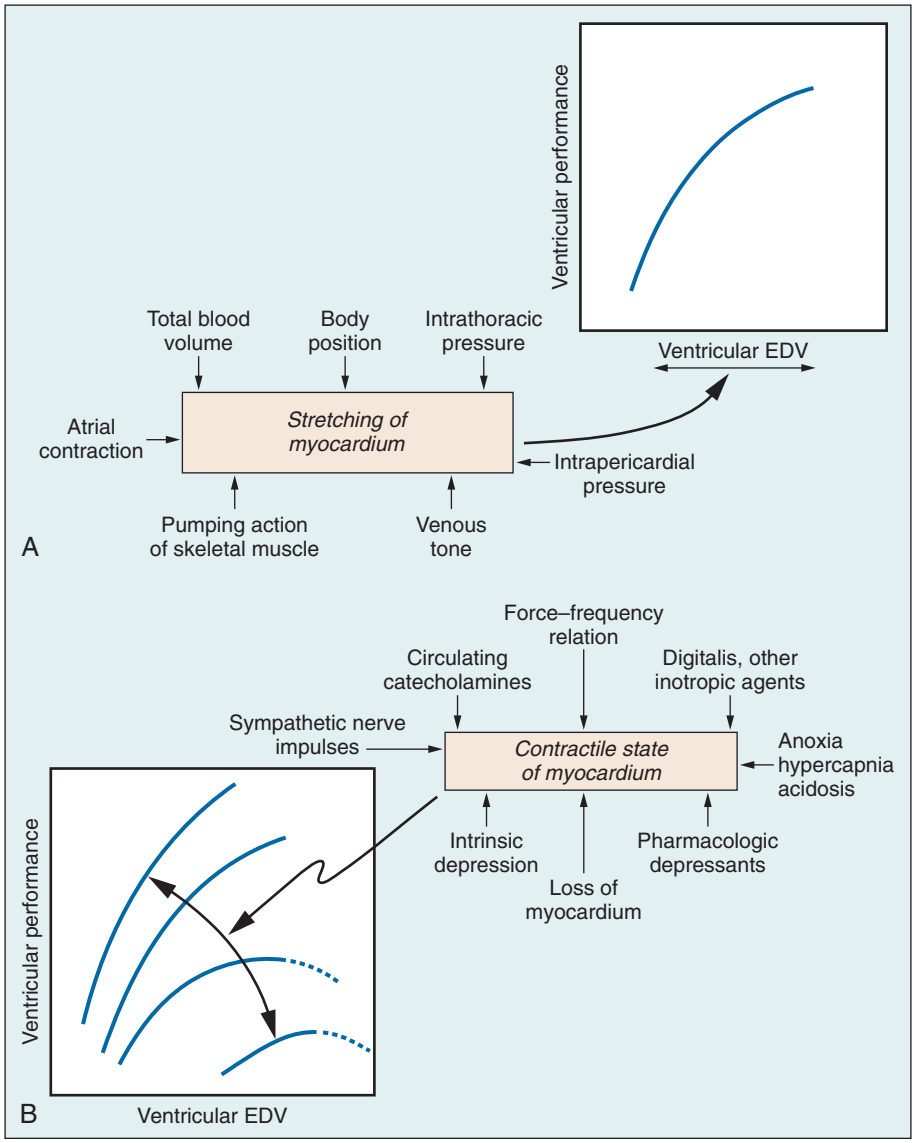
Afterload is defined as the force opposing fiber shortening during ventricular ejection.[7] It is not synonymous with systemic arterial pressure, vasomotor tone, or vascular resistance. Instead, it should be thought of as the tension or stress in the ventricular wall during ejection. In accordance with the law of Laplace, afterload is directly related to intraventricular pressure and size and inversely related to wall thickness. Because of changing size, pressure, and wall thickness, afterload varies continuously during ventricular ejection. Thus it is difficult to quantify with precision. Despite the widespread use of aortic pressure for the LV and pulmonary artery pressure for the RV as indices of afterload in vivo, this approach should not be considered quantitative.

In isolated heart preparations, in which preload, inotropic state, and heart rate are controlled, increases in afterload cause reductions in left ventricular output (i.e., stroke volume; Fig. 24.5A).[8] In the intact circulation, this impairment in cardiac performance can be avoided by compensatory increases in contractility and/or venous return (preload). As demonstrated in Fig. 24.5B, there is no change in stroke volume when normal hearts are exposed to increased afterload (outflow resistance), but a decrease in stroke volume when failing hearts pump against similar conditions.[9]

The Cardiac Cycle

The events of the cardiac cycle are shown on Fig. 24.6. The salient points are as follows:

1. Atrial systole begins after the P wave of the electrocardiogram; ventricular systole begins near the end of the R wave and ends just after the T wave.
2. When ventricular pressure exceeds aorta pressure, the aortic valve opens, and ventricular ejection begins (at point O in Fig. 24.6).
3. The amount of blood ejected by the ventricle (stroke volume) is typically approximately 65% of end-diastolic volume (ejection fraction).
4. Most ventricular filling occurs prior to atrial systole.

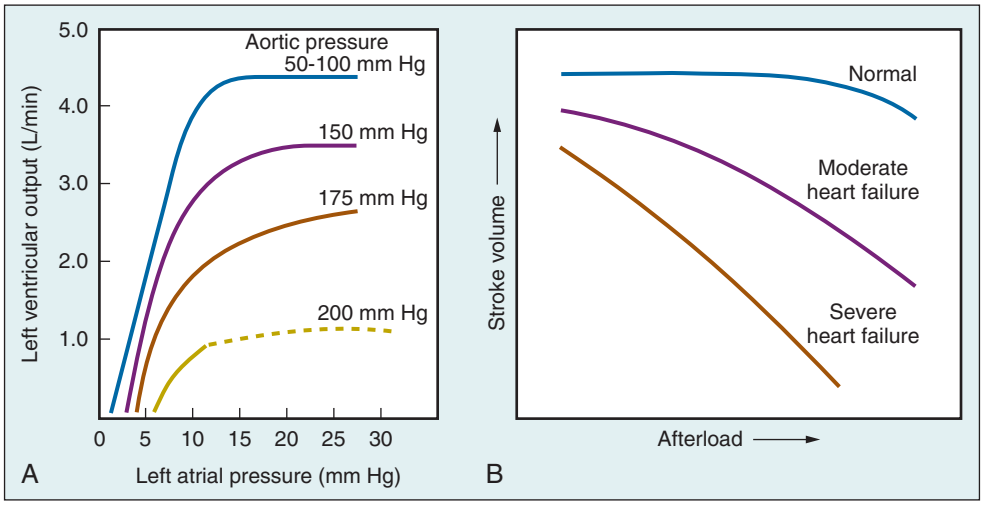


• **Fig. 24.4** A, Diagram of a cardiac function curve, relating ventricular end-diastolic volume *(EDV)* to ventricular performance. *Bottom left:* Major factors determining the degree of stretching of the myocardium, that is, the magnitude of EDV. B, Diagram showing major factors affecting myocardial contractility. *Bottom left:* Family of cardiac function curves demonstrating the effect of contractility on cardiac performance. (Reprinted with permission from Braunwald E, Ross J Jr, Sonnenblick EH. *Mechanisms of Contraction of the Normal and Failing Heart*. Boston: Little, Brown; 1968:275, 280.)

5. Events on the right side of the circulation are similar to those on the left side but are somewhat asynchronous. Right atrial systole precedes left atrial systole, and contraction of the RV typically begins after that of the LV. However, because pulmonary arterial pressure is less than aortic pressure, RV ejection precedes LV ejection.

Ventricular diastole is defined as the period in the cardiac cycle from the end of ejection until the onset of ventricular tension development of the succeeding beat and is composed of four phases: isovolumic relaxation, early rapid filling, diastasis, and atrial systole.[6,10–14] Ventricular lusitropy is defined as the active relaxation of the ventricles that requires expenditure of energy by ventricular myocytes, which coincides with the isovolumic relaxation phase. This active process can be quantified most precisely as a time constant of the isovolumic pressure decline (the Greek letter tau, τ), calculated as the mono-exponential decline of pressure during the isovolumic phase of the cycle. A prolonged τ indicates impaired relaxation, and thus impaired ventricular filling. This occurs in chronic pathologic conditions, such as hypertrophy and cardiomyopathy, and in acute processes, such as ischemia and administration of negative inotropic drugs. In contrast, a short τ indicates enhanced relaxation and ventricular filling, which can occur following administration of positive inotropic drugs.

The phase of rapid early filling follows isovolumic relaxation and begins when ventricular pressure falls below atrial pressure. During this period, elastic recoil of the myocardium in combination with continued relaxation create an atrial/ventricular pressure gradient (sometimes characterized as suction) that greatly facilitates ventricular filling. As the atrial/ventricular pressure gradient diminishes, the phase of diastasis (slow ventricular filling) begins,



• **Fig. 24.5** A, Left ventricular output as a function of left atrial pressure, plotted at several aortic pressures (afterloads). Note that an increase in aortic pressure reduces left ventricular output at each filling pressure. B, Effect of increased afterload on stroke volume in normal and compromised hearts. (A, Reprinted with permission from Sagawa K. Analysis of the ventricular pumping capacity as function of input and output pressure loads. In: Reeve EB, Guyton AC, eds. *Physical Bases of Circulatory Transport: Regulation and Exchange*. Philadelphia: WB Saunders; 1967;141–149. B, Modified from Cohn JN, Franciosa JA. Vasodilator therapy of cardiac failure. *N Engl J Med*. 1977;297:27–31.)

continuing until atrial systole. Early rapid filling normally accounts for 80% to 85% of ventricular end-diastolic volume; diastasis and atrial systole provide approximately 3% to 5% and 15% to 25%, respectively.[6,14] Multiple processes can alter diastolic filling dynamics, most notably ectopy arising from the atrioventricular node and ventricular pacing (no atrial systole), and reductions in ventricular compliance, such as concentric hypertrophy, ventricular interaction, and pericardial constraint.

The pattern of contraction differs for the LV and RV. The LV contracts in a relatively homogeneous fashion with both the short and long axes shortening simultaneously. In contrast, the RV, which normally develops a pressure only 20% of that in the LV, contracts sequentially from the inflow tract to the outflow tract. The mechanical significance of this sequential pattern of contraction is unclear, but the process appears to reflect the different embryology of the inflow and outflow tracts, and is altered by sympathetic stimulation, positive inotropic drugs, autonomic blockade, and volatile anesthetics.

Indices of Cardiac Function

Calculation of Cardiac Output Using the Thermodilution Method

The thermodilution method was first described by George Neil Stewart at the end of the 19th century when he injected a bolus of sodium chloride solution into a central vein, which was detected in a contralateral femoral artery.[15] The change in concentration of the sampled blood was proportional to the cardiac output. Later Hamilton et al.[16,17] modified this method and promoted the concept of an explicit time-concentration curve. Cardiac output was calculated as the amount of indicator injected/area of dilution curves. Indocyanine green was the conventional indicator used until the 1970s.[18]

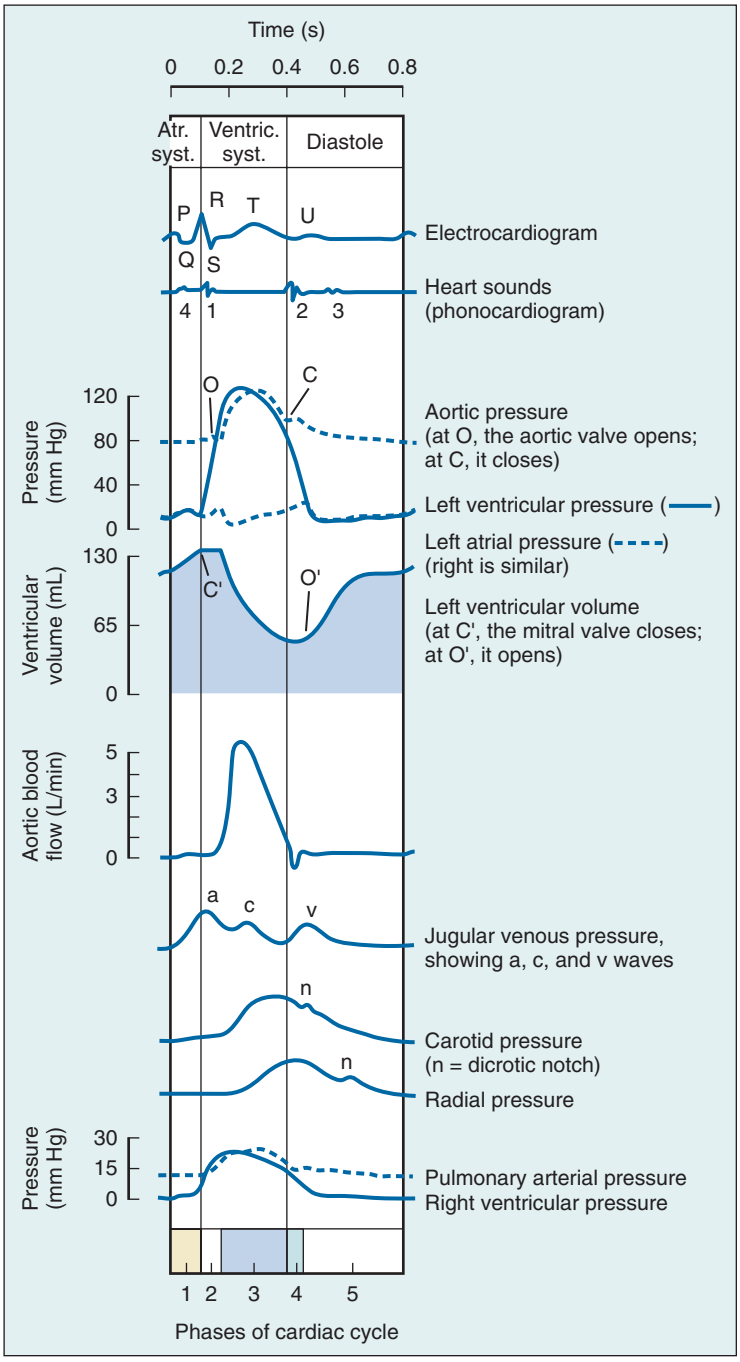
Cardiac Function Curves With the Pulmonary Artery Catheter

Introduction of the flow-directed pulmonary artery catheter (PAC) in the late 1960s allowed measurement of both cardiac output using a Stewart-Hamilton thermodilution curve and pulmonary capillary wedge pressure, which is a reflection of LV preload.[19–21] The measurement of cardiac output entails injection of an indicator (usually 10 mL of 0.9% sochloride), with a known temperature, into a central vein and detection of the change in blood temperature downstream at the tip of the PAC. This approach made it possible for clinicians to construct ventricular function curves at the bedside and to use this information to guide treatment. Its validity requires several conditions[22]:

1. Pressure from the left atrium (which is on average equal to LV end-diastolic pressure) must be reflected back through the pulmonary circulation; thus the tip of the pulmonary artery catheter must be wedged in a small pulmonary vessel so blood cannot flow beyond it. In addition, the mitral valve should not have significant stenosis or regurgitation.
2. Changes in the relationship between ventricular volume and pressure during diastole (compliance) must be taken into account. A stiff or noncompliant ventricle, as evidenced by impaired diastolic filling and exaggerated pressure increase, erroneously implies an increased preload, even though muscle stretch may be unaltered or even reduced. A stiff ventricle is characteristic of a variety of pathologic states, including myocardial ischemia, healing or healed myocardial infarction, myocardial hypertrophy, and constrictive pericarditis.
3. Afterload and heart rate must be constant when multiple cardiac function curves are used to assess changes in myocardial contractility, as reflected in stroke volume at a given preload.
4. The tricuspid valve cannot have significant regurgitation because this causes variation in the transit time of the indicator, yielding both underestimates and overestimates of cardiac output.[18]

Cardiac Function Using the Transpulmonary Thermodilution Method

This method also applies to the Stewart-Hamilton principle to calculate cardiac output. However, in this case, cold saline solution is injected into a central vein and the change in temperature is



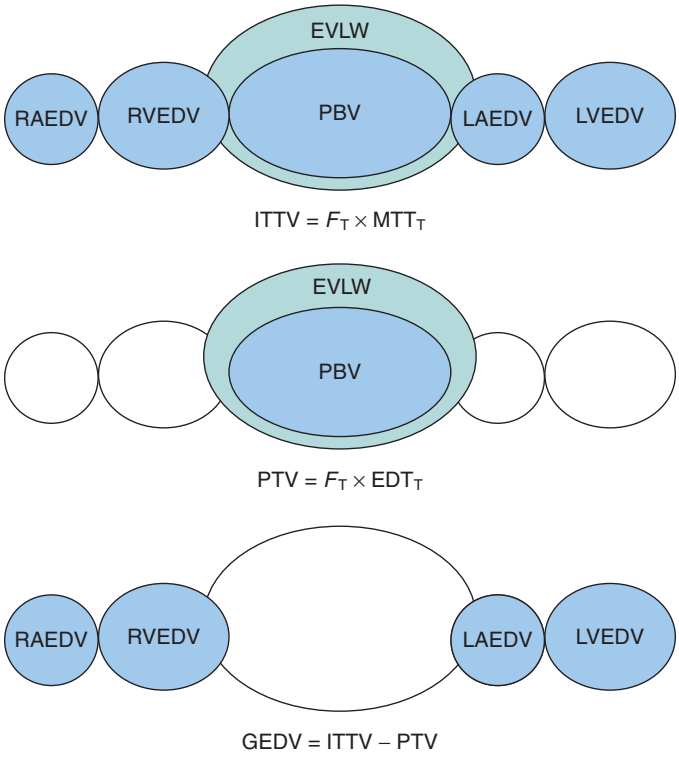
• **Fig. 24.6** Events of a cardiac cycle. The phases of the cardiac cycle are identified at the bottom of the figure as follows: (1) atrial systole, (2) isovolumic ventricular contraction, (3) ventricular ejection, (4) isovolumic relaxation, (5) ventricular filling. (Reprinted with permission from Ganong WF. *Review of Medical Physiology*. Norwalk, CT: Appleton & Lange; 1987:467.)

detected with thermistor-tipped catheter placed in a central artery, commonly the femoral artery or the axillary artery. This method differs from that using a PAC in that it measures LV rather than RV cardiac output. The transpulmonary thermodilution method allows the calculation of additional indices of cardiac function such as the following:

1. Global end-diastolic volume (GEDV). GEDV is the volume of blood present in the four chambers of the heart. This parameter provides a better estimate for preload than pulmonary artery occlusion pressure because it is an actual volume rather than a pressure surrogate. Thus the use of GEDV avoids erroneous conclusions based on high LV filling pressure in the stiff noncompliant ventricle.[23,24]
2. Extravascular lung water. The transpulmonary thermodilution method allows the calculation of pulmonary blood volume and thus an estimation of extravascular lung volume (Fig. 24.7). The latter findings provide an early index of pulmonary edema and fluid overload in critically ill patients.[24]

Isovolumic Contraction Index

One of the most common and useful indices of contractility is the maximal rate of change of the ventricular pressure pulse, so-called dP/dt max.[25] Historically, a high-fidelity catheter was inserted into the LV to obtain these measurements. Currently the use of echocardiography allows the determination of dP/dt max noninvasively.[26] Interventions that acutely augment myocardial contractility, such



• **Fig. 24.7** The transpulmonary thermodilution method to calculate global end-diastolic volume *(GEDV)* and extravascular lung water *(EVLW)*. Upper row: The intrathoracic thermal volume *(ITTV)* is the complete volume of distribution of the thermal indicator, encompassing the right atrium *(RAEDV)*, right ventricle *(RVEDV)*, left atrium *(LAEDV)*, left ventricle end-diastolic *(LVEDV)* volumes, the pulmonary blood volume *(PBV)*, and EVLW. It is calculated by multiplying cardiac output *(F_T)* with the mean transit time *(MTT)* of the indicator. Middle row: The pulmonary thermal volume *(PTV)* is the largest mixing chamber of the system and it includes the PBV and the EVLW. It is calculated by multiplying the F_T with the exponential decay time *(EDT)* of the indicator. Bottom row: GEDV is the difference between ITTV and PTV. Intrathoracic blood volume (ITBV) is calculated by multiplying GEDV × 1.25. EVLW is calculated by subtracting ITBV from ITTV. (Modified with permission from Reuter DA, Huang C, Edrich T, et al. Cardiac output monitoring using indicator-dilution techniques: basics, limits, and perspectives. *Anesth Analg.* 2010;110:799–811.)

as exercise and catecholamines, increase this index.[25,27] Values in the normal LV are approximately 1000 mm Hg/sec, whereas those in the RV average only 400 mm Hg/sec.[25,28] This difference has been attributed to the fact that peak dP/dt usually occurs at the instant of the opening of the semilunar valves and that developed pressure is substantially higher in the LV compared with the RV, and not to a difference in contractile state between ventricles.[19] Disadvantages of dP/dt max as an index of contractility include distortion by wall properties and valvular dysfunction, and dependence on loading conditions and heart rate. To correct for load dependency, the ratio of dP/dt to developed pressure or to a standard pressure has been used.

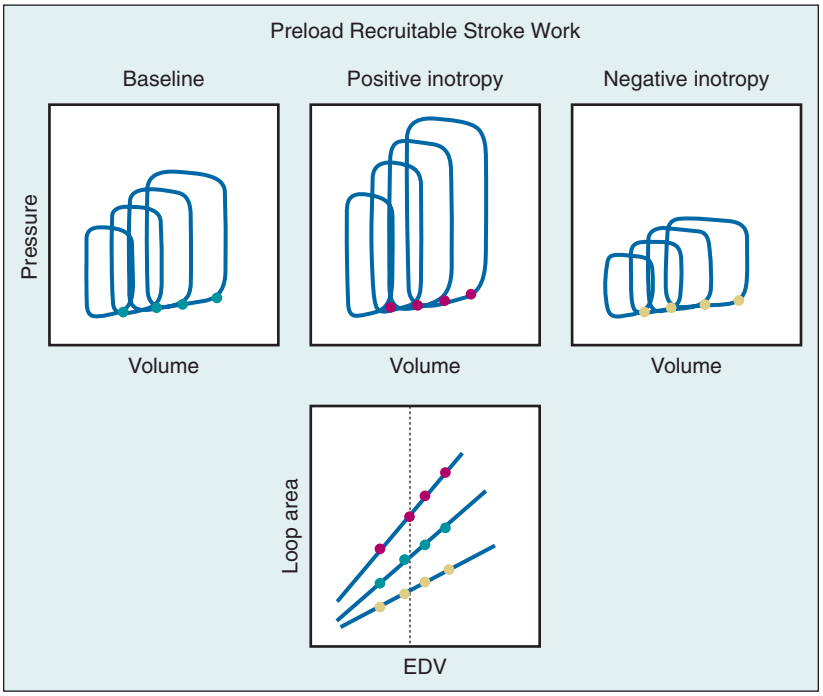
Ejection Phase Index

The most frequently used clinical index of global contractile function is ejection fraction. Both invasive and noninvasive techniques have been used to determine ejection fraction from image-based volume measurements (echocardiography, angiography, magnetic resonance imaging, positron emission tomography scanning) or indicator dilution techniques. Although the ejection fraction provides useful information about systolic pump performance, it is heavily influenced by afterload. Such load dependence is common to virtually all indices of contractility based on ejection phase parameters. Another ejection phase index of contractility is the preload recruitable stroke work (PRSW) relationship.[29] To measure PRSW, venous return is decreased by inferior vena cava occlusion, resulting in a progressive reduction in ventricular end-diastolic volume. The area of the pressure-volume loop (which represents external work) is plotted for each beat as a function of end-diastolic volume (Fig. 24.8). The slope of this relationship defines the work the ventricle can perform for a given preload and is a reflection of contractility; increased slope indicates increased contractility, and a fall in slope indicates decreased contractility. An advantage of PRSW is that it provides an index of overall ventricular performance, combining both systolic and diastolic components; however, it is not practical in the clinical environment.

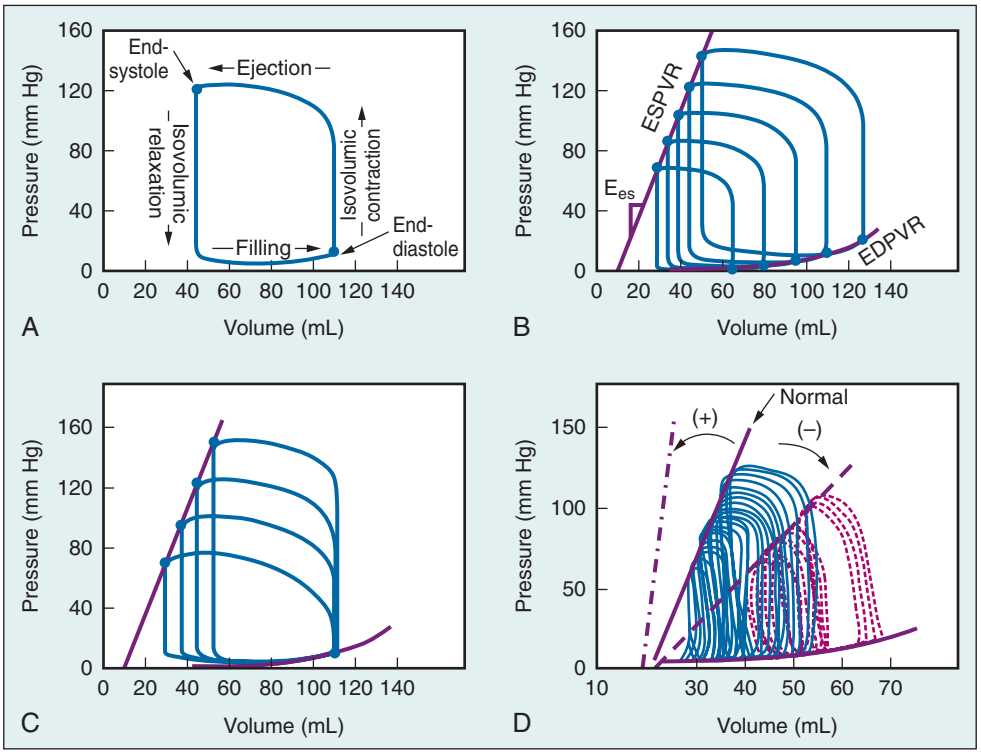
Ventricular Pressure-Volume Loop: End-Systolic Pressure-Volume Relations

In 1898 Otto Frank, using data from studies in isolated frog ventricles, presented the cycle of ventricular contraction as a loop defined by pressure (P) in the vertical axis and volume (V) in the horizontal axis.[30] Because of difficulties in measuring ventricular volume in vivo, research on pressure-volume relationships proceeded slowly during the first two-thirds of the 20th century.[31] With the development of the isolated blood-perfused canine heart preparation, echocardiography, and ventriculography for studies in humans, there was a resurgence of activity in the 1970s and 1980s.[32–34] The use of pressure-volume analysis has been established as a powerful method to characterize ventricular pump properties throughout the cardiac cycle independent of loading conditions. However, the method is highly sophisticated, laborious, and requires specialized equipment and training.

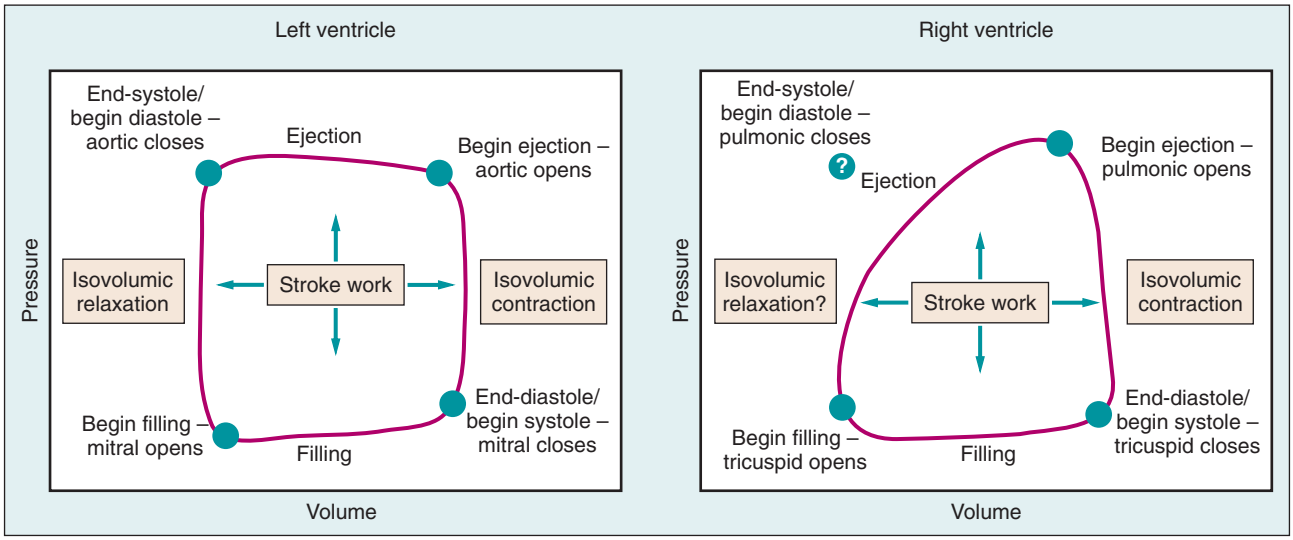
The hemodynamic changes during a single cardiac cycle are displayed by plotting instantaneous ventricular pressure versus volume (Fig. 24.9A).[31] Under steady-state conditions, this loop is repeated with each contraction. For a given cardiac cycle, there is a pressure-volume point that coincides with end-diastole (at the lower end of the loop). The increase in ventricular pressure during this period of filling, which ends when the mitral valve closes, reflects the compliance of the ventricular wall. During isovolumic contraction, pressure increases steeply while volume remains constant. Ventricular pressure rises to a level in excess of aortic pressure, the aortic valve opens, and blood is ejected. Ventricular ejection (systole) continues until ventricular pressure falls below aortic pressure and the aortic valve closes. The upper left-hand corner of the loop coincides with end-systole. The period of isovolumic relaxation follows, which is characterized by a sharp decrease in pressure and no change in volume. The mitral valve then opens, thus completing one cardiac cycle. The area within the pressure-volume loop represents the internal work of the ventricle, whereas external work is determined by the product of stroke volume and aortic pressure. An intervention that acutely changes loading conditions but has no effect on contractility, such as transient caval occlusion to reduce preload (see Fig. 24.9B) or administration of phenylephrine to increase afterload (see Fig. 24.9C), generates a family of loops.[31,32] The end-systolic points in the series of loops conform to a linear pressure-volume relationship, which defines the end-systolic pressure-volume relationship (ESPVR). End-systolic elastance (Ees) defines the slope of ESPVR and is a load-independent



• **Fig. 24.8** Use of the preload recruitable stroke work to assess the inotropic state of the ventricle. Vena caval occlusion causes a progressive reduction in ventricular end-diastolic volume. The area of the pressure-volume loop is plotted for each beat as a function of the end-diastolic volume. The slope of this relationship defines how much work the ventricle can perform for a given preload and is a reflection of contractility—that is, a rise in the slope indicates increased contractility, and a fall in the slope indicates decreased contractility. *EDV,* End-diastolic volume.



• **Fig. 24.9** A, Pressure-volume loop of the left ventricle. B, Multiple pressure-volume loops generated by progressive reductions in preload. C, Multiple pressure-volume loops generated by progressive increases in afterload. D, Use of pressure-volume loops to provide a load-dependent index of myocardial contractility. An increase in end-systolic elastance *(Ees)* indicates an increase in the slope of end-systolic pressure-volume relationship *(ESPVR)* and an increase in myocardial contractility (positive inotropy), whereas a decrease in Ees indicates a decrease in the slope of ESPVR *(red loops)* and a decrease in myocardial contractility (negative inotropy) compared with normal *(blue loops)*. *EDPVR,* End-diastolic pressure-volume relationship; *ESPVR,* end-systolic pressure-volume relationship. (Reprinted with permission from Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. *Am J Physiol Heart Circ Physiol*. 2005;289:H501–H512.)



• **Fig. 24.10** A comparison of the pressure-volume characteristics for the left and right ventricles.

index of contractility. The diastolic pressure-volume points define a nonlinear end-diastolic relationship (EDPVR). With a constant contractile state and afterload, the progressive reduction in preload causes the loops to shift toward lower volumes at end-systole and end-diastole, resulting in a decrease in stroke volume (see Fig. 24.9B). A selective increase in afterload causes narrowing and elongation of the loops, which results in a decrease in stroke volume (see Fig. 24.9C). The ESPVR responds to acute changes in myocardial contractility; an increase in its slope, Ees, indicates a positive inotropic intervention and a decrease in Ees indicates a negative inotropic intervention (see Fig. 24.9D).

The pressure-volume characteristics for the RV differ markedly from those of the LV (Fig. 24.10).[35] Although clear in the pressure-volume loop of the LV, end-systole is not well defined in the normal RV. Owing primarily to the sequential pattern of right ventricular free wall contraction, the low resistance of the pulmonary vascular bed, and the fact that blood ejected from the RV has inertia, the peak pressure within the RV normally occurs very early in systole and blood continues to leave via the pulmonic valve for an extended period. Consequently, the pressure-volume loop for the RV has a more triangular shape, with only a brief period of isovolumic relaxation. The prolonged low-pressure emptying of the RV renders this chamber very sensitive to changes in afterload. Because the RV does not demonstrate a defined end-systolic point, Ees analysis is not readily applicable, and PRSW is considered far superior for assessment of contractility. With pulmonary hypertension, the pressure-volume loop in the RV is not triangular but resembles that of the LV, largely because of a change in both the magnitude and timing of peak RV pressure.[35]

Hemodynamics and Systemic Vascular Control

Pressure Changes in Systemic and Pulmonary Circulations

Fig. 24.11 compares the pressure changes as blood flows through the series-coupled components of the systemic and pulmonary circulations, from the large arteries to the arterioles, capillaries, and veins.[36] The normal pulmonary circulation is a low-pressure, low-resistance circuit that accommodates the entire output of the RV.[37] This results in a smaller workload for the RV. Although pressure in the ventricles falls nearly to zero during diastole, pressure is maintained in the large arteries. This is possible because a portion of the energy released by cardiac contraction during systole is stored in the distensible large arteries (the Windkessel effect). During diastole, the elastic recoil of the vessels converts this potential energy into forward blood flow, which ensures that capillary flow is continuous throughout the cardiac cycle. The most severe drop in pressure occurs in the arterioles; hence they are often termed resistance vessels. The diameter of arterioles is regulated by contractile activity of vascular smooth muscle. Variations in arteriolar diameter are an important determinant of local capillary blood flow and hydrostatic pressure. The summed effect of all the systemic resistance vessels—that is, the total peripheral resistance—is a major determinant, along with cardiac output, of arterial pressure, and thus of the driving force for tissue blood flow (see Fig. 24.1).

Determinants of Blood Flow: Poiseuille's Law

Blood flow (F) is a function of arteriovenous pressure gradient (Pa – Pv) and local vascular resistance (R), according to the equation:

[1]

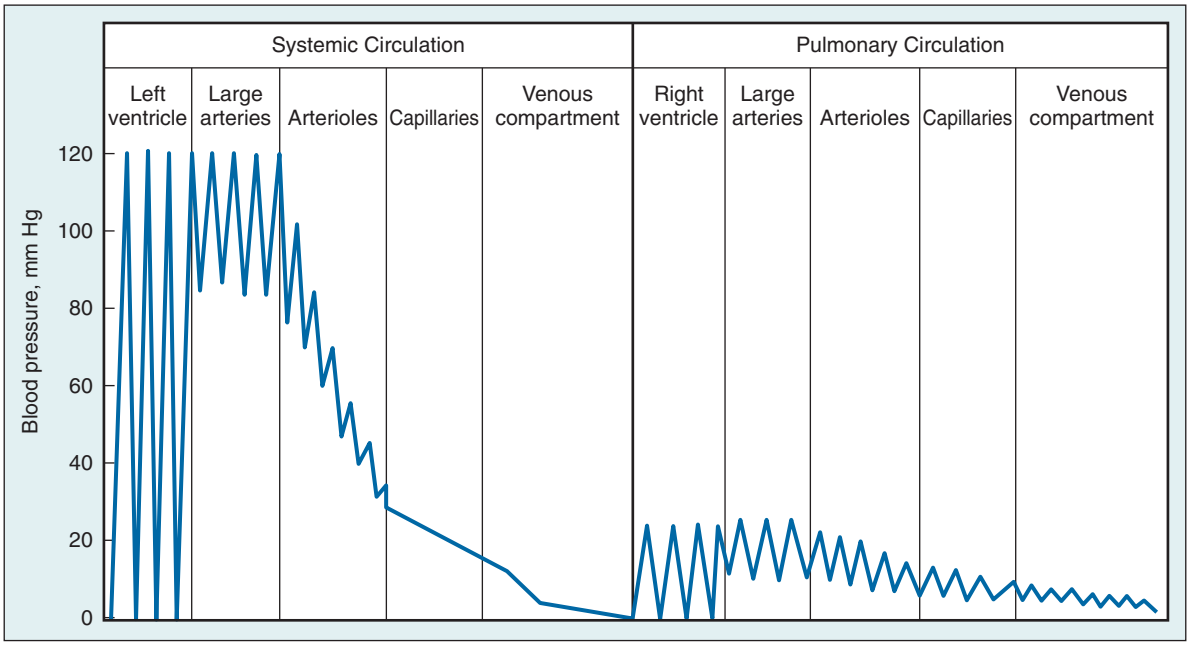
$$F = (Pa - Pv)/R$$

This is analogous to Ohm's law in an electrical circuit. Because arterial and venous blood pressures are normally well maintained within narrow limits by homeostatic mechanisms, tissue blood flow usually varies inversely as a function of vascular resistance.

Poiseuille performed studies that yielded an equation describing resistance to flow in a straight, rigid tube of length (l) and radius (r):

[2]

$$R = \eta 8l/r^4$$



• **Fig. 24.11** Blood pressure in the series coupled components of the systemic and pulmonary circulations. (Modified from Folkow B, Neil E. *Circulation*. New York: Oxford University Press; 1971:6.)

where η is the viscosity. Of note is that flow resistance varies inversely with tube radius raised to the fourth power. Thus small changes in tube radius cause large changes in resistance.

Because the length of blood vessels is relatively fixed, geometric changes in blood flow resistance occur by variations in vessel radius. These adjustments are primarily the result of contraction or relaxation of the smooth muscle investing the arterioles, which are the principal site of vascular resistance. However, in certain vascular beds (e.g., the left ventricular myocardium), extravascular compressive forces also play a role (see later text). Chemical factors, which are linked to the metabolic activity of the tissue (e.g., carbon dioxide) modulate vascular resistance so that blood flow (and oxygen delivery) is commensurate with local oxygen demands.

Blood Viscosity

Viscosity is the internal friction resulting from intermolecular forces operating within a flowing liquid. The term *internal friction* emphasizes that as a fluid moves within a tube, laminae in the fluid slip on one another and move at different speeds. The movement produces a velocity gradient in a direction perpendicular to the wall of the tube termed the *shear rate*. Shear rate shows a direct correlation to rate of blood flow. Viscosity is defined as the factor of proportionality relating shear stress and shear rate for the fluid.

[3]

$$\text{Viscosity} = \text{shear stress}/\text{shear rate}$$

Newton assumed that viscosity was a constant property of a particular fluid and independent of shear rate. Fluids that demonstrate this behavior are termed *Newtonian*. The units of viscosity are dynes per second per square centimeter, or *poise*.

The viscosity of blood varies as a direct function of hematocrit (Fig. 24.12A); the greater the hematocrit, the more friction there is between successive layers.[38] Plasma is a Newtonian fluid, even at high protein concentrations. However, because blood consists of erythrocytes suspended in plasma, it does not behave as a homogeneous Newtonian fluid; the viscosity of blood increases sharply with reductions in shear rate (see Fig. 24.12A). This non-Newtonian behavior of blood has been attributed to changes in the behavior of erythrocytes at low flow rates. At low flow, erythrocytes lose their axial position in the stream of blood, lose their ellipsoidal shape, form aggregates, and adhere to the endothelial walls of microvessels. The tendency toward erythrocyte aggregation appears dependent on the plasma concentration of large proteins such as fibrinogen that form cell-to-cell bridges. Fig. 24.12B, demonstrates that non-Newtonian behavior is localized on the venous side of the circulation because of its lower shear rates, but that this behavior can be blunted or abolished by hemodilution.[39]

The tendency for increased hematocrit to increase blood viscosity is attenuated when blood flows through tubes of capillary diameter (see Fig. 24.12C).[40] This is because erythrocytes are normally very deformable, and with a diameter similar to that of the capillary, they can squeeze through the vessel lumen in single file with minimal extra force required. Thus the rate at which erythrocytes pass through the capillary has little influence on blood viscosity there.

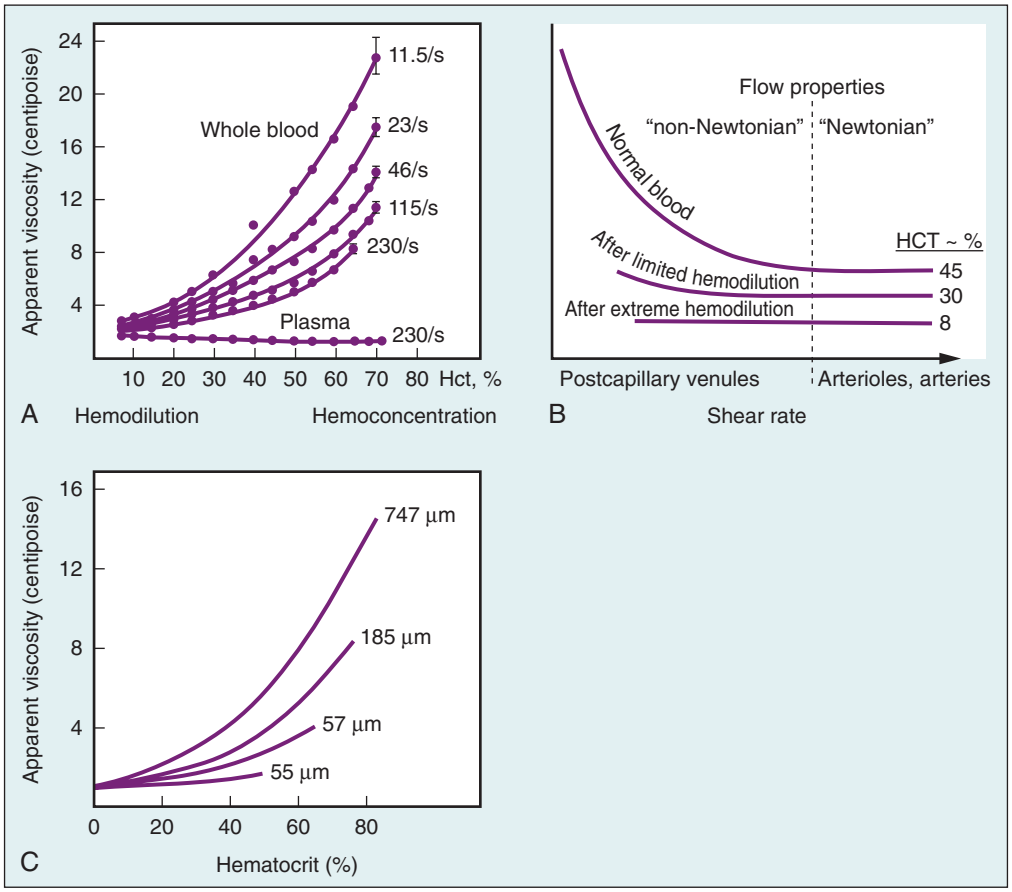
Blood viscosity varies inversely with temperature. This is important during hypothermic cardiopulmonary bypass. After circulatory arrest, the shear stress required to reinitiate flow and to break up red cell aggregates is higher. Additional rheologic benefit may be gained by a further decrease in hematocrit.

Turbulent Flow

A principal condition of Poiseuille's law is that flow be laminar. Above a critical flow rate, the laminae break down into eddies that move in all directions. Such flow is said to be turbulent (Fig. 24.13).[40] The tendency for turbulence is given by the Reynolds number (Re):

[4]

$$\text{Re} = v\text{D}\delta/\eta$$



• **Fig. 24.12** A, Viscosity of whole blood at various hematocrits as a function of shear rate. Hematocrit *(HCT)* was varied by addition of dextran and packed red blood cells. Note that viscosity increases with hematocrit and that these increases are greatest at the lower shear rates. B, Graphic representation of the level of blood viscosity in the various vascular compartments. Under normal conditions (hematocrit = 45%), viscosity increases in postcapillary venules because of reduced shear rate. Hemodilution can blunt or even completely eliminate this regional variation in viscosity. C, The effect of hematocrit on viscosity of blood in tubes of varying radii. In wide tubes, increasing hematocrit raises viscosity, whereas in narrow tubes it has no effect. (A, Reprinted with permission from Messmer K. Hemodilution. *Surg Clin North Am*. 1975;55:659–678; B, Reprinted with permission from Messmer K, Sunder-Plassman L. Hemodilution. *Prog Surg*. 1974;12:208–245; C, Reprinted with permission from Feigl EO. Physics of cardiovascular system. In: Ruch TC, Patton HD, eds. *Physiology and Biophysics II: Circulation, Respiration, and Fluid Balance*. Philadelphia: WB Saunders; 1974:19.)

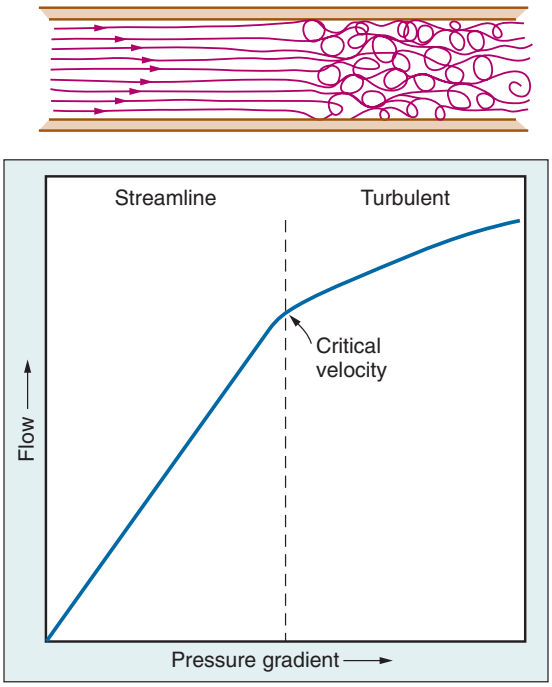
where v is linear velocity, D is diameter, δ is density, and η is viscosity. Re is dimensionless because it is the ratio of inertial and cohesive forces. Inertial forces tend to disrupt the stream, whereas cohesive forces tend to maintain it. In long straight tubes, turbulence occurs when Re exceeds a value of approximately 2000. However, the critical Re is much less because of pulsatile flow patterns and complicated vascular geometries. When flow is turbulent, a greater portion of total fluid energy is dissipated as heat and vibration; thus the pressure drop is greater than predicted from the Poiseuille equation (see Fig. 24.13). The vibrations associated with turbulent flow can often be heard by auscultation as a murmur.

Major Vessel Types: Structure and Function

The various vessel types have structural and geometric features (Fig. 24.14A) that determine their functional characteristics within the circulation (Fig. 24.14B).[41] The large conduit arteries are predominantly elastic structures, which allows them to convert intermittent cardiac output into continuous peripheral flow. Because the cross-sectional area of these vessels is small, the velocity of flow in them is high. The resistance to flow in the arteries is small, and thus the pressure drop is also small. The arterioles and the terminal arterioles have significant smooth muscle in their walls, which permits active changes in vascular diameter and modulation of local vascular resistance and blood flow. Capillaries have a very large aggregate cross-sectional area (which decreases flow velocity) and a thin wall, both factors favoring blood-tissue gas exchange. The veins and venules have the greatest volume, which makes an appropriate site for blood storage.

Factors Influencing the Balancing Between Capillary Filtration and Absorption

On the basis of his findings in the dog hind limb, in 1896 Ernest Starling presented a model to describe fluid exchange between the



• **Fig. 24.13** The linear relationship between pressure gradient and flow is shown. Beyond a critical velocity, turbulence begins and relationship between pressure and flow is no longer linear. (Reprinted with permission from Feigl EO. Physics of cardiovascular system. In: Ruch TC, Patton HD, eds. *Physiology and Biophysics II: Circulation, Respiration, and Fluid Balance.* Philadelphia: WB Saunders; 1974:19.)

capillary and the interstitial space. The model proposed that the capillary wall is highly permeable to water and to almost all plasma solutes except plasma proteins, and that it acts like a porous filter through which protein-free fluid moves by bulk flow under the influence of a hydrostatic pressure gradients.[42,43] Transcapillary filtration is defined as follows:

[5]

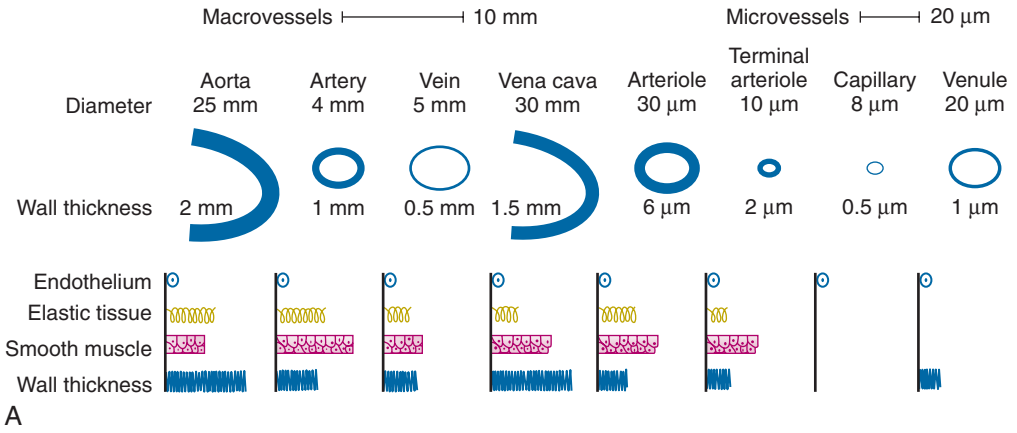
$$\text{Fluid filtration} = C_F[(P_{cap} - P_{IF}) - (\Pi_{cap} - \Pi_{IF})]$$

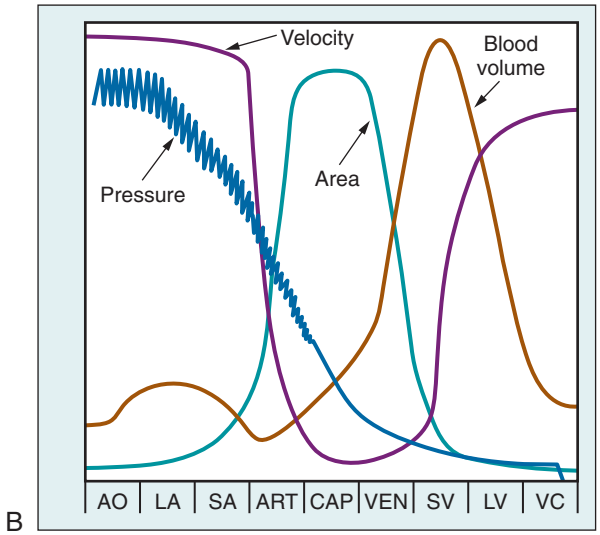
where C_F is the capillary filtration coefficient; P_{cap} is the capillary hydrostatic pressure; P_{IF} is interstitial fluid hydrostatic pressure; Π_{IF} is interstitial fluid oncotic pressure; and Π_{cap} is capillary oncotic pressure. P_{cap} and Π_{IF} are forces of filtration. P_{cap} is determined by arterial pressure, venous pressure, and the ratio of postcapillary to precapillary resistance. Elevations of arterial pressure, venous pressure, or venous resistance/arterial resistance produce elevations of P_{cap}. P_{cap} is approximately 35 mm Hg at the arterial end of the capillaries and approximately 15 mm Hg at the venous end. Π_{IF} is due to plasma proteins that have passed through the capillary wall and is normally very low compared with P_{cap}. Thus P_{cap} is normally the major force for filtration. P_{IF} and Π_{cap} are forces favoring absorption. P_{IF} is determined by the volume of fluid and the distensibility of the interstitial space, and is normally nearly equal to zero. Π_{cap} is due to plasma proteins (predominantly albumin) and is approximately 25 mm Hg. Π_p is normally the major force for absorption. The direction and magnitude of capillary bulk flow is essentially a function of the ratio of P_{cap} to Π_{cap}.[44]

Fluid transport across capillary endothelium takes place through several pathways that include tight junctions, breaks in tight junctions, vesicular transport, and leaky junctions (Fig. 24.15). The tight junctions allow transport of small water-soluble solutes (<2 nm in diameter) and are sealed by proteins linked to the cytoskeleton. Breaks in the tight junctions allow transport of larger water-soluble solutes up to 20 nm in diameter. Vesicular transport carries molecules up to 80 nm in diameter. Finally, leaky junctions associated with cell death allow transport of solutes up to 1330 nm in diameter.[45] Filtered fluid that reaches the extravascular spaces is returned to the circulatory system via the lymphatic network. Under normal conditions (Fig. 24.16A), filtration dominates at the arterial end of the capillary and absorption at the venous end because of the gradient of hydrostatic pressure; there is a small net filtration, which is compensated by lymph flow. Edema is a condition of excess accumulation of fluid in the interstitial space and occurs when net filtration exceeds drainage via the lymphatics. Edema can be caused by (1) increased capillary pressure, (2) decreased plasma protein concentration, (3) accumulation of osmotically active substances in the interstitial space, (4) increased capillary permeability, or (5) inadequate lymph flow. Conditions resulting in edema are depicted in Fig. 24.16B.D.

The pulmonary circulation has distinctive features that affect fluid exchange. It has the ability to accommodate substantial changes in cardiac output without an increase in pulmonary capillary pressure.[43] Under normal conditions, some of the pulmonary capillaries are either closed or open with no blood flow. When cardiac output increases, pulmonary capillary recruitment and distention reduce vascular resistance, which tends to normalize pulmonary capillary pressure.[46] In an animal study, these mechanisms allowed a doubling of the left atrial pressure before a significant increase in pulmonary capillary permeability occurred.[47] If these adaptive pulmonary mechanisms are overwhelmed, fluid begins to accumulate in the interstitial space and must be cleared by the lymphatic system. Lymph flow can increase 5- to 10-fold in response to chronic elevations in interstitial pressure in the lung.[48] The rise in interstitial volume in response to an increase in pulmonary hydrostatic pressure is limited by the low compliance of the interstitial compartment. However, this protective mechanism is short-lived because of fragmentation within the proteoglycan skeleton of the interstitial matrix.[49] The alveolar epithelial cells represent the last line of defense against pulmonary edema. An enhanced clearance of alveolar fluid via the epithelial sodium channels (ENaCs) can produce a rapid resolution of alveolar edema. ENaCs are stimulated by β-adrenergic agonists[50] and inhibited by endothelin-1.[51]

The traditional Starling model of transcapillary exchange has been revised and updated to include a role for the glycocalyx in the semipermeable layer of the capillary endothelium.[52] The glycocalyx is a complex network of negatively charged glycosaminoglycans (GAGs), proteins and glycolipids. The most prominent GAGs are heparan sulfate, chondroitin sulfate, and hyaluronic acid (Fig. 24.17A). Recent studies suggest that the glycocalyx is a major determinant of capillary permeability, acting as a molecular sieve limiting water and protein flux across the cell-cell junction.[53] Breakdown of the glycocalyx is associated with increased vascular permeability owing to loss of the junctional barrier and an opening of the intracellular junction (Fig. 24.17B). The glycocalyx also functions as a mechanotransducer that can sense increases in hydrostatic pressure (Fig. 24.17C and D). Heparan sulfate plays an important role in the transmission of this fluid shear stress through stimulation of endothelial nitric oxide synthesis.[45,54] Recent evidence suggests that downstream microvessels are not in a continual state of fluid absorption, as described by the traditional





• **Fig. 24.14** A, Dimensions and structural attributes of the various vessel types. B, Velocity, cross-sectional area, blood volume, and pressure within the various vessel types. *AO,* Aorta; *LA,* large arteries; *SA,* small arteries; *ART,* arterioles; *CAP,* capillaries; *VEN,* venules; *SV,* small veins; *LV,* large veins; *VC,* venae cavae. (Modified from Berne RM, Levy MN. *Principles of Physiology*. St. Louis: CV Mosby; 1990:195.)

Starling model, and that maintenance of tissue fluid balance is more critically dependent on lymphatic function.[51]

Major Cardiovascular Reflexes

The salient features of the major cardiovascular reflexes are presented in Table 24.1.[55]

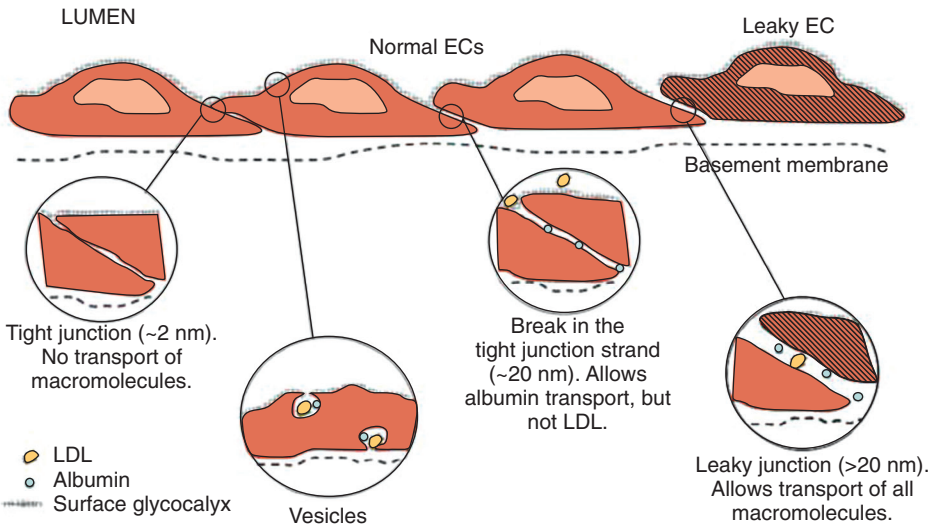
Arterial Baroreceptor Reflex

Arterial blood pressure is maintained within narrow limits by a negative feedback system called the arterial baroreceptor reflex.[56,57] The major components of this system are shown in (Fig. 24.18A): (1) an afferent limb composed of baroreceptors in the carotid artery and aortic arch and their respective afferent nerves, the glossopharyngeal and vagus nerves; (2) cardiovascular centers in the medulla that receive and integrate sensory information; and (3) an efferent limb composed of sympathetic nerves to the heart and blood vessels and the parasympathetic (vagus) nerve to the heart. Fig. 24.18B presents the neural relationships of the arterial baroreceptor reflex.[58]

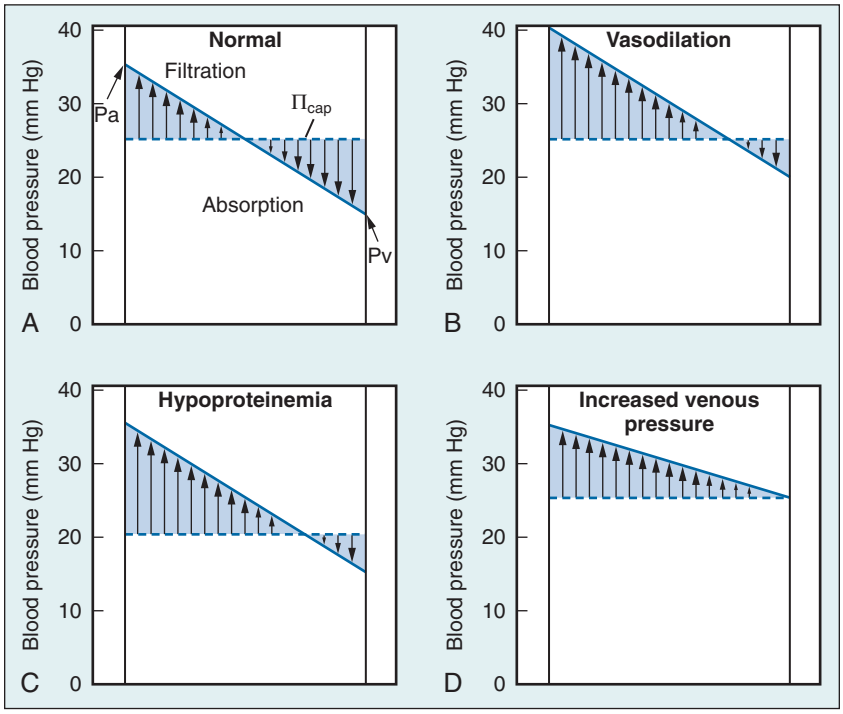
Baroreceptors are stimulated by stretch of the vessel wall by increased transluminal pressure. Impulses originating in the baroreceptors tonically inhibit discharge of sympathetic nerves to the heart and blood vessels, and tonically facilitate discharge of the vagus nerve to the heart. A rise in arterial pressure reduces baroreceptor afferent activity, resulting in further inhibition of the sympathetic and facilitation of parasympathetic output. This produces vasodilation, venodilation, and reductions in stroke volume, heart rate, and cardiac output, which combine to normalize arterial pressure. A decrease in arterial pressure has opposite effects. The cardiovascular centers in the medulla are also under the influence of neural influences arising from the arterial chemoreceptors, hypothalamus, and cerebral cortex, and of local changes in the partial pressure of carbon dioxide (P_{CO_2}) and the partial pressure of oxygen (P_{O_2}).

Bezold-Jarisch Reflex

The Bezold-Jarisch reflex is a triad of responses (bradycardia, hypotension, and apnea) first observed following injection of *Veratrum* plant alkaloids in animals by von Bezold and Hirt in 1867.[40,59–61] Seventy years later, Jarisch and Richter[62,63] demonstrated

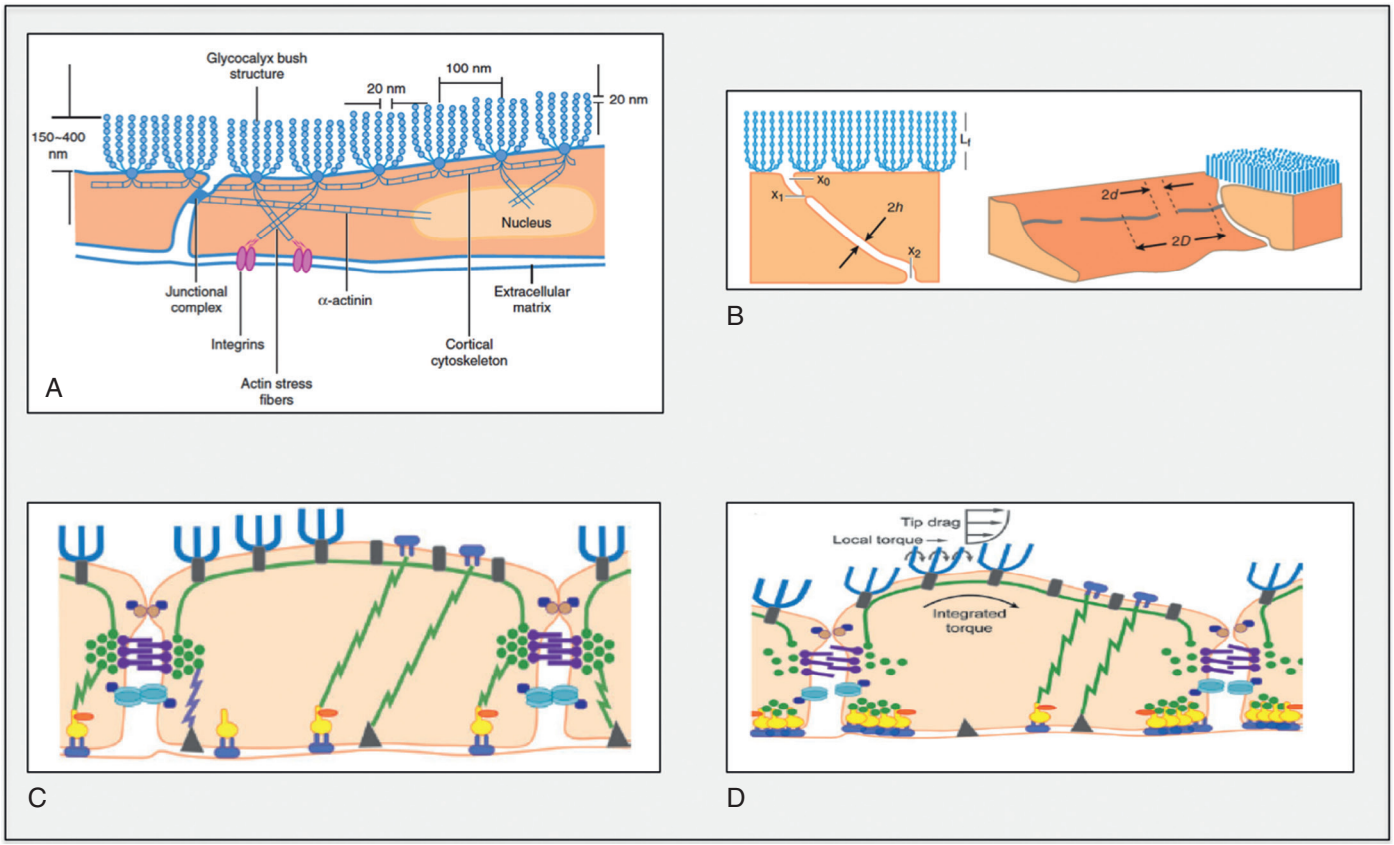


• **Fig. 24.15** Fluid transport pathways across the endothelium. The major pathways are (1) tight junctions allowing passage of water and small molecules, (2) vesicles, (3) breaks in the tight junctions allowing the transport of albumin, (4) leaky junctions allowing passage of all macromolecules. *EC,* Endothelial cell; *LDL,* low-density lipoprotein. (Reprinted with permission from Tarbell JM, Shear stress and the endothelial transport barrier. *Cardiovasc Res.* 2010;87:320–330.)



• **Fig. 24.16** Capillary-tissue fluid exchange. See text for details. Π_{cap}, Capillary oncotic pressure; *Pa,* hydrostatic pressure at arterial end of capillary; *Pv,* hydrostatic pressure at venous end of capillary. (Modified from Friedman JJ. Microcirculation. In: Selkurt EE, ed. *Physiology*. Boston: Little, Brown and Company; 1971:269.)

that the receptor area was in the heart (not the great vessels), the afferent pathway was in the vagus nerve, and the efferent pathway involved inhibition of sympathetic outflow to peripheral vessels and increased activity in the vagus nerve to the heart. The ventricular receptors underlying the Bezold-Jarisch reflex are nonencapsulated terminals of unmyelinated vagal C-fiber afferents in the walls of the ventricles.[64] Although *Veratrum* alkaloids are not normally present in animals, physiologic factors, including mechanical stimulation, can trigger the Bezold-Jarisch reflex.[65] The literature contains reports of "paradoxical" bradycardia during severe hemorrhage in humans.[66,67] Studies in a rabbit model demonstrated that this response is mediated by the ventricular receptors and by the ability of the Bezold-Jarisch reflex to override the arterial baroreceptor response.[68,69] During severe hemorrhage, the ventricular receptors can be excited by abnormal squeezing of the myocardium owing to vigorous contraction around a nearly empty chamber.

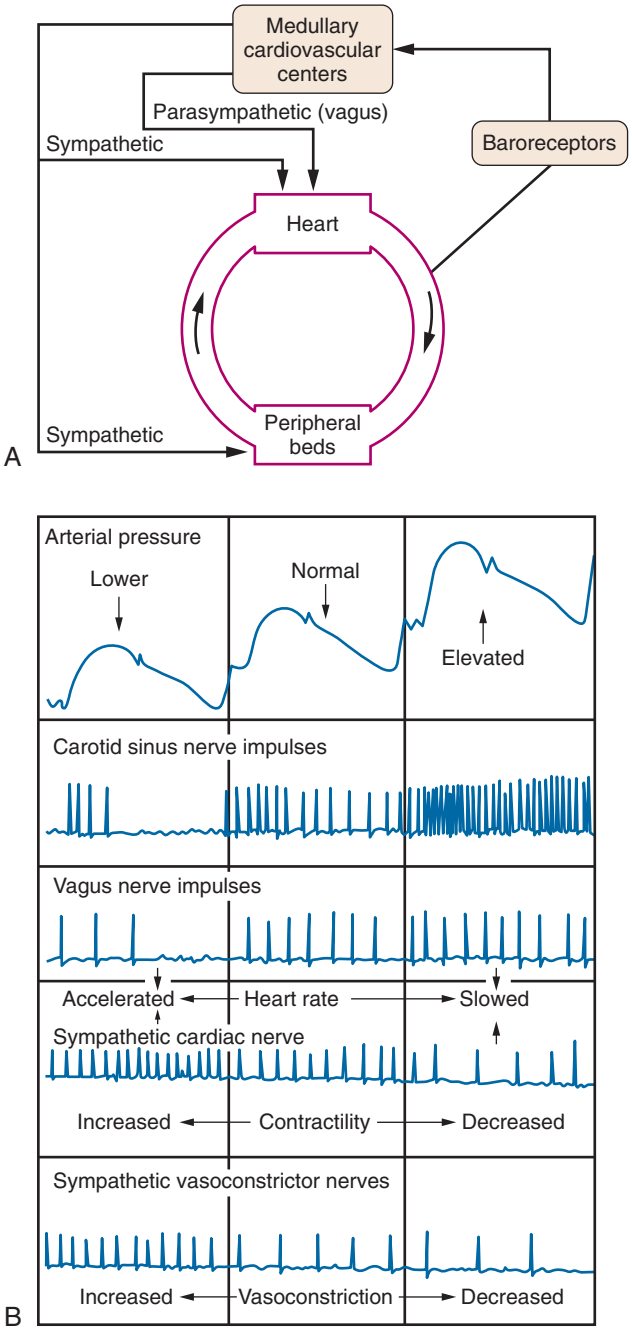


• **Fig. 24.17** A, Sketch of the configuration of the glycocalyx on the luminal side of the capillary endothelium. B, Cross section and a three-dimensional sketch of the glycocalyx covering the interendothelial cleft. C, The mechanism of mechanotransduction of the glycocalyx in response to fluid shear stress (FSS). It resembles the bumper-car model. At rest (with no FSS), the base of the actin cortical web (ACW) is formed by an intact dense peripheral actin band (DPAB) localized to the adherens junction. D, In response to FSS, local torque is applied on the bushlike glycocalyx resulting in translocation of the cytoskeleton and opening of the tight junctions allowing transudation of fluids. *2d,* Llength of tight junction strand gaps; *2D,* mean distance between strand gap centers (equal to functional unit length); *2h,* orientation of cleft width; x_0, luminal cleft opening; x_1, tight junction strand; x_2, abluminal cleft exit. (Reprinted with permission from Weinbaum S, Tarbell JM, Damiano ER. The structure and function of the endothelial glycocalyx layer. *Annu Rev Biomed Eng.* 2007;9:121–167.)

TABLE 24.1 Major Cardiovascular Reflexes

Reflex	Receptors and Location	Afferent Limb	Efferent Limb and Response
Arterial baroreceptor	Stretch receptors in vessel wall of carotid sinus and aortic arch respond to changes in arterial blood pressure	Fibers in glossopharyngeal and vagus nerves to medulla	Homeostatic control of arterial blood pressure via changes in cardiac output and systemic vascular resistance mediated by the autonomic nervous system
Bezold-Jarisch	Mechanical and chemosensitive receptors in ventricular walls	Nonmyelinated vagal C-fibers to medulla	Inhibition of sympathetic outflow resulting in bradycardia, peripheral vasodilation, and hypotension
Bainbridge	Stretch receptors at junction of the vena cava and right atrium and at junction of the pulmonary vein and left atrium respond to changes in volume in central thoracic compartment	Fibers in vagus nerve to medulla	Inhibition of vagal outflow and enhancement of sympathetic outflow to sinoatrial node causing tachycardia

Reprinted with permission from Crystal GJ, Salem MR. The Bainbridge and the "reverse" Bainbridge reflexes: history, physiology, and clinical relevance. *Anesth Analg.* 2012;114:520–532.



• **Fig. 24.18** A, Diagram of arterial baroreceptor reflex loop. B, Effect of changes in arterial pressure on carotid sinus nerve discharge and impulse rate of efferent nerves. (A, Modified from Rothe CF, Friedman JJ. Control of the cardiovascular system. In: Selkurt EE, ed. *Physiology*. Boston: Little, Brown; 1971:372; B, Modified from Rushmer RF. *Cardiovascular Dynamics*. 3rd ed. Philadelphia: WB Saunders; 1970:165.)

Bainbridge Reflex

In 1915 Bainbridge demonstrated that intravenous infusion of saline solution or blood in the anesthetized dog produced tachycardia.[55,70] The elimination of the response following transection of the cardiac autonomic nerve supply and injection of the anticholinergic drug atropine demonstrated that the tachycardia was reflexive in origin, with the vagus nerves constituting the afferent limb and withdrawal of vagal tone the primary efferent limb. The increase in venous return is detected by stretch receptors in the right and left atria.[71,72] The Bainbridge reflex is present in primates, including man, but is much less prominent than in the dog, attributed to a more dominant arterial baroreceptor reflex in humans.[73] The Bainbridge reflex is obtunded or absent when the heart rate is high.[74] A "reverse" Bainbridge reflex has been proposed to explain decreases in heart rate observed under conditions in which venous return is reduced, such as during spinal and epidural anesthesia and controlled hypotension.[55]

Tissue Oxygen Transport

General Concepts

Oxygen serves as an electron acceptor in oxidative phosphorylation, enabling production of adenosine triphosphate (ATP) along efficient aerobic pathways. The high-energy phosphate bonds of ATP provide energy for functional and biochemical cellular processes within the cell, such as contraction of muscle proteins and ion transport.

The cardiovascular system acts in concert with the respiratory system in transporting oxygen to tissue mitochondria from its source in inspired air. Oxygen transport is comprised of a series of steps down a gradient in partial pressure, each associated with a P_{O_2} cost (Fig. 24.19).[75] Normal oxygen delivery maintains P_{O_2} in the vicinity of mitochondria at 0.1 mm Hg, the level required for unimpaired O_2 consumption ($\dot{V}_{O_2}$) (Fig. 24.20).[76] The only effect of greater P_{O_2} values is to provide a gradient for diffusion of oxygen to mitochondria remote from capillaries.

The amount of oxygen carried from the lungs to tissues by circulating blood (i.e., convective systemic oxygen delivery [DO_2]), is given by the equation:

[6]

$$DO_2 = CO \times CaO_2$$

where CO is cardiac output in L/min and CaO_2 is the arterial oxygen content in volume percent.

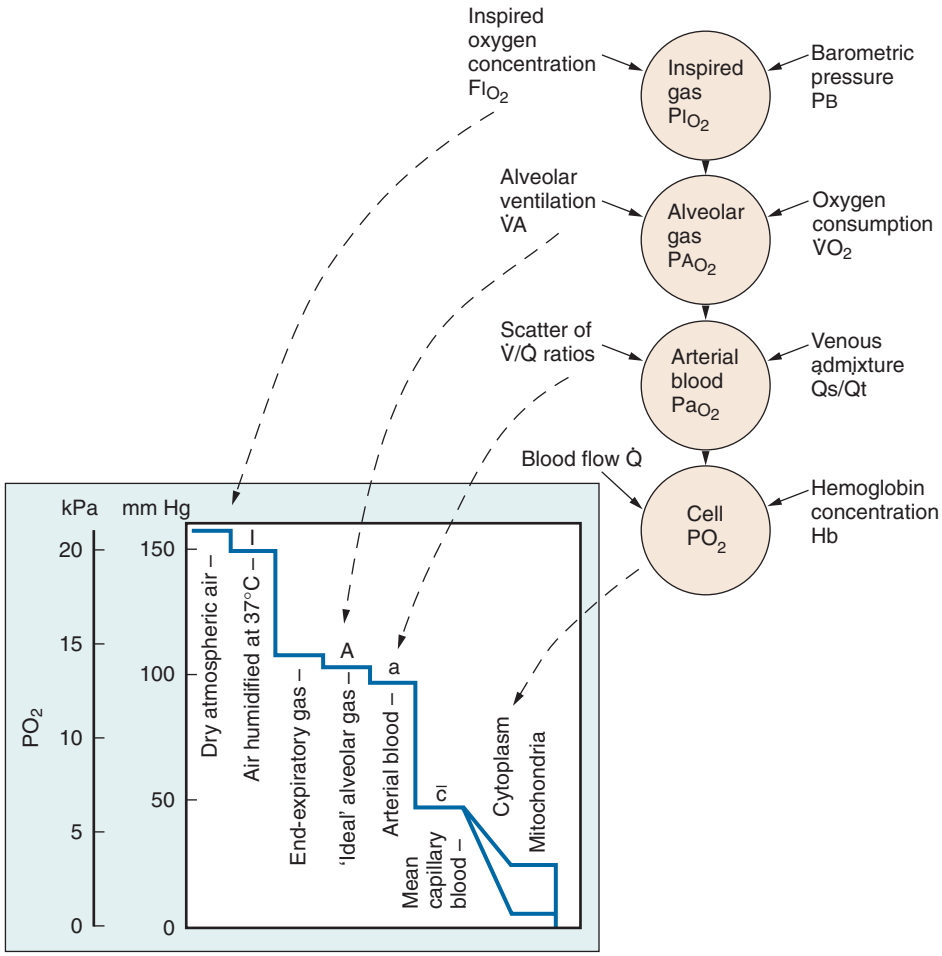
Oxygen Transport in the Blood

CaO_2 is composed of oxygen bound to hemoglobin and dissolved in plasma. Oxygen bound is a function of hemoglobin concentration (Hb), oxygen carrying capacity for hemoglobin (1.39 mL O_2/g hemoglobin), and oxygen saturation of hemoglobin (SaO_2), according to the equation:

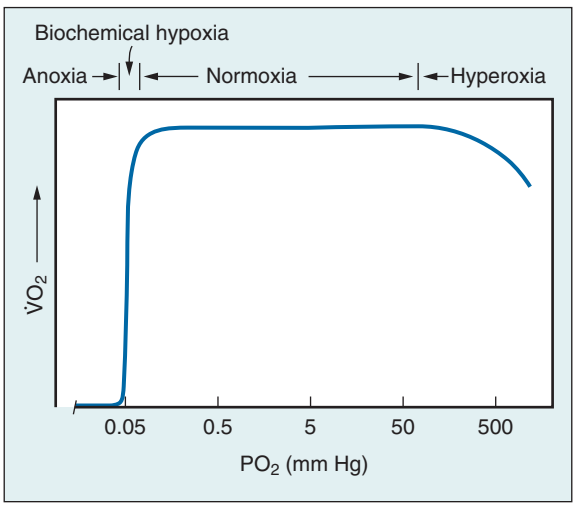
[7]

$$O_2 \text{ bound} = (Hb \times SaO_2 \times 1.39)$$

Oxygen saturation of hemoglobin is a function of P_{O_2} as reflected in the oxyhemoglobin dissociation curve (Fig. 24.21A), a plot of oxyhemoglobin saturation as a function of P_{O_2}.[46] At a P_{O_2} of 100 mm Hg, normal for arterial blood, SaO_2 is approximately 97%; at 40 mm Hg, a typical value for mixed venous oxygen tension (PvO_2) in a resting person, the saturation is about 75%. The sigmoid shape of the curve reflects the fact that the four oxygen-binding sites on the tetrameric hemoglobin molecule interact cooperatively with each other. When the first site binds a molecule of oxygen, the binding of the next site is facilitated, and so forth. The result is a curve that



• **Fig. 24.19** On the lower left is the oxygen cascade with the partial pressure of oxygen *(P_{O_2})* decreasing from the level in the ambient air down to the level in the mitochondria. The right side lists the factors influencing P_{O_2} at various steps in the cascade. *F_{IO_2},* Fraction of inspired oxygen; *Hb,* hemoglobin; *P_{AO_2},* alveolar oxygen partial pressure; *P_{aO_2},* arterial pressure of carbon dioxide; *P_{IO_2},* partial pressure of inspired oxygen; *$\dot{V}A$,* alveolar ventilation; *$\dot{V}O_2$,* oxygen consumption; *$\dot{V}/\dot{Q}$,* ventilation-perfusion ratio. (Reprinted with permission from Nunn JF. *Nunn's Applied Respiratory Physiology*. Oxford: Butterworth Heinemann; 1993:255.)

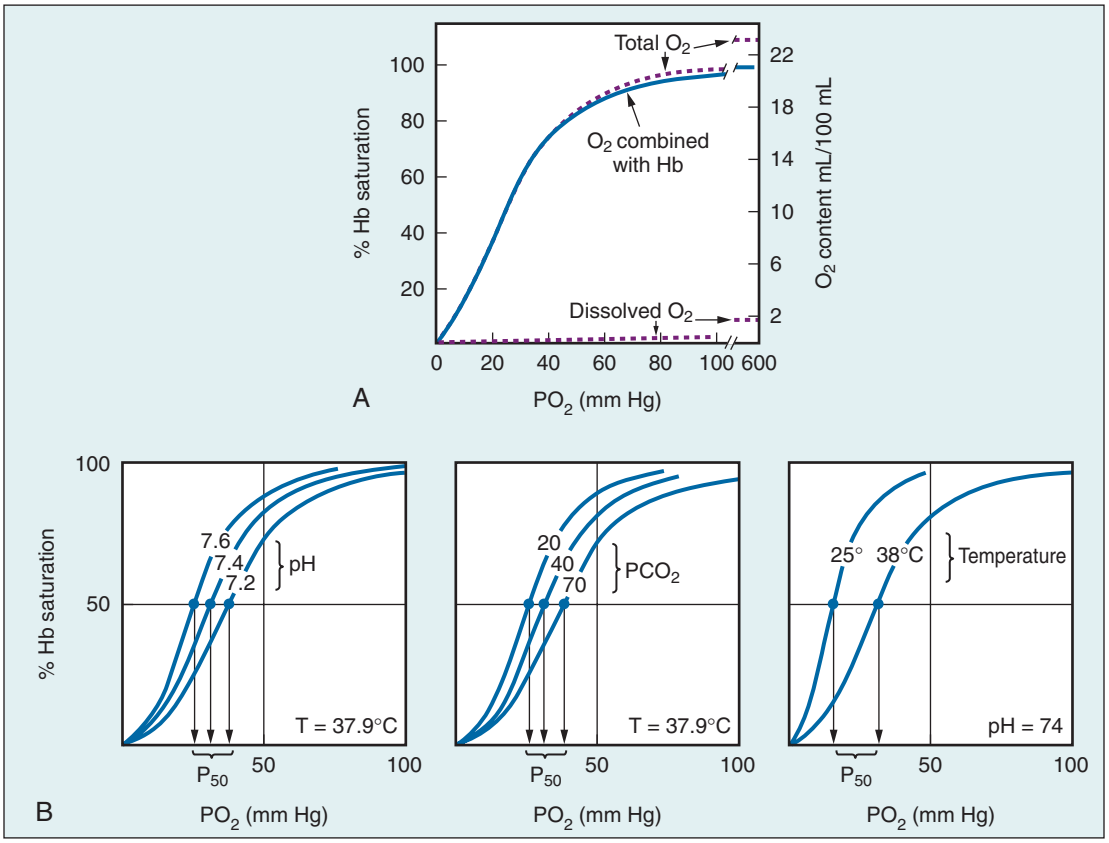


• **Fig. 24.20** Oxygen consumption *($\dot{V}O_2$)* of isolated mitochondria as a function of partial pressure of oxygen *(P_{O_2})*. Oxygen consumption remains unchanged as long as P_{O_2} is above 0.5 mm Hg. (Reprinted with permission from Honig CR. *Modern Cardiovascular Physiology*. Boston: Little, Brown and Company; 1981:185.)

is steep up to P_{O_2} of 60 mm Hg and more shallow thereafter, approaching 100% saturation asymptomatically.

The shape of the oxyhemoglobin dissociation curve has important physiologic implications. The flatness of the curve above a P_{O_2} of 80 mm Hg ensures a relatively constant oxyhemoglobin saturation for arterial blood despite wide variations in alveolar oxygen pressure. The steep portion of the curve between 20 and 60 mm Hg permits unloading of oxygen from hemoglobin at relatively high P_{O_2} values, which permits delivery of large amounts of oxygen into the tissue by diffusion.

The oxygen-binding properties of hemoglobin are influenced by a number of factors, including pH, P_{CO_2}, and temperature (see Fig. 24.21B).[77] These factors cause shifts of the oxyhemoglobin dissociation curve to the right or left without changing the slope. An increase in temperature or P_{CO_2}, or a decrease in pH, all of which occur in active tissues, decreases the affinity of hemoglobin for oxygen and shifts the oxyhemoglobin dissociation curve to the right. Thus a higher P_{O_2} is required to achieve a given saturation, which facilitates unloading of oxygen in the tissue. The extent of a shift in the oxyhemoglobin dissociation curve is quantified as the P_{50} (P_{O_2} required for 50% saturation). The P_{50} of normal adult hemoglobin at 37°C and normal pH and P_{CO_2} is 26 to 27 mm Hg.



• **Fig. 24.21** A, The oxyhemoglobin dissociation curve. The oxygen content of blood has two components: oxygen binding to hemoglobin *(Hb)* follows an *S*-shaped curve up to full saturation; the amount of oxygen in solution increases linearly with the partial pressure of oxygen *(PO_2)* without limit. B, Effects of variations in pH, partial pressure of carbon dioxide *(PCO_2),* and temperature *(T)* on the oxyhemoglobin dissociation curve. *P_{50},* Oxygen half-saturation pressure. (A, Reprinted with permission from West JB. *Respiratory Physiology: the Essentials*. Baltimore: Williams & Wilkins; 1974; B, Reprinted with permission from Weibel ER. *The Pathway for Oxygen*. Cambridge, Mass: Harvard University Press; 1984:149.)

The metabolite 2,3-diphosphoglycerate (2,3-DPG) is an intermediate in anaerobic glycolysis (the biochemical pathway by which red blood cells produce ATP) that binds to hemoglobin. Increased erythrocyte 2,3-DPG concentration reduces the affinity of hemoglobin for oxygen (i.e., shifts the oxyhemoglobin dissociation curve to the right), whereas decreases have the opposite effect. Several factors influence red cell 2,3-DPG concentrations. For example, after storage in a blood bank for only 1 week, 2,3-DPG concentrations are one-third normal, resulting in a shift to the left in the oxyhemoglobin dissociation curve. On the other hand, conditions associated with chronic hypoxia (e.g., living at high altitude or chronic anemia) stimulate production of 2,3-DPG, which causes a rightward shift of the oxyhemoglobin dissociation curve.

Oxygen dissolved in blood is linearly related to PO_2. At 37°C it is defined by the equation:

[8]

$$O_2 \text{ dissolved} = 0.003 \text{ vol\% mm Hg } PO_2$$

Dissolved oxygen normally accounts for only 1.5% of total blood oxygen, but this contribution increases when the bound component is reduced during hemodilution. Because hemoglobin is essentially saturated at a PO_2 of 100 mm Hg, increases in arterial PO_2 (PaO_2) to above 100 mm Hg increase CaO_2 by raising the dissolved component.

Characteristic Values for Parameters of Oxygen Delivery

For an individual with a hemoglobin concentration of 15 g/100 mL, PaO_2 of 100 mm Hg, PvO_2 of 40 mm Hg, and cardiac output of 5000 mL/min:

[9]

$$CaO_2 = (15 \times 0.97 \times 1.39) + (0.003 \times 100) = 20.5 \text{ vol\%}$$

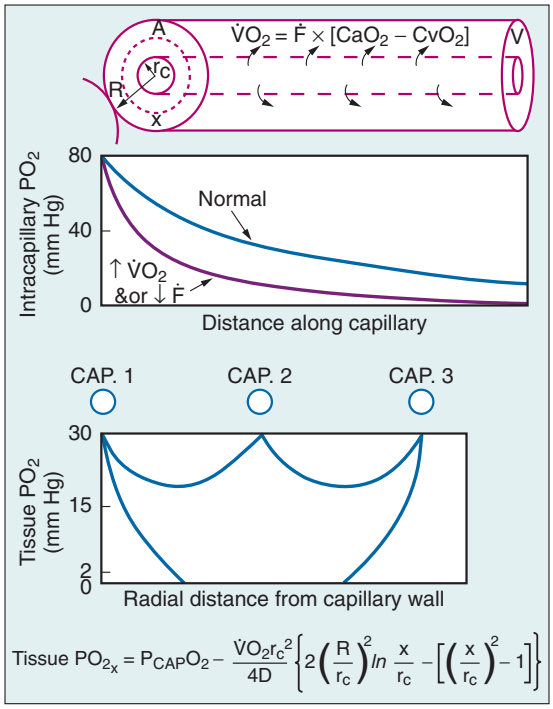
$$DO_2 = (5000 \times 20.5/100) = 1025 \text{ mL} \times \text{min}$$

$$CvO_2 = (15 \times 0.75 \times 1.39) + (0.003 \times 40) = 15.8 \text{ vol\%}$$

and the arteriovenous oxygen content difference (CaO_2– CvO_2) = 20.5 − 15.8 = 4.7 vol%.

Diffusion of Oxygen to Tissues: Capillary to Cell Oxygen Delivery

The final step in the delivery of oxygen to tissue mitochondria is diffusion from the capillary blood. This process is determined by the capillary-to-cell PO_2 gradient and the diffusion parameters, capillary surface area, and blood-cell diffusion distance. In 1919 August Krogh formulated the capillary recruitment model to describe the processes underlying oxygen transport in tissue, which was



• **Fig. 24.22** Longitudinal and radial oxygen gradients within tissue in accordance with Krogh cylinder model. See text for details. *A,* Arterial end of capillary; *CAP,* capillary; Ca_{O_2}, arterial oxygen content; Cv_{O_2}, central venous oxygen content; *D,* diffusion coefficient for oxygen; $\dot{F}$ blood flow; $[Ca_{O_2} - Cv_{O_2}]$, arteriovenous oxygen content difference; P_{O_2}, partial pressure of oxygen; $P_{cap}O_2$, oxygen tension of capillary blood; *R,* tissue cylinder radius; r_c, capillary radius; *V,* venous end of capillary; $\dot{V}_{O_2}$, Oxygen consumption; *x,* point within tissue cylinder. (Reprinted with permission from Honig CR. *Modern Cardiovascular Physiology*. Boston: Little, Brown; 1981:183.)

later expanded and refined.[78,79] Although Krogh's model is limited by multiple simplifying assumptions, it has value as a tool for appreciating the role of vascular control mechanisms in the transport of oxygen to tissue.

The model consists of a single capillary and the surrounding cylinder of tissue that it supplies (Fig. 24.22).[76] Two interrelated oxygen gradients are involved: a longitudinal gradient within the capillary and a radial gradient extending into the tissue. Most oxygen in capillary blood is bound to hemoglobin and cannot leave the capillary. This bound oxygen is in equilibrium with the small amount of oxygen dissolved in the plasma. The consumption of oxygen by tissue creates a transcapillary gradient for oxygen. Diffusion of oxygen into tissue shifts the equilibrium between bound and dissolved oxygen so that more oxygen is released from hemoglobin. By this mechanism, oxygen dissociation from hemoglobin is controlled by tissue oxygen consumption.

The longitudinal oxygen gradient is created by extraction of oxygen by tissue as blood passes from the arterial to venous ends of the capillary. The arteriovenous oxygen difference is equivalent to the ratio of oxygen consumption to blood flow (Fick equation). An increase in oxygen consumption, a decrease in blood flow, or both, steepens the longitudinal oxygen gradient. Proportional changes in oxygen consumption and blood flow are required to maintain the longitudinal oxygen gradient constant.

A corresponding value for capillary PO_2 (PcO_2) can be estimated from the value for capillary oxygen content, taking into account hemoglobin concentration and the oxyhemoglobin dissociation curve. The shape of the longitudinal gradient in PO_2 within the capillary is approximately exponential because of the influence of the oxyhemoglobin dissociation curve. The PcO_2 is the driving force for oxygen diffusion into tissue. Since PcO_2 is at minimum at the venous end of the capillary, mitochondria in this region are most vulnerable to oxygen deficits.

The radial PO_2 gradient can be described by a value for mean tissue PO_2 (PtO_2) according to the equation:

[10]

$$\text{Mean } PtO_2 = PcO_2 - A\left(\dot{V}O_2 \times r^2/4D\right)$$

where PcO_2 is blood oxygen tension midway in the capillary, A is a constant related to the relationship between capillary radius and tissue cylinder radius, $\dot{V}O_2$ is oxygen consumption of the tissue cylinder, r is the radius of the tissue cylinder (½ intercapillary distance), and D is the oxygen diffusion coefficient. r is determined by the number of capillaries perfused with red blood cells per volume of tissue and is controlled by precapillary sphincters. The favorable influence of capillary recruitment on tissue PO_2 is evident in Fig. 24.22 (lower panel). If only capillaries "1" and "3" are open, diffusion distance is so large that PO_2 falls to zero toward the center of the tissue cylinder. The low tissue PO_2 (PtO_2) causes relaxation of the precapillary sphincter controlling capillary "2." Perfusion of capillary "2" decreases diffusion distance and increases tissue PO_2 to an adequate level throughout the tissue.

Mean PtO_2 is a reflection of the overall balance between oxygen supply and demand within a particular tissue. An increase in blood flow without a change in oxygen demand (i.e., luxuriant perfusion) raises mean PtO_2, whereas reduction in blood flow without a change in oxygen demand lowers mean PtO_2. If mean PtO_2 falls below a critical level, tissue oxygen consumption is impaired. Measurements of mean PtO_2 have been obtained in laboratory animals in various tissues, including the myocardium and skeletal muscle, using a polarographic technique involving bare-tipped platinum electrodes.[80,81] The invasiveness of the technique has curtailed use of mean PtO_2 measurements in patients. Measurements of local venous PvO_2 provide an approximation for average end-capillary PO_2, and although they neglect the radial PO_2 gradient, they generally show a reasonable correlation to mean PtO_2.[82]

Measurement of Oxygen Consumption

In a clinical setting, there are several methods to measure $\dot{V}O_2$: oxygen loss or replacement into a closed breathing system, subtraction of expired from inspired volume of oxygen, and use of the Fick principle.[83,84] These techniques are used in cardiopulmonary exercise testing to determine fitness and reserve for preoperative risk stratification.

Oxygen loss or replacement into a closed breathing system is the most fundamental method. It is well validated and has an accuracy well in excess of clinical requirements. However, it is cumbersome and requires meticulous attention to detail. The second method, subtraction of expired from inspired volume of oxygen, is a difficult and potentially inaccurate method because $\dot{V}O_2$ is a small number that is calculated as the difference between two large numbers.

Under steady-state conditions, the Fick equation can be used to calculate systemic $\dot{V}O_2$ as:

[11]

$$\dot{V}O_2 = CO \times (CaO_2 - CvO_2)$$

where ($CaO_2 - CvO_2$) is the systemic arteriovenous oxygen content difference expressed in volume percent. In this approach, CO is usually measured by thermodilution using a pulmonary artery catheter. Samples of blood are collected from a systemic artery and the pulmonary artery (mixed venous sample) and analyzed for oxygen content. The values for blood oxygen content are used to calculate the systemic arteriovenous oxygen content difference. Using values for CO and ($CaO_2 - CvO_2$) at rest, the Fick equation can be used to calculate a value for whole-body oxygen consumption:

[12]

$$\dot{V}O_2 = 5000 \times 4.7/100 = 228 \text{ mL/min}$$

The Fick technique is popular in the intensive care setting because the necessary arterial and pulmonary artery catheters are frequently used. An important advantage is that it also provides a measurement of DO_2 (see Eq. 6), which permits analysis of the relationship between DO_2 and $\dot{V}O_2$. A drawback of the Fick technique is that it excludes oxygen consumption of the lungs. Although this component is negligible for normal lungs, simultaneous measurements of $\dot{V}O_2$ by the Fick and gasometric methods indicate that it can be significant (as much as 20% of total $\dot{V}O_2$) in critically ill patients.[85] The increased $\dot{V}O_2$ in the lung is related to production of the superoxide and in turn hydroxyl free radicals, hydrogen peroxide, and hypochlorous acid.[86]

The oxygen extraction ratio (EO_2 in percent) is defined by the equation:

[13]

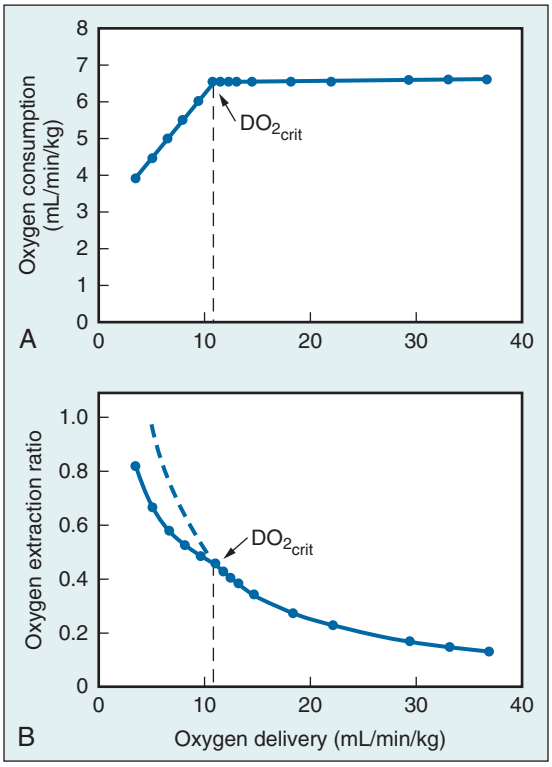
$$EO_2 = (CaO_2 - CvO_2)/CaO_2$$

EO_2 is equal to the ratio of $\dot{V}O_2$ to DO_2 and thus reflects the balance between systemic oxygen demand and delivery. Measurements of EO_2, as well as of mixed venous oxygen saturation (SvO_2), are used clinically to assess overall adequacy of DO_2 in critically ill patients.[87–89]

A decrease in DO_2 can follow a significant reduction in any one of its major factors (hemoblogin, SaO_2, or CO) or a smaller reduction in more than one of these factors, such as can occur in critical illness. If reduction in DO_2 is severe, it can produce tissue hypoxia (a fall in tissue PO_2 sufficient to limit mitochondrial $\dot{V}O_2$ and to stimulate lactate production). Old terminology referred to the conditions of hypoxia resulting from reductions in hemoglobin, SaO_2, and CO as anemic, hypoxic, and stagnant hypoxia, respectively.[90]

Critical Oxygen Delivery

DO_2 greatly exceeds $\dot{V}O_2$ at rest (in the prior example, above 1025 compared with 228 mL/min) and thus EO_2 is relatively modest (25%), resulting in a substantial reserve for increased EO_2. This results in a biphasic relation between DO_2 and $\dot{V}O_2$ (Fig. 24.23).[91] At normal or high DO_2, $\dot{V}O_2$ is constant and independent of DO_2 (see Fig. 24.23A). As DO_2 is gradually reduced, increased EO_2 maintains $\dot{V}O_2$ (see Fig. 24.23B). Eventually a point is reached where EO_2 cannot increase sufficiently. Below this threshold, the so-called critical DO_2, $\dot{V}O_2$ is limited by the supply of oxygen, about 10 mL/min per kilogram in anesthetized dogs.[92] A normal biphasic DO_2-$\dot{V}O_2$ relationship exists in patients without respiratory failure undergoing coronary artery bypass surgery, whereas a direct linear relationship between DO_2 and $\dot{V}O_2$ occurs in patients with acute respiratory distress syndrome, implying a pathologic impairment to tissue extraction of oxygen.[93–95]



• **Fig. 24.23** Changes in systemic oxygen consumption (A) and oxygen extraction ratio (B) during progressive reduction in oxygen delivery. An increased oxygen extraction ratio maintains oxygen consumption constant until oxygen delivery is lowered to a critical value *(DO_2 crit)*. The *dashed line* demonstrates the theoretical increase in oxygen extraction required to maintain oxygen consumption for levels of oxygen delivery below DO_2 crit. (Reprinted with permission from Schumacker PT, Cain SM. The concept of critical oxygen delivery. *Intensive Care Med*. 1987; 13:223–229.)

Eqs. 6, 11, and 12 can be applied to individual tissues by substituting local blood flow for cardiac output and local venous oxygen measurements for mixed venous oxygen measurements. Body tissues vary widely with respect to the relation between baseline DO_2 and $\dot{V}O_2$, and thus in their baseline EO_2 (Table 24.2). For example, in the LV, baseline EO_2 is 70% to 75%, whereas in kidney it is only 5% to 10%. The high baseline EO_2 of the LV renders it extremely dependent on changes in blood flow to maintain adequate oxygen delivery.

Determinants of Myocardial Oxygen Supply and Demand

Control of Coronary Blood Flow

Blood flow to the myocardium, like that to other vascular beds, is a function of the arteriovenous pressure gradient and local vascular resistance (see Fig. 24.1). In the left ventricular wall, coronary vascular resistance is determined by the throttling effect of extravascular compressive forces during systole (owing to the high intracavitary and tissue pressures) and by active changes in the

TABLE 24.2 Interorgan Variation in Baseline Values for Blood Flow, Oxygen Consumption, Arteriovenous Oxygen Difference, and Oxygen Extraction in the Average Human

Organ	Blood Flow (mL/min/100 g)	Oxygen Consumption (mL/min/100 g)	Arteriovenous O_2 Difference (Vol%)	O_2 Extraction (%)
Left ventricle	80	8	14	70
Brain	55	3	6	30
Liver	55	2	6	30
Gastrointestinal tract	40			
Kidneys	400	5	1.3	6.5
Muscles	3	0.16	5	25
Skin	10	0.2	2.5	12.5
Rest of body	3	0.15	4.4	22

Adapted from Folkow B, Neil E. *Circulation*. New York: Oxford University Press; 1971:12.

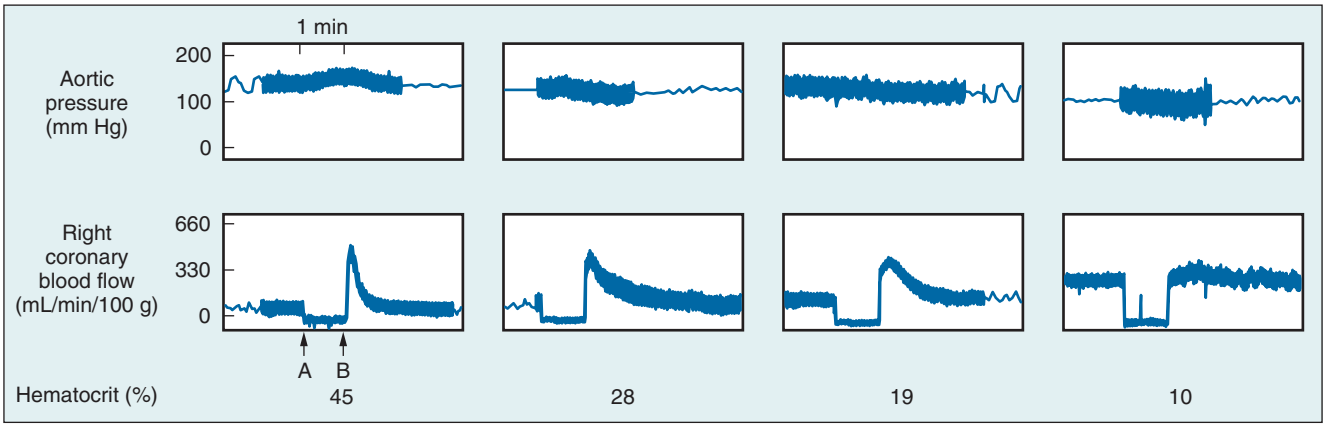
tone of arteriolar smooth muscle.[96] The systolic compressive forces, which are most prominent in the subendocardium, result in maximal left coronary blood flow occurring during diastole. The pressure gradient for blood flow to the LV is estimated from the difference between aortic diastolic pressure and left ventricular end-diastolic pressure. Because of a lower developed systolic pressure, right ventricular blood flow is substantial throughout the cardiac cycle and is modestly higher during systole, essentially following the contour of aortic pressure. The left ventricular pressure gradient is estimated from the difference between mean aortic pressure and mean right ventricular pressure. In pulmonary arterial hypertension, the systolic component of blood flow to the RV is impaired, resulting in a greater dependence of the RV on blood flow during diastole, a condition resembling that in the normal LV.[97]

Local metabolic mechanisms predominate in the active control of coronary vasomotor tone.[96] These mechanisms ensure a close coupling between coronary blood flow and myocardial oxygen demand, which serves to maintain myocardial P_{O_2} (and coronary venous P_{O_2}) nearly constant. Current concepts of metabolic control propose a feed-forward mechanism whereby vasodilating metabolites are produced by the myocardium in proportion to the level of cardiac work.[98] Metabolites that have been suggested include carbon dioxide, which is generated in decarboxylation reactions of the citric acid cycle, and reactive oxygen species, which are formed in the mitochondrial respiratory chain. The flow response initiated by these metabolites is mediated by several downstream mechanisms, including the ATP-sensitive potassium channels and the voltage-gated potassium channels. Adenosine, a breakdown product of ATP, is a potent endogenous vasodilator that was traditionally considered to play a central role in metabolic regulation of coronary blood flow. It is now thought that adenosine is involved only when the stimulus for its production, low tissue P_{O_2}, is present.[98] Increases in arterial P_{CO_2} (and the attendant decreases in arterial pH), decreases in arterial P_{O_2}, and decreases in hemoglobin concentration are accompanied by coronary vasodilation; opposite changes in arterial P_{CO_2} and P_{O_2} are accompanied by coronary vasoconstriction.[99–102] Autoregulation refers to the intrinsic capability of the coronary circulation to maintain a relatively constant coronary blood flow over a wide range of perfusion pressures (about 60–120 mm Hg).[96] This can be due to metabolic and/or myogenic mechanisms. A myogenic response refers to the intrinsic tendency of vascular smooth muscle to contract in response to increased distending pressure and to relax in response to decreased distending pressure. Higher tissue pressures in the subendocardium of the LV wall result in a reduced autoregulatory capability compared with the subepicardium. This contributes to greater vulnerability of that region to infarction during coronary insufficiency.

The coronary arterioles are endowed with both α- (constricting) and β_2- (dilating) adrenergic receptors and muscarinic receptors, and are supplied by sympathetic and parasympathetic (vagus) fibers.[96] Activation of muscarinic receptors associated with the vascular endothelium causes production of nitric oxide that diffuses to underlying vascular smooth muscle, producing relaxation and vasodilation.[103] Neural pathways are normally subordinate to local metabolic mechanisms in coronary vascular regulation.

Coronary Flow Reserve

Coronary flow reserve is the ratio of maximum coronary blood flow to resting coronary blood flow.[104] Local infusion of a vasodilating drug, such as adenosine or the reactive hyperemic response (the transient increase in blood flow that follows an interval of arterial occlusion), can be used to assess coronary flow reserve (Fig. 24.24).[101] The temporal characteristics of the reactive hyperemic response have been explained by metabolites produced in ischemic tissue first dilating the resistance vessels and then washing out during reperfusion. Coronary occlusion of 60 seconds is usually required to maximally dilate the coronary circulation and thus to assess coronary reserve. Longer occlusions only increase the duration of the reactive hyperemic response. Coronary flow reserve in the normal right and left ventricular walls is appreciable (approximately 400% to 500%) but is reduced in a variety of conditions, including left ventricular hypertrophy, coronary stenosis, and hemodilution (see Fig. 24.24).[101] In the presence of coronary stenosis, dilation of downstream resistance vessels (i.e., recruitment of the coronary flow reserve) tends to maintain coronary blood flow (and myocardial oxygen supply) commensurate with myocardial oxygen demand. Coronary reserve is exhausted when the stenosis reaches about



• **Fig. 24.24** Coronary flow reserve assessed by analysis of the reactive hyperemic response in the right coronary circulation of a dog. Graded hemodilution was associated with a progressive diminution of this response. *A,* begin occlusion of coronary artery; *B,* release occlusion. (Reprinted with permission from Crystal GJ, Kim S-J, Salem MR. Right and left ventricular O_2 uptake during hemodilution and β-adrenergic stimulation. *Am J Physiol*. 1993;265:H1769–H1777.)

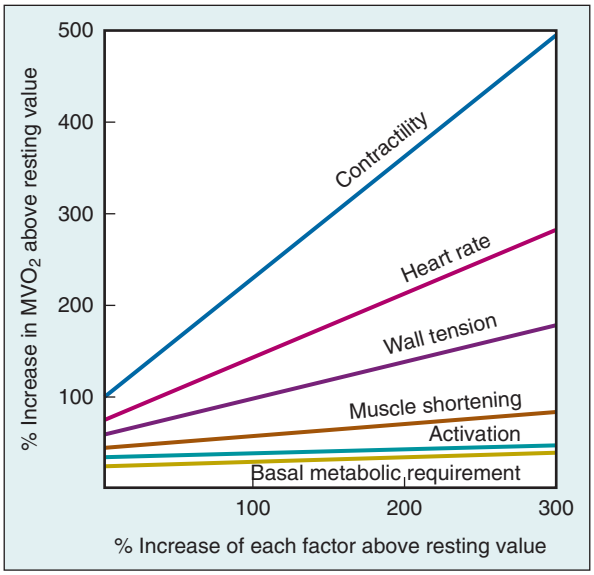
90%, resulting in a decrease in resting blood flow.[105] Diminished coronary flow reserve renders the myocardium more vulnerable to ischemia secondary to increases in cardiac work or reductions in perfusion pressure. During exercise, turbulence can enhance the decrease in blood flow across a stenosis.

Myocardial Oxygen Demand

The heart is continuously active and normally depends almost exclusively on aerobic metabolism to meet its energy demands. Although the heart constitutes less than 0.5% of body weight, it accounts for about 7% of basal oxygen consumption. The most important determinants of myocardial oxygen demand are contractility, heart rate, and wall tension (Fig. 24.25).[106,107] Wall tension is directly proportional to the pressure and radius of the heart and inversely proportional to wall thickness (law of Laplace). The area beneath the left ventricular pressure pulse per minute, the time-tension index, bears a direct relationship to myocardial oxygen consumption. When external work (pressure × stroke volume) is considered, pressure work has a much greater oxygen cost than does flow work. Muscle shortening per se has only a small influence on myocardial oxygen consumption. Basal metabolism reflects ATP-requiring processes not directly related to contraction, such as activity of cell membrane sodium-potassium adenosine triphosphatase (Na,K-ATPase) for maintaining the ionic environment, as well as other cellular processes such as protein synthesis. The oxygen cost of activation consists of two components: (1) electrical activation and (2) release and uptake of Ca^{2+} by the sarcoplasmic reticulum. The RV has a smaller baseline oxygen demand than the LV, consistent with a smaller pressure workload.[101,108]

Impaired Myocardial Oxygen Balance: Mechanisms of Myocardial Ischemia

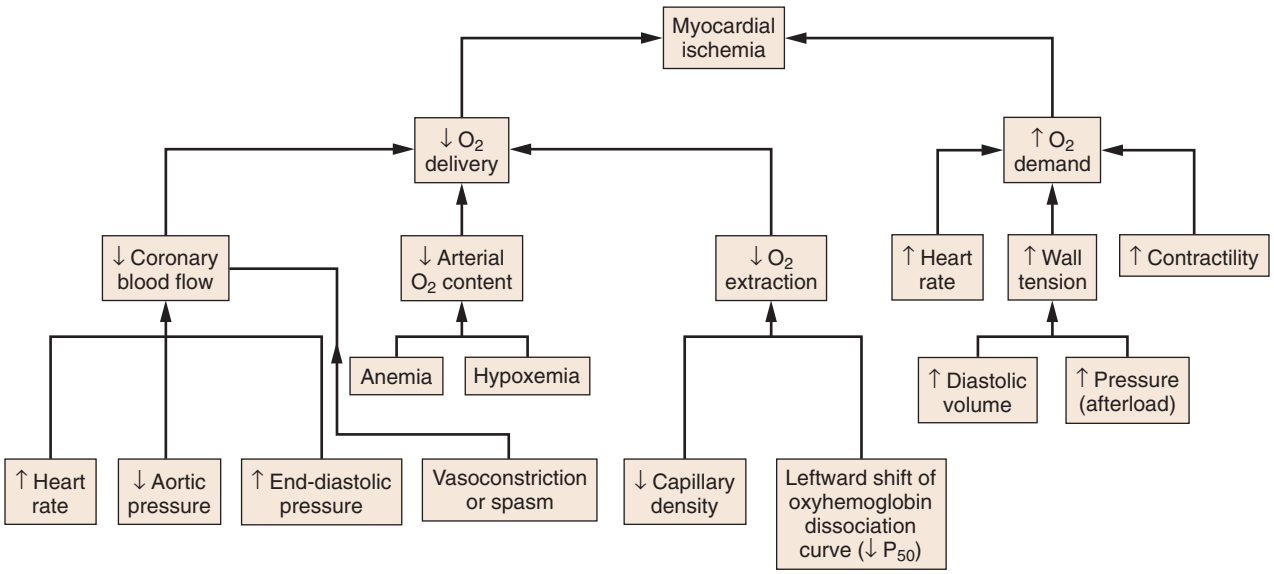
Oxygen extraction in the LV is nearly maximal at baseline; thus increases in myocardial oxygen consumption are critically dependent on proportional increases in coronary blood flow through the action of locally produced vasodilating metabolites. If coronary blood flow is insufficient to meet myocardial oxygen demand, compensatory mechanisms can be marshaled to preserve cell viability:



• **Fig. 24.25** Determinants of myocardial oxygen consumption *(MVO_2)*. It is noteworthy that the major determinants—contractility, heart rate, and wall tension—are hemodynamic variables that can be controlled by the anesthesiologist. (Reprinted with permission from Marcus ML. *The Coronary Circulation in Health and Disease*. New York: McGraw-Hill; 1983:70.)

an increase in the number of open capillaries, consumption of glycogen stores, and utilization of oxygen bound to tissue myoglobin.[106] However, these compensatory mechanisms are limited and can preserve cell viability in the presence of severe ischemia for only 20 minutes.[109]

When the vasodilator reserve of the coronary bed is compromised by a proximal stenosis (or by hypoxemia or anemia), the myocardium, especially the subendocardium, becomes vulnerable to ischemia (oxygen demand exceeding oxygen supply). Factors tending to promote this condition are presented in Fig. 24.26. An increase in heart rate is detrimental to the oxygen supply/demand balance since it decreases myocardial oxygen supply by decreasing coronary blood flow (via shortening of the diastolic period), while also



• **Fig. 24.26** Conditions having detrimental influence on myocardial oxygen balance: mechanisms of myocardial ischemia. *O_2*, Oxygen; *P_{50}*, Oxygen half-saturation pressure.

increasing myocardial oxygen demand. An increase in preload also reduces myocardial oxygen supply (by reducing the pressure gradient for coronary blood flow) and increases myocardial oxygen demand (via an increase in wall tension). An increase in aortic pressure increases myocardial oxygen supply by increasing coronary blood flow, but it also increases myocardial oxygen demand via an increase in wall tension; its net effect depends on the balance between these factors. Under conditions of restricted coronary vasodilator reserve, the most favorable hemodynamic situation is characterized by low heart rate and preload, normal aortic pressure, and normal to moderate inotropic state.[105]

Emerging Developments

Noninvasive Perioperative Monitoring

Understanding of cardiovascular physiology from a systems perspective has changed little in recent years. However, there have been substantial advances in the ability to apply these basic concepts at the bedside using minimally or entirely noninvasive technologies. For example, the improved accuracy and ease of use of noninvasive methods for beat-by-beat measurements of blood pressure has permitted evaluations of autonomic responsiveness, in addition to continuous perioperative monitoring. Recent evidence suggests that loss of autonomic responsiveness as the result of age or chronic illness can have prognostic value.[110] Furthermore, noninvasive methods to quantify endothelial function have emerged, and data suggest that these assessments have prognostic significance.[111]

Extensive effort has been made toward developing and applying minimally or noninvasive methods for continuous measurement of cardiac output in patients who are not sufficiently compromised to justify the risk associated with insertion of a pulmonary artery catheter.[112] The new technologies to monitor cardiac output have fostered an awareness of the importance of fluid management in optimizing cardiac performance. These technologies also have the potential to provide objective information that can help guide perioperative fluid management and optimize cardiac performance. Studies showing improved outcome when goal-directed fluid administration algorithms are applied have provided the basis for the concept of "fluid responsiveness," which is essentially an assessment of where a patient's heart is in relation to the Starling curve.[113]

Continuous measurements of blood flow combined with measurements of hemoglobin concentration and oxygen saturation make it possible to calculate tissue oxygen delivery. Appreciation of the physiologic significance of this concept has provided the impetus for development of commercially available, noninvasive devices that assess oxygen saturation directly in various tissues, including skeletal muscle and brain, as a means to evaluate whether the circulation is providing sufficient oxygen to meet tissue metabolic demands.[114] Although the accuracy and interpretation of these measurements remain controversial, these devices have demonstrated potential utility and promise.

Key Points

- Tissue blood flow depends on arterial pressure, which is the product of cardiac output and total peripheral resistance, and on local vascular resistance, which is a function of local vasomotor tone.
- The left and right ventricles have important functional and structural differences. These include lower developed pressure and workload, and a thinner wall for the right ventricle. The ventricles demonstrate a high degree of interdependence because of their shared interventricular septum and the restraining influence of the surrounding pericardium.
- Studies in isolated animal heart models show that stroke volume is directly related to both end-diastolic volume or preload (Starling's law) and myocardial contractility, and inversely related to afterload. The normal heart in vivo can compensate for an increase in afterload by increases in end-diastolic volume and contractility.

- A cardiac function curve is a plot of ventricular performance (e.g., stroke volume, as a function of end-diastolic volume). Contractility can be illustrated graphically using a family of curves. When cardiac function curves are constructed in vivo using a pulmonary artery catheter, accurate representation requires careful attention to several assumptions relating to compliance, afterload, and heart rate.
- Ventricular diastole consists of four phases: isovolumic relaxation, early rapid filling, diastasis, and atrial systole. Of these phases, only isovolumic relaxation is an active process that requires expenditure of energy by ventricular myocytes. Early rapid filling normally accounts for 80% to 85% of ventricular end-diastolic volume and diastasis and atrial systole provide approximately 3% to 5% and 15% to 25%, respectively.
- Ejection fraction is the most frequently used clinical index of global contractile function. It provides useful information about systolic pump performance but is heavily influenced by afterload. Other more load-independent indices of contractility are preload recruitable stroke work index (PRSWI) and end-systolic elastance (Ees).
- The most severe drop in blood pressure occurs in the arterioles; hence they are often termed the *resistance vessels*. Arteriole diameter is regulated by the contractile activity of vascular smooth muscle. Variations in arteriolar diameter are an important determinant of local capillary blood flow and hydrostatic pressure.
- Viscosity is the internal friction resulting from intermolecular forces operating within a flowing liquid. Vascular resistance is directly related to blood viscosity and varies with hematocrit. Because of the presence of erythrocytes, blood is a non-Newtonian fluid (i.e., its viscosity increases sharply with reductions in shear rate).
- In accordance with the Starling model, capillary hydrostatic pressure (P_{cap}) is the major force of filtration across the capillary wall. Capillary oncotic pressure (Π_{cap}) is the major force of absorption. The direction and magnitude of capillary bulk flow is essentially a function of the ratio of P_{cap} to Π_{cap}. Under normal conditions, filtration dominates at the arterial end of the capillary and absorption at the venous end. A small net filtration is usually observed, which is compensated for by lymph flow
- The traditional Starling model of transcapillary exchange has been updated to include an important role for glycocalyx, located in the capillary membrane, in determining capillary permeability.
- The cardiovascular reflexes are neural feedback loops that regulate and modulate cardiac function and vascular tone. They are composed of an afferent (sensory) limb, integration in the medulla oblongata of the central nervous system, and an efferent (motor) limb.
- The arterial baroreceptor reflex is a primary homeostatic mechanism that maintains arterial blood pressure within narrow limits based on feedback from high-pressure stretch receptors in the aortic arch and carotid sinus.
- Systemic oxygen delivery (DO_2) is the product of cardiac output and arterial oxygen content. At rest, DO_2 greatly exceeds systemic oxygen consumption ($\dot{V}O_2$), and thus the oxygen extraction ratio (EO_2) is relatively modest (~25%). At normal or high levels of DO_2, $\dot{V}O_2$ is constant and independent of DO_2. As DO_2 is gradually reduced, increased EO_2 maintains $\dot{V}O_2$ until a threshold is reached, the so-called critical DO_2, below which $\dot{V}O_2$ is limited by the supply of oxygen.
- The final step in oxygen delivery to tissue mitochondria is diffusion from capillary blood. This process is determined by the capillary-to-cell PO_2 gradient and the diffusion parameters, capillary surface area and blood-cell diffusion distance. Capillary recruitment is an important mechanism for maintaining tissue PO_2 at the level required for unimpaired oxidative metabolism.
- In a clinical setting, there are several methods to measure systemic $\dot{V}O_2$: (1) oxygen loss or replacement into a closed breathing system, (2) the difference between expired and inspired volume of oxygen, and (3) use of the Fick principle, the most commonly used method. The oxygen extraction ratio (EO_2), defined as the arteriovenous oxygen difference divided by arterial oxygen content, reflects the balance between oxygen demand and delivery.
- In the left coronary circulation, extravascular compressive forces during systole (owing to a high developed intracavitary pressure) result in blood flow occurring predominantly during diastole. The pressure gradient for blood flow in the left ventricular wall is approximated by the difference between aortic diastolic pressure and left ventricular end-diastolic pressure. In the right coronary circulation, the flow is relatively constant during systole and diastole and the pressure gradient for blood flow is determined by the difference between mean aortic pressure and mean right ventricular pressure.
- Metabolic mechanisms coupling coronary blood flow to myocardial oxygen demand normally predominate in control of coronary vascular resistance, although parasympathetic (vasodilator) and sympathetic (vasoconstrictor) effects also play a role.
- Coronary flow reserve, the ratio of maximum coronary blood flow to resting coronary blood flow, is appreciable in the normal right and left ventricular walls (approximately 400% to 500%), but is reduced in a variety of conditions, including left ventricular hypertrophy, hemodilution, and coronary stenosis. Coronary reserve is exhausted when the stenosis reaches approximately 90%, resulting in a decrease in resting blood flow.
- The most important determinants of myocardial oxygen demand are contractility, heart rate, and wall tension. Wall tension is directly proportional to the pressure and radius of the heart and inversely proportional to wall thickness (law of Laplace). When external work (pressure × stroke volume) is considered, pressure work has a much greater oxygen cost than does flow work.
- Oxygen extraction by the LV is nearly maximal at baseline; thus increases in myocardial oxygen consumption critically depend on proportional increases in coronary blood flow via locally produced vasodilating factors. When the vasodilator reserve of the coronary bed is compromised—for example, by a proximal stenosis—the myocardium becomes vulnerable to ischemia (oxygen demand > oxygen supply). With reduced coronary reserve, increases in heart rate and preload are detrimental in that both these factors reduce oxygen supply (coronary blood flow) while increasing oxygen demand. An increase in aortic pressure augments myocardial oxygen supply by increasing blood flow, but it also increases myocardial oxygen demand by increasing wall tension.

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Anatomy and Imaging: The Cardiovascular System

Rebecca Desso and Jeffrey D. Swenson

This special section on Anatomy and Imaging outlines important anatomic structures and imaging techniques for the cardiovascular system, including the heart and major vessels in the neck and groin. Key structures are reviewed in anatomic drawings, anatomic dissections, magnetic resonance imaging (MRI) scans, and ultrasound (US) images. Modern imaging techniques that enable "real-time" visualization of relevant clinical anatomy are emphasized.

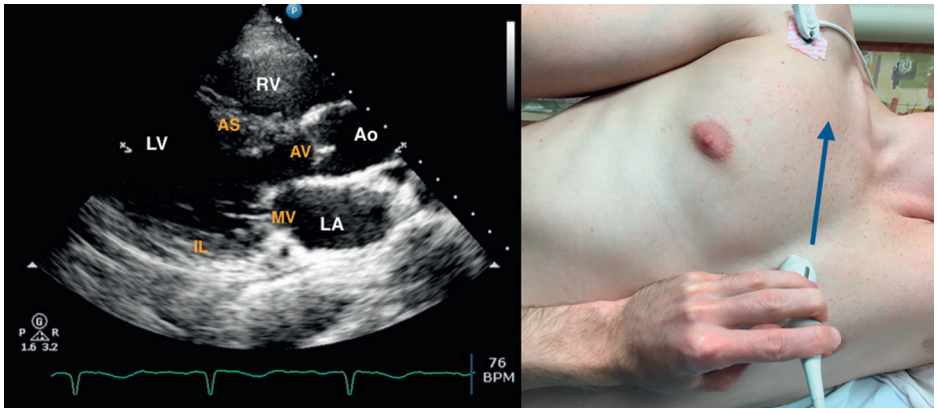
Much like transesophageal echocardiography (TEE), transthoracic echocardiography (TTE) is emerging as an important technique for anesthesiologists. Although a comprehensive review of TTE is not within the scope of this text, it is appropriate to present an overview of the anatomic basis of this developing area of proficiency for anesthesiologists. Focused Cardiac Ultrasound (FoCUS) is a point-of-care US examination approach aimed at assessing key elements of cardiac anatomy and physiology that can guide treatment or lead to further testing. Any significant abnormalities detected by FoCUS should lead to a full echocardiographic examination (among other techniques). Figs. AI2.1 to AI2.5 give an overview of the basic assessment of cardiovascular function that can be performed using TTE. The necessary probe manipulations are shown in this series of figures.[1]

The patient is positioned in left lateral decubitus with the left arm above the head (Fig. AI2.1). **The right panel** shows the transducer positioned with the indicator toward the right shoulder at the third to fourth intercostal interspace. **The left panel** shows a parasternal long axis image with the **right ventricle (RV)**, **left ventricle (LV)**, **aorta (Ao)**, **aortic valve (AV)**, **mitral valve (MV)**, and **left atrium (LA)** labeled. This view allows evaluation of chamber sizes, global function with thickening of the **anteroseptal (AS)** and **inferolateral (IL)** walls, the aortic valve, the left ventricular outflow track (LVOT), and mitral valve motion and anatomy.

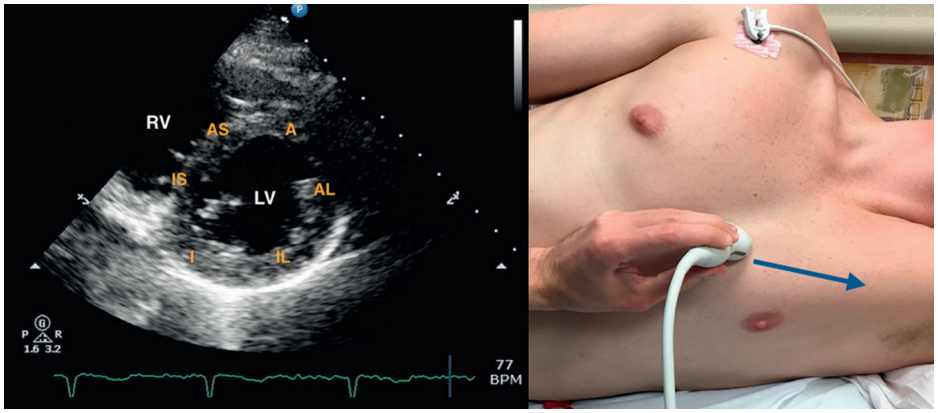
This image is obtained with rotation of the probe clockwise from the parasternal long axis so that the indicator points to the left shoulder, as seen in **the right panel** (Fig. AI2.2). **The left panel** shows the parasternal short axis view with the **RV** and the **LV** walls labeled: **anterior (A)**, **anterolateral (AL)**, **inferolateral (IL)**, **interior (I)**, **inferoseptal (IS)**, and **anteroseptal (AS).** From here, the transducer is angled to the floor to scan the LV base and to the right shoulder to scan the apex. This view allows evaluation of global LV function and filling as well as thickening of the walls.

With the patient in the left lateral decubitus position at the edge of the examination table, the transducer is placed with the indicator toward the floor, as shown in **the right panel** (Fig. AI2.3). The transducer is angled to the floor to see the AV or to the right shoulder to see the coronary sinus (CS). **The left panel** shows the **LV**, **LA**, **MV**, **RV**, **RA**, and **TV**, as labeled. The size of the chambers, thickening of the LV walls, descent of the base of the **TV** and **MV**, and structure and function of the **MV** and **TV** are examined.

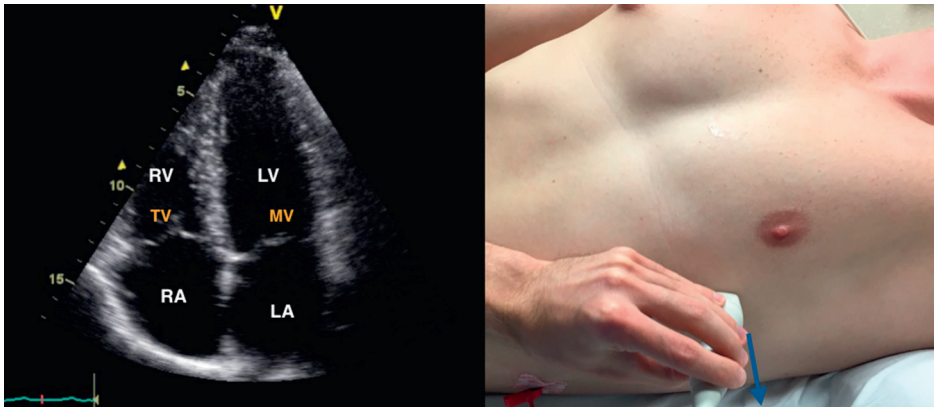
The patient is positioned supine, with the abdomen relaxed (Fig. AI2.4). **The right panel** shows probe placement below the xiphoid, with the indicator to the left. **The left panel** shows the image with the **RV**, **RA**, **TV**, **LA**, **LV**, and **MV** labeled. The RV size, RV function and thickness, and the pericardium are examined.



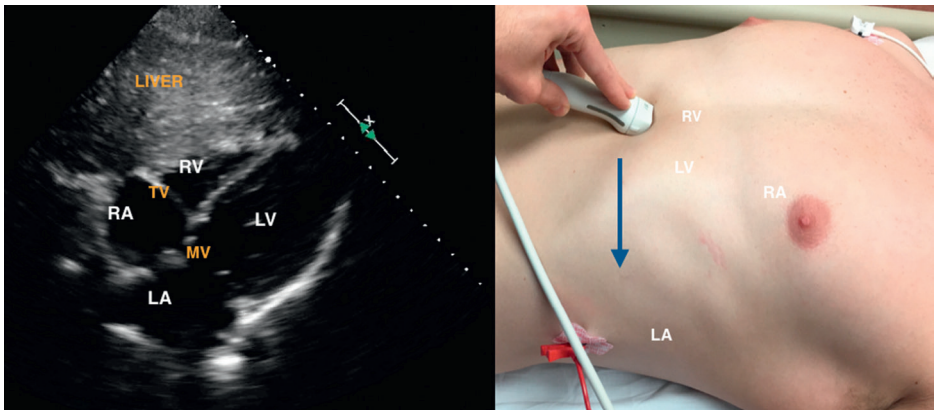
• **Fig. AI2.1** Cardiac anatomy, as visualized in the parasternal long axis by transthoracic echocardiography.



• **Fig. AI2.2** Cardiac anatomy, as visualized by the parasternal short axis by transthoracic echocardiography.



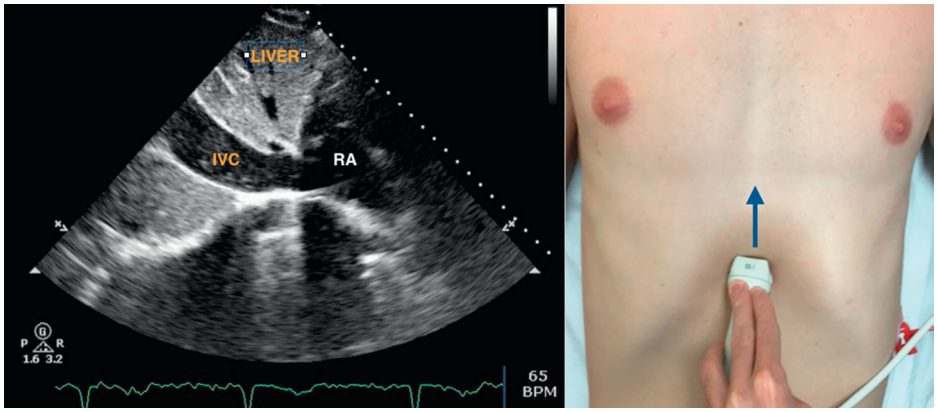
• **Fig. AI2.3** Cardiac anatomy, as visualized by the apical 4-chamber view by transthoracic echocardiography.



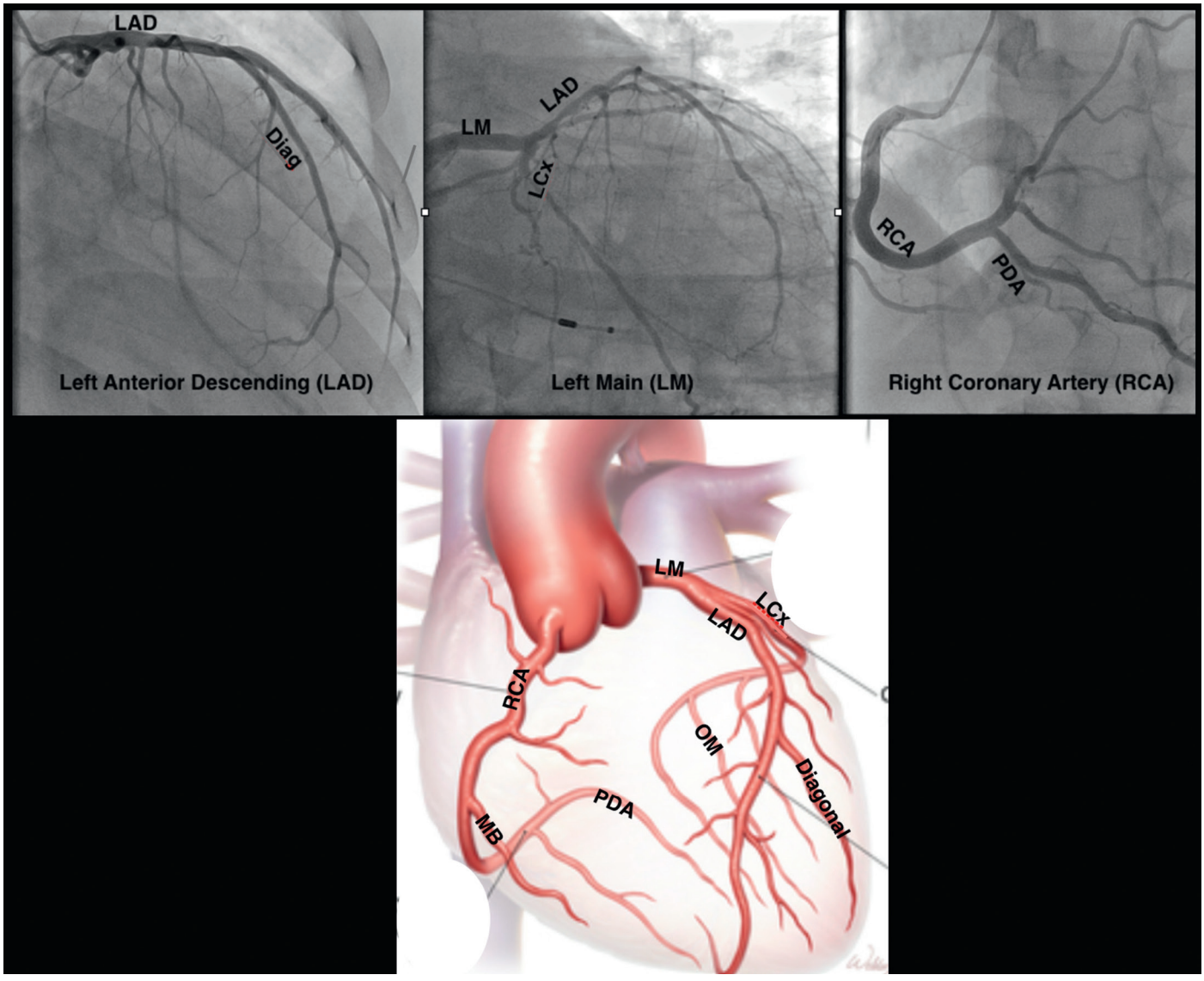
• **Fig. AI2.4** Cardiac anatomy, as visualized by the subcostal 4-chamber view by transthoracic echocardiography.

Subcostal Inferior Vena Cava Long Axis: The probe is rotated 90 degrees counterclockwise, as shown in **the right panel** (Fig. AI2.5). **The left panel** shows the **inferior vena cava (IVC)** as it enters the **RA**. An **IVC** that is small and collapses with the patient sniffing is indicative of low central venous pressure while a large and noncollapsing **IVC** indicates elevated central venous pressure.

The lower panel is a diagram of coronary artery anatomy (Fig. AI2.6). The **left main (LM)** and **right coronary artery (RCA)** are shown with their respective branches. Important branches of the **RCA** include the **marginal branch (MB)** and the **posterior descending artery (PDA)**. Left or right vessel dominance of the coronary vasculature is determined by the vessel from which the PDA arises. In approximately 85% of individuals, the **PDA** arises



• **Fig. AI2.5** Vena caval and right atrial anatomy, as viewed by the vena cava long axis view by transthoracic echocardiography.



• **Fig. AI2.6** Coronary artery anatomy, as shown by an idealized anatomic drawing and angiograms.

from the **RCA** (right vessel dominant). The **left main (LM)** coronary artery is typically short in length and gives rise to the **left anterior descending (LAD)** artery and the **left circumflex (LCx)** artery. The **LAD** gives rise to one or more **diagonal** branches while the **LCx** gives rise to one or more **obtuse marginal (OM)** branches.

Coronary angiography is an invasive procedure that allows visualization of coronary artery anatomy and is considered the gold standard for diagnosis of coronary artery stenosis. Common images are named according to the relation of the image intensifier (located above the patient) to the patient.[2] For example, the **left upper and left middle panel** show the **right anterior oblique (RAO)** view of the **left main coronary artery (LM)**, the **left anterior descending artery (LAD)** with **diagonal branch (Diag)**, and the **left circumflex artery (LCx)**. In the **RAO** view, the intensifier is over the right shoulder. The **right upper panel** shows the **right coronary artery (RCA)** and **posterior descending artery (PDA)** from the **left anterior oblique (LAO)** view, in which the intensifier is over the left shoulder.

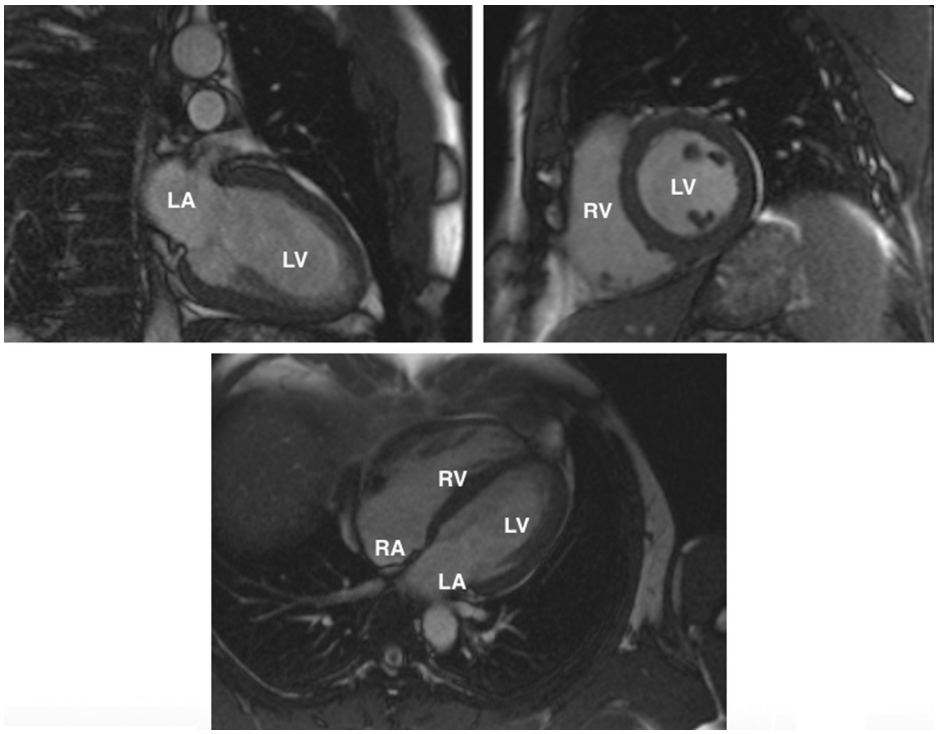
Cardiac magnetic resonance imaging (MRI) can be used to quantify LV and RV function, define cardiac and coronary artery anatomy, evaluate myocardial perfusion, quantify blood flow, and assess myocardial viability (Fig. AI2.7).[3] Cardiac MRI allows high temporal and spatial resolution without the need for heart rate control and allows imaging of heavily calcified structures that may not be clearly evaluated via other techniques. **The left panel** shows the 2-chamber window with the **left atrium (LA)** and **left ventricle (LV)**. The **bottom panel** shows the 4-chamber window including the **LA, LV, right atrium (RA)** and **right ventricle (RV)**. The **right panel** shows the short axis of the **LV** and **RV**. These images correspond to the echocardiogram apical 2-chamber, apical 4-chamber and parasternal short-axis views.

Cardiac and coronary computed tomography (CCT) are used to assess coronary atherosclerosis as well as pericardial, valvular, and myocardial heart disease (Fig. AI2.8). CCT is best used for identification of coronary artery disease in patients of low to intermediate risk. CCT is limited, as a heart rate of 60 to 70 is necessary and severe calcification of structures obscures the image. Three-dimensional renderings allow evaluation of cardiac structures.[4] An example of a 4-chamber view is shown in the **left panel**. Three-dimensional renderings of cardiac anatomy are illustrated in the **middle panel** and in the **right panel**.

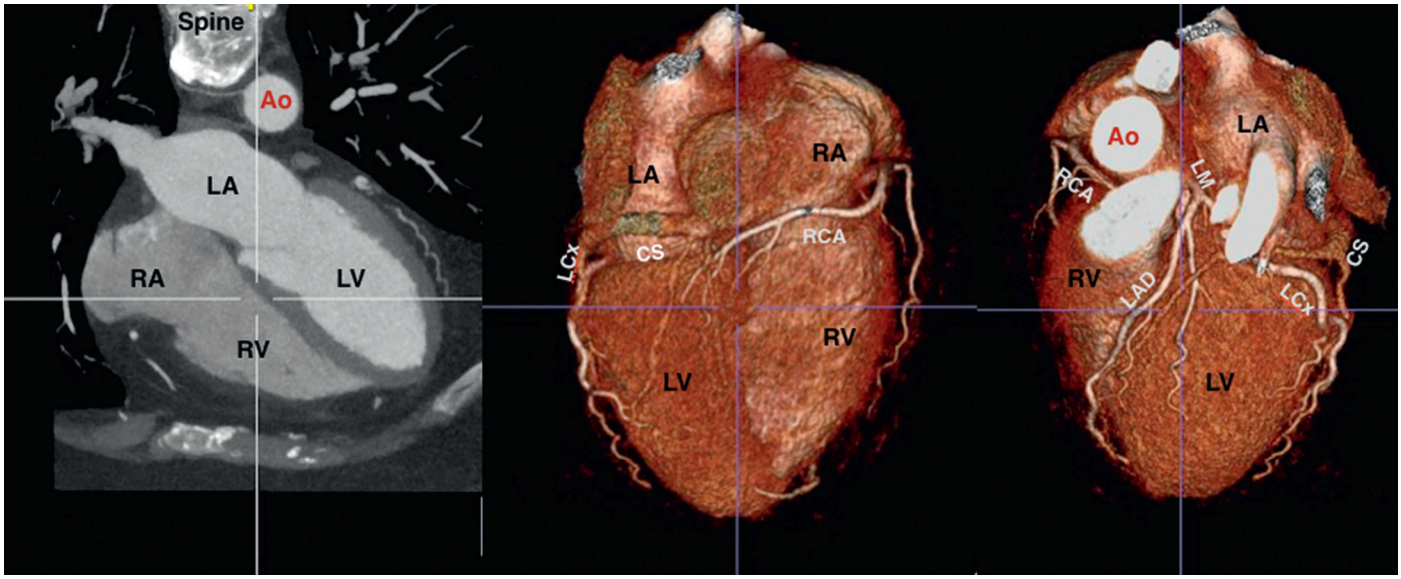
This image illustrates lower extremity vascular anatomy at the level of the inguinal ligament (Fig. AI2.9). The **top left panel** is a fresh cadaver dissection of the right inguinal region. The **inguinal ligament**, **femoral vein (FV)**, **femoral artery (FA)**, **profunda femoris artery (PF)**, and **superficial femoral artery (SFA)** are displayed. The forceps indicate the position of the **femoral nerve (FN)**, which is deep to the intact fascia iliaca and not visible. The **right upper and lower panels** are corresponding ultrasound images; the **bottom left** panel shows the position of the transducer used to visualize these structures.

The top right panel is an ultrasound image of the right inguinal region immediately proximal to the take-off of the **PFA** (not visible). The **FA**, **FV**, and **FN** are visible. The lower right panel illustrates how easily the femoral vein is compressed using gentle pressure with the transducer. Images such as these are important in vascular access and nerve block techniques in the groin, such as femoral artery cannulation and fascia iliaca nerve block catheters.

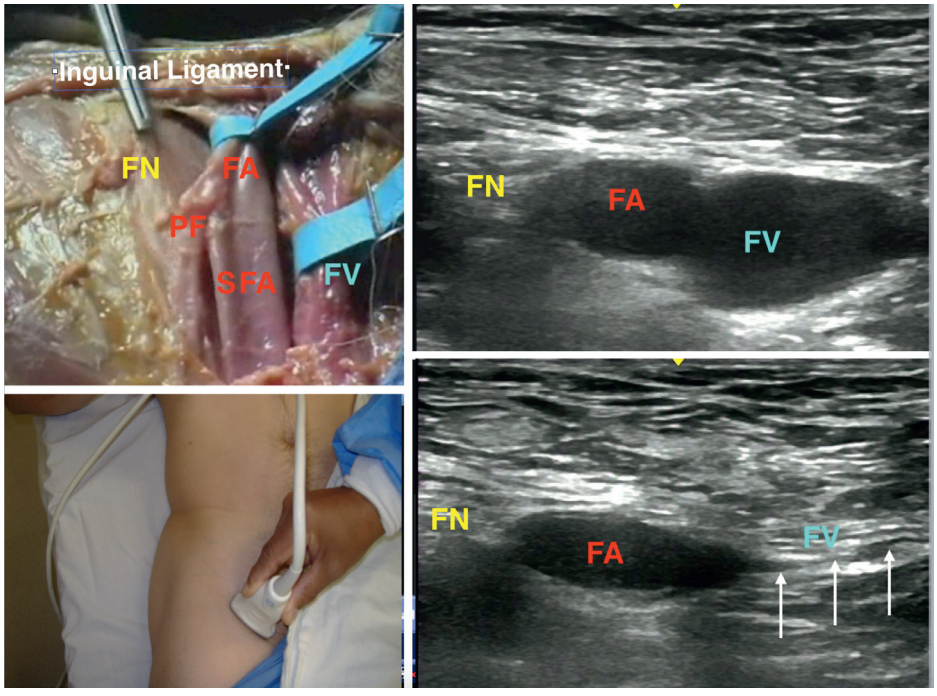
The **right panel** of this figure shows the transducer position used to image the right **carotid artery (CA)** and **internal jugular vein (IJ)** at the level of the sixth cervical vertebra (Fig. AI2.10). The linear transducer is positioned at the level of the cricoid cartilage



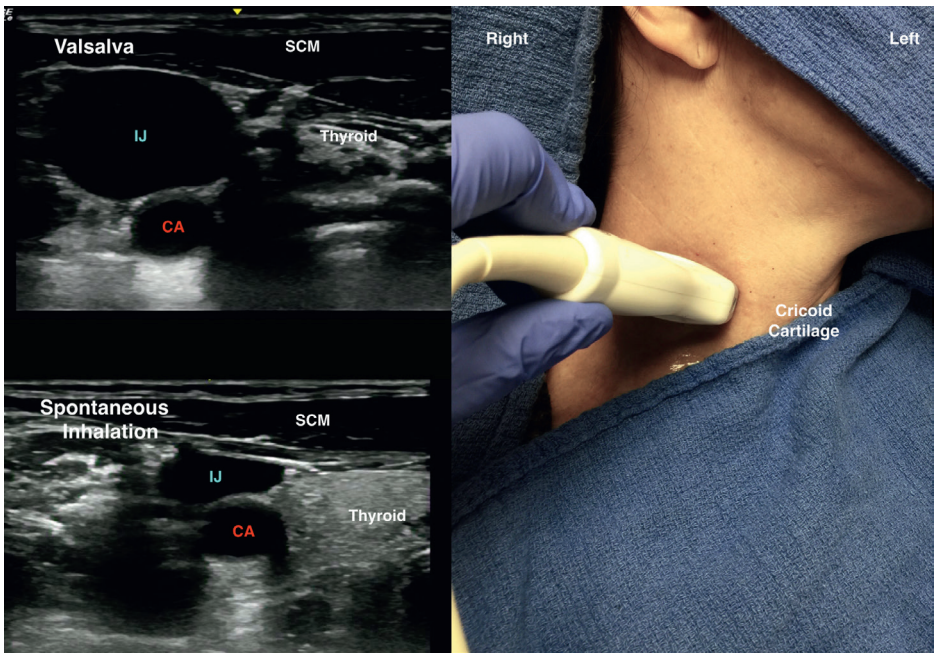
• **Fig. AI2.7** Cardiac anatomy, as assessed by cardiac magnetic resonance imaging.



• **Fig. AI2.8** Cardiac anatomy, as assessed by cardiac and coronary computed tomography.



• **Fig. AI2.9** The vascular anatomy of the groin, as shown by anatomic dissection and ultrasonography.



• **Fig. AI2.10** The vascular anatomy of the lateral neck, as visualized by ultrasonography.

while the head is rotated away from the transducer. The **left panels** are ultrasound images showing the **CA**, **IJ**, **thyroid tissue**, and **sternocleidomastoid muscle (SCM)**.

Two important features are illustrated. First, there is considerable variability in the size of venous capacitance vessels associated with changes in intrathoracic pressure. In the **top left image**, the subject is performing a voluntary Valsalva maneuver. The **lower left image** shows the same subject during spontaneous inhalation. Second, in both images the position of the **CA** is deep rather than medial to the **IJ**. Although not typically visualized in ultrasound images, the **thoracic duct** drains lymph into the circulatory system via the left brachiocephalic vein between the left subclavian and left internal jugular veins. Thus, damage to the thoracic duct that can result in chylothorax is a potential complication of central venous access procedures on the left side of the body but not on the right.

A. The Aortic Arch in an Idealized Anatomic Drawing

Major vessels of the head and upper extremities arise from the convex surface of the aortic arch (Fig. AI2.11A). There is asymmetry of these vessels in that **right subclavian** and **right common carotid** arteries arise from the **brachiocephalic artery**. By contrast, the **left subclavian** and **common carotid** arteries arise directly from the arch. It is also important to note that the **vertebral** arteries arise from the **subclavian** arteries. Occasional anatomic variations can produce unexpected findings on ultrasound and radiographic examinations.

B. Arteries of the Upper Extremity in an Idealized Anatomic Drawing

The **subclavian artery** transitions to the **axillary artery** at the lateral border of the first rib (Fig. AI2.11B). The **axillary artery** then transitions to the **brachial artery** at the lower border of the teres major muscle**.** The **anterior and posterior circumflex arteries** form an anastomosing circle around the surgical neck of the humerus.

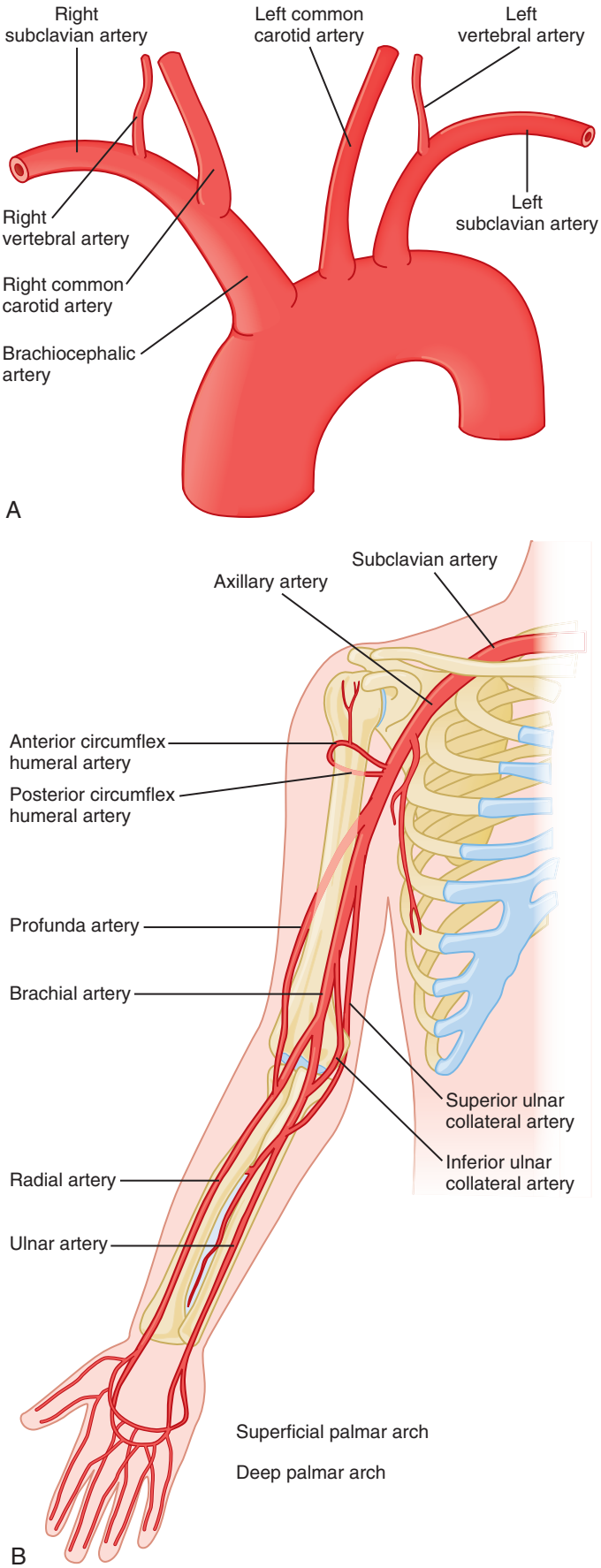
The **profunda artery** arises from the brachial artery at the level of the proximal humerus and follows the radial nerve. The **superior** and **inferior ulnar collateral arteries** arise from the **brachial artery** proximally and anastomose distally with the **ulnar artery**. The **superior ulnar collateral artery** can be visualized adjacent to the ulnar nerve in the upper arm. The **brachial artery** terminates at the neck of the radius by dividing into the **radial** and **ulnar arteries**. The **superficial** and **deep palmar arches** are direct continuations of the **ulnar** and **radial** arteries, respectively.

C. Relationships of the Subclavian Vessels, Scalene Muscles, and Brachial Plexus Visualized in an Idealized Anatomic Drawing and by Ultrasonography

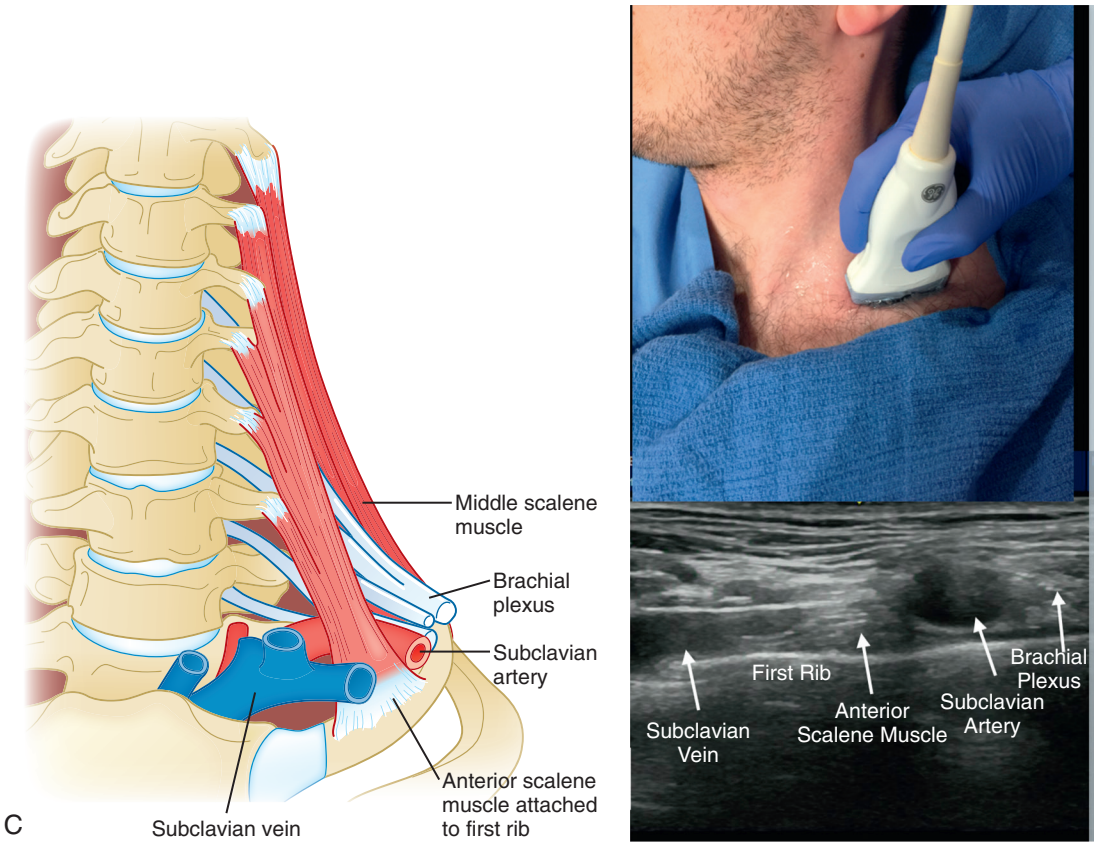
An important anatomic feature of the **subclavian artery** is its separation from the **subclavian vein** by the **anterior scalene muscle** (Fig. AI2.11C). While the **subclavian artery** is consistently within the same fascial compartment as the **brachial plexus**, the same is not true for the **subclavian vein**. These features are illustrated in the diagram and by an ultrasound image at the level of the **first rib**.

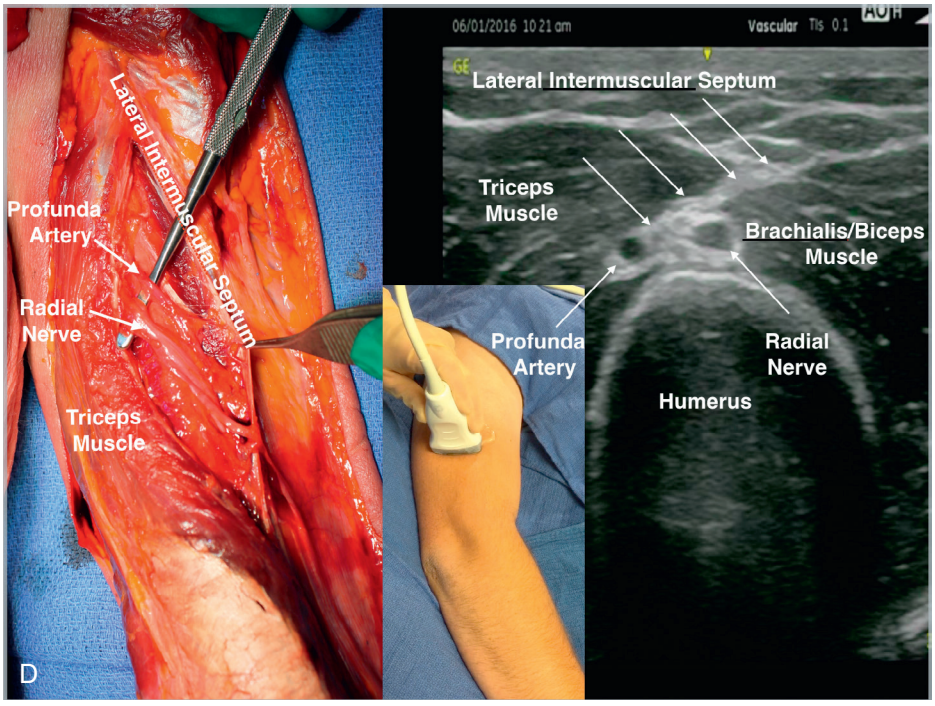
D. The Profunda Artery as Visualized in an Anatomic Dissection and by Ultrasonogaphy

The **profunda artery** is part of the arterial anastomosis **around** the elbow joint (Fig. AI2.11D). This image features a fresh cadaver dissection showing the proximity of the **radial nerve** and **profunda artery** within the **lateral intermuscular septum**.



• **Fig. AI2.11** **(A-F)** Arteries of the upper extremity with clinically relevant features.





• **Fig. AI2.11, cont'd**

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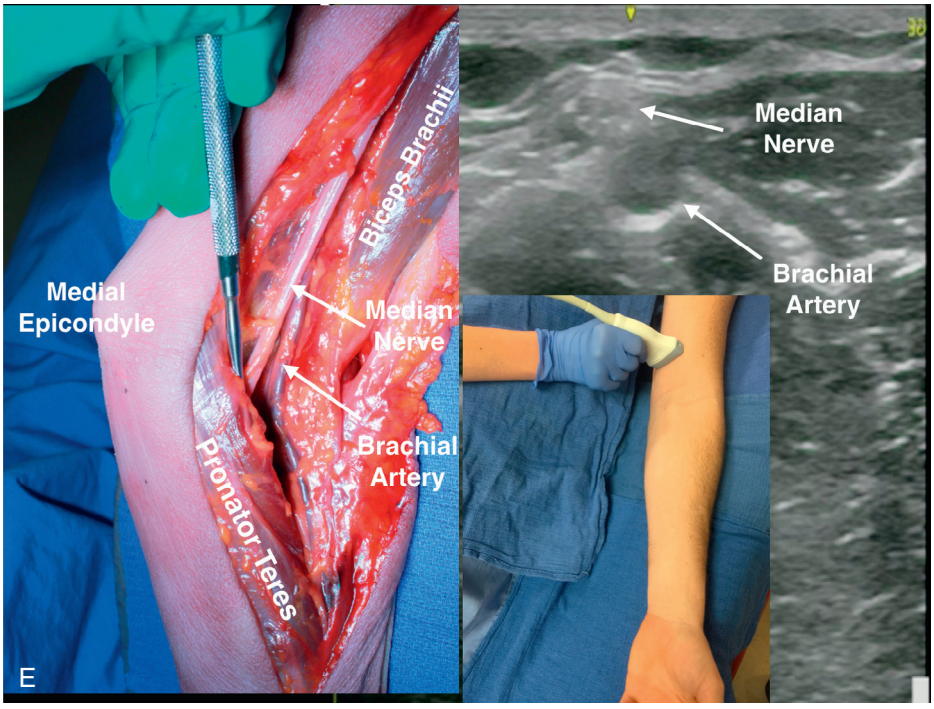

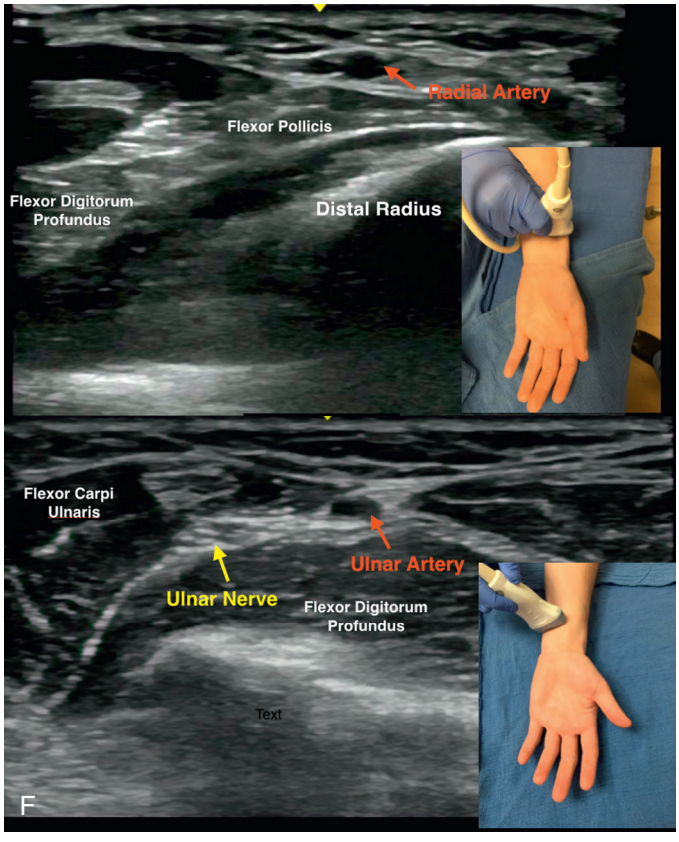

• **Fig. AI2.11, cont'd**

E. the Brachial Artery as Visualized in an Anatomic Dissection and by Ultrasonography

The **brachial artery** is displayed in these images at a level proximal to the antecubital fossa (Fig., AI2.11E). Note that the **brachial artery** is in close proximity to the **median nerve** along its course. The cadaver dissection shows the gradual transition of the nerve from a position superficial to the **brachial artery** to a more medial position at the level of the elbow.

F. The Ulnar and Radial Arteries as Visualized in an Anatomic Dissection and by Ultrasonography

The **ulnar** and **radial arteries** in the distal forearm are unique in that the **ulnar nerve** (see ultrasound image) lies in close proximity on the ulnar side of the **ulnar artery** (Fig. AI2.11F). By contrast, the **radial artery** travels in proximity to the **superficial branch of the radial nerve** in the middle third of the forearm but this branch passes deep to the tendon of the **brachioradialis muscle** at the distal forearm. Thus, no neural structures are visible on ultrasound in proximity to the **radial artery** at the level of the wrist.

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Physics: Fluid Dynamics

Patrick Kolbay and Kai Kuck

OUTLINE

Background

Fluid Flow
- Volumetric Flow
- Mass Flow

Viscosity

Types and Properties of Flow
- Laminar Flow
- Turbulent Flow
- Convection
- Bernoulli's Law

Flow Meters
- Differential Pressure Sensors
- Rotameters
- Vane Anemometers
- Hot-Wire Anemometers
- Ultrasonic Anemometers

Background

Ventilation and delivery of inhaled anesthetics involves the flow of gases to and from the patient. Differences in gas properties can have a significant impact on the dynamics of these flows, influencing how anesthetic and ventilation equipment performs. Understanding the basics of fluid dynamics will not only aid in using anesthetic and ventilation equipment efficiently but also help in understanding their limitations. Key concepts that are important to master include fluid flow (e.g., volumetric vs. mass flow), flow properties (e.g., turbulent vs. laminar flow), and common methods to measure gas flows.

Fluid Flow

A **fluid** is a substance that flows freely and takes the shape of its container. Of the 3 phases of matter, gases and liquids are both considered to be fluids. **Fluid flow** is the motion of a gas or liquid from one location to another. The rate at which fluids flow can be described in 2 ways: volumetric flow and mass flow.

Volumetric Flow

Volumetric flow is the rate at which a volume of fluid passes per unit time. Like Ohm's Law, in which electrical current is proportional to a voltage difference between 2 points and the electrical resistance of the conductor in between, the volumetric flow of a fluid is determined by the difference in pressure between 2 points and the mechanical resistance of the tube in between:

$$volumetric\ \ fluid\ \ flow = \frac{pressure\ difference}{resistance}$$

Volumetric flow is used in anesthesia, for example, when describing the flow of gases. The unit for volumetric flow (according to the International System of Units [SI]) is cubic meters per second (m^3/sec); another more commonly used unit in everyday practice is liters per minute (L/min).

Mass Flow

Mass flow is the rate at which a mass of fluid passes per unit of time. Mass flow and volumetric flow are related to one another by the **density** of the fluid, in which density is the mass of a fluid per unit volume as measured in kilograms per cubic meter (kg/m^3):

$$mass\ \ fluid\ \ flow\ rate = density \times volumetric\ \ fluid\ \ flow\ rate$$

In anesthesia, mass flow is used, for example, when describing intravenous delivery of medication, although in this case the mass refers to just 1 component of the fluid. The SI unit for mass flow rate is kilograms per second (kg/sec). More commonly used units are milligrams per minute or micrograms per minute.

Gases change volume with changes in pressure and temperature, resulting in changes in their density. Consider, for example, delivery of oxygen to a patient at 2.0 L/min at sea level, where atmospheric pressure is 760 mm Hg. Given that the density of oxygen is 1.35 g/L at sea level, the mass flow rate can be determined as follows:

$$\text{Mass flow rate} = 2.0\frac{L}{min} \times 1.35\frac{g}{L} = 2.70\frac{g}{min}$$

If, however, the same volumetric flow rate of 2.0 L/min is delivered at 5000 feet above sea level, where the atmospheric pressure is 630 mm Hg, the mass flow rate changes. Boyle's Law can be used to determine the change in volume:

$$760\ mm\ Hg \times 2.0\ L = 630\ mm\ Hg \times volume\ at\ altitude$$

$$volume\ at\ altitude = \frac{760\ mm\ Hg \times 2.0\ L}{630\ mm\ Hg} = 2.41\ L$$

Because the mass of oxygen has not changed (only volume has changed), the density can be recalculated:

$$density = \frac{2.70\ g}{2.41\ L} = 1.12\ \frac{g}{L}$$

Using this new density, the new mass flow rate can be determined for an elevation of 5000 feet:

$$\text{mass flow rate} = density \times volumetric\ \ fluid\ \ flow\ rate$$
$$= 1.12\ \frac{g}{L} \times 2.0\ \frac{L}{\text{min}} = 2.24\ \frac{g}{\text{min}}$$

The important clinical point is that, at higher elevation, the mass of oxygen delivered decreases even when the volume flow rate is the same.

Viscosity

Viscosity can be described as the resistance of a fluid to flow. Honey, having a high viscosity, resists being poured and drips slowly from a bottle, while water, having a lower viscosity, readily pours from a bottle (Fig. P5.1). This physical property occurs owing to both the friction between layers of a fluid as well as intermolecular forces within that fluid. The SI unit for viscosity is the pascal second (Pa s) and is often abbreviated as μ (Greek letter *mu*).

Types and Properties of Flow

Flow is classified into 2 types of movement: **laminar** and **turbulent** flow. Laminar flow is smooth, uniform flow in 1 direction, whereas turbulent flow is more chaotic and contains swirls of eddies (Fig. P5.2). Popularized in 1883 by Reynolds, the **Reynolds number** (Re) is used to predict whether flow will be laminar or turbulent:

$$Reynolds\ number = \frac{density \times velocity \times tube\ \ diameter}{viscosity}$$
$$= \frac{4 \times density \times volumetric\ \ flow}{viscosity \times tube\ \ diameter \times \pi}$$

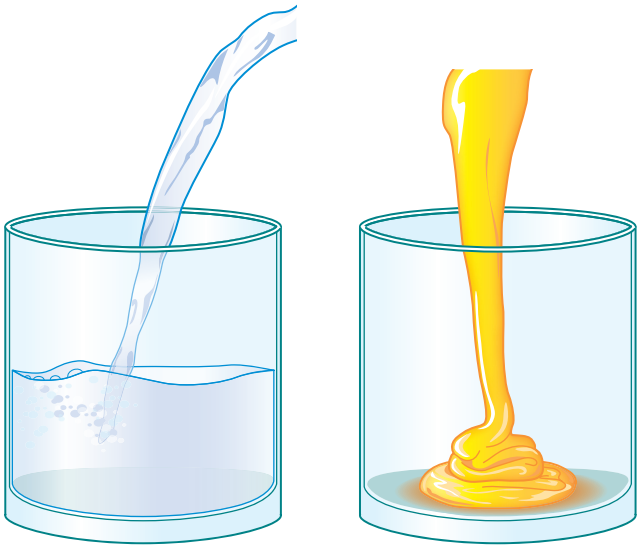
From empirical testing in cylindrical tubes, flows with a Reynolds number below 2000 are likely to be laminar, while those above 2000 tend to be turbulent. Additionally, obstructions, sharp corners, or other irregularities in a tube can also cause turbulent flow. It should be noted that the Reynolds number is not only dependent on the physical properties of the fluid but is also dependent on the properties of the tube within which fluid is flowing.

Laminar Flow

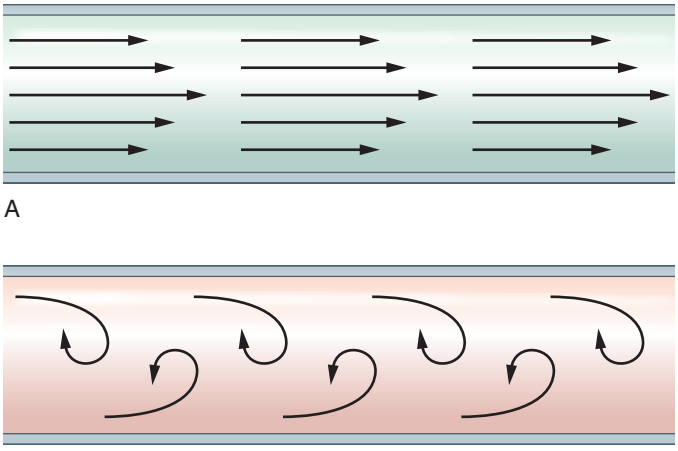
The predictable and smooth behavior of laminar flows make them ideal in a variety of ways. Volumetric flow is dependent on both the difference in pressure between two points and the resistance of the tube that it is flowing through. In 1838, French physicist and physiologist Poiseuille was able to describe this relationship for laminar flows as what is now known as **Poiseuille's Law**:

$$volumetric\ \ flow\ rate = \frac{pressure\ \ difference}{resistance}$$
$$= \frac{pressure\ \ difference \times tube\ radius^4 \times \pi}{8 \times viscosity \times length\ of\ \ tube}$$

According to the equation, the radius of the tube dramatically impacts flow rate because flow is proportional to the 4th power of the radius. Similarly, a longer tube generates more friction, causing overall flow to decrease. These principles have important implications in anesthesia, such as the selection of the optimal tracheal tube size.



• **Fig. P5.1** Water *(left)* will pour quickly and easily while honey *(right)*, being more viscous, will flow slowly from its container.



• **Fig. P5.2** Fluid flow through a tube. Laminar fluids flow in even layers all in one direction (A), while turbulent fluids swirl and eddy in their flow (B). Determining whether a fluid will be laminar or turbulent is dependent on whether the Reynolds number is below or above 2000.

Turbulent Flow

Unlike laminar flow, the resistance of a tube for turbulent flows is not easily calculated. Owing to the chaotic and unpredictable nature of turbulent flow, resistance of a tube is dependent on the volumetric flow itself; thus, it is not possible to calculate the resistance without knowing the flow beforehand. When flow is turbulent, a larger pressure difference between points is required compared to laminar flow.

Most fluid flows relevant to anesthesia, such as blood flow and gas flow during normal respiration, exhibit laminar flow. There are a few exceptions, however. Many patients experience momentary turbulence in blood flow in the ascending aorta depending on the compliance of the vascular walls. Additionally, patients suffering from bronchospasm can also exhibit turbulent air flow in the lungs owing to the narrowing of the bronchial lumen. When delivering a mixture of oxygen and helium (known as Heliox), the overall density of the fluid dramatically decreases since helium has 1/8 the density of oxygen. As a result, the Reynolds number also decreases, making the fluid flow more laminar and allowing a higher volumetric flow to the lungs, counteracting the constriction due to bronchospasm.

Convection

When fluids have a different temperature than their surroundings, they begin to exchange thermal energy (heat) in a process known as **convection**. Convection can occur naturally or can be forced. Heated fluids are a good example of natural convection. As fluid temperature increases, the fluid begins to expand and decrease in density. This causes the fluid to rise and to be replaced by cooler, denser fluid, generating a current flow, or a convection current.

Forced convection occurs when fluids are forced to flow over a surface, thereby adding or removing heat. An example of this is an air conditioning system blowing cold air into a hot room and cooling down the room. Hot-wire flow meters (see later discussion) that are used in many anesthesia machines and ventilators are based on this convection principle. Convection is also the mechanism whereby movement of cold air around an anesthetized patient results in heat loss from the patient. Convection plays an important role in heat loss from anesthetized patients, but the main mechanism of heat loss in these patients is radiation.

Bernoulli's Law

The total energy of a fluid moving horizontally can be described as a combination of the potential energy caused by pressure differences and the kinetic energy from fluid velocity. In 1738, Daniel Bernoulli determined the precise relation of potential and kinetic energy known as **Bernoulli's Law**:

$$energy = pressure\ difference + \frac{1}{2} \times density \times velocity^2$$

An interesting phenomenon occurs if a fluid flows through a constriction. Because of conservation of mass, the velocity of the fluid must increase to maintain the same flow rate as it enters the constriction. Based on Bernoulli's Law, since total energy has not changed, pressure must decrease as the velocity increases. This is known as the **Bernoulli Effect** and is the basis for differential pressure flow sensors used to measure gas flows in anesthesia (see later discussion).

Flow Meters

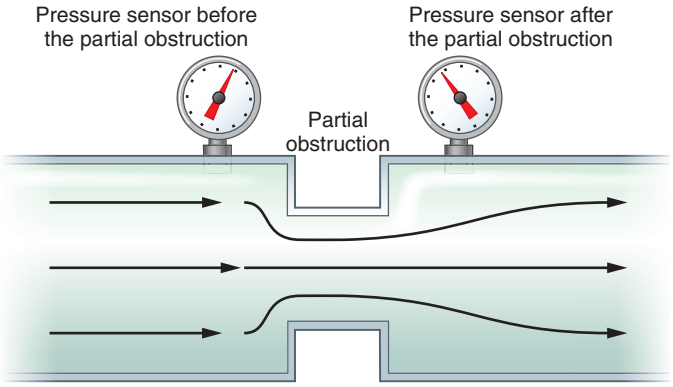
Many flow meters used in anesthesia measure fluid velocity instead of flow rate. Volumetric flow rate is then determined by multiplying the cross-sectional area of the tube with the measured fluid velocity.

Differential Pressure Sensors

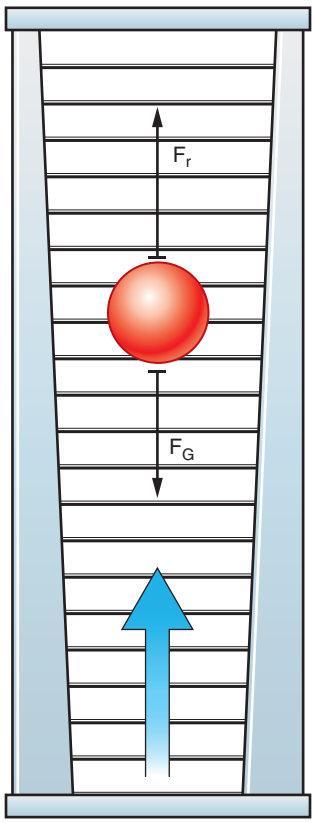
A differential pressure sensor uses the Bernoulli Effect to measure fluid velocity. Two pressure sensors are inserted into a tube with a short constriction in between the sensors (Fig. P5.3). When fluid is not flowing, there is no pressure difference between before and after constriction. However, as fluid begins to flow, there is a decrease in pressure after the constriction due to the Bernoulli Effect that is directly proportional to the fluid velocity. Turbulent flows can cause small sections of higher or lower pressures, making differential pressure sensors not ideal for turbulent flows. Differential pressure sensors are commonly used to measure the flow rates in anesthesia machines and other respiratory devices.

Rotameters

Rotameters are simple flow meters used to determine volumetric flow rates of fresh gas flows, often coming from wall sources. The flow meter is a vertical tapered tube that contains a weight inside, also known as a *float* (Fig. P5.4). As fluid flows up into the tapered tube, a force is generated that pushes the float up and away from the constriction. As the float rises, more fluid passes around the float, until an equilibrium is reached. The position of the float is then compared to the calibrated tick marks on the tube, which correspond to a given flow rate. If the flow rate decreases, so will the generated force against the float, causing the float to sink, reflecting the flow rate of the system. Rotameters are entirely passive and require no electric power. However, what they gain in their simplicity, they lack in accuracy. Small changes in density (which can be affected by pressure, temperature, and gas composition) and generally poor resolution make rotameters less reliable compared to other types of flow meters.



• **Fig. P5.3** Fluid flow from left to right through a tube with a partial obstruction. The pressure that the fluid exerts on the wall of the tube decreases after the partial obstruction, as indicated by the pressure sensors before and after the partial obstruction. The higher the fluid velocity, the higher the pressure drop. This principle is used in differential pressure flow sensors.



• **Fig. P5.4** Rotameter for measuring fluid flow rate. The red float will change height based on the amount of force exerted from the flowing fluid (F_r) compared to the force of gravity (F_G). As the float rises, F_r decreases due to the increased opening of the tapered column. The float rises until F_r and F_G have the same value. The height of the float can then be used to indicate the volumetric fluid flow rate.

Vane Anemometers

Volumetric flow can also be measured using a propeller or turbine. A vane anemometer consists of an embedded propeller within a pipe and rotates as fluid flows past. The faster the fluid flows, the faster the propeller spins. The blades of the propeller can be designed to measure precise volumetric flow regardless of changes in density, fluid composition, or turbulence. These devices, too, are often found in anesthesia machines.

Hot-Wire Anemometers

Hot-wire anemometers use convective heat transfer properties to measure fluid flow. A heated wire or film is placed within the fluid stream. As the fluid flows across the heated surface, the heated material begins to cool. The amount of energy needed to maintain the temperature of the wire or film is proportional to fluid velocity. As in differential pressure sensors, small eddy currents from turbulent flow can momentarily increase or decrease fluid velocity at the sensor location and cause inaccurate or noisy readings. For this reason, hot-wire anemometers are typically used only in situations in which flow is laminar. Many anesthesia machines and critical care ventilators use hot-wire anemometers to measure gas flows.

Ultrasonic Anemometers

Ultrasonic anemometers determine the velocity of a fluid by how long it takes a sound wave to travel through the fluid. An ultrasonic pulse is generated in the direction of fluid flow and a sensor downstream records this pulse. Because sound is a mechanical wave that propagates through a medium (in this case, a fluid), if the medium is moving, it carries sound with it. As a result, an ultrasonic pulse traveling in a flowing fluid reaches the downstream sensor sooner than if the fluid is stationary. Therefore, the time it takes for an ultrasonic pulse to travel is proportional to fluid velocity. Some infusion pumps use ultrasonic anemometers.

Physics: Invasive and Noninvasive Blood Pressure Measurement

Jennifer A. Decou and Kai Kuck

OUTLINE

Background

Noninvasive Blood Pressure Measurement
- Palpation and Oscillometric Method
- Korotkoff Sounds

Continuous, Invasive Blood Pressure Monitoring
- Resonant or Natural Frequency
- Damping
- Fast-Flush Test
- Morphology of the Arterial Waveform
- Leveling and Zeroing

Background

Systemic arterial blood pressure monitoring is one of the minimum standards of patient monitoring recommended by the American Society of Anesthesiologists (ASA). Together with other monitors, it will help detect up to 93% of adverse events under anesthesia.[1] Arterial blood pressure can be obtained intermittently and noninvasively using oscillometry or continuously and invasively with an arterial catheter. An understanding of the physics underpinning the use of noninvasive and invasive blood pressure monitoring techniques facilitates proper interpretation of blood pressure measurements, improving quality of patient care and patient safety.[2,3]

Noninvasive blood pressure monitoring carries relatively low risk and historically has been interpreted by palpation or auscultatory methods. Oscillometric methods often replace these techniques, but values can be inaccurate, for example, when using a cuff that is too small or too large.[4] Invasive blood pressure monitoring provides continuous beat-to-beat measurements and can be useful when titrating vasoactive drugs or when hemodynamic changes are occurring rapidly. Clinicians should understand the concepts of resonance, damping, wave reflection, and leveling or zeroing to correctly interpret the values and waveform morphologies recorded. Ultimately, blood pressure measurements represent a surrogate for tissue perfusion and are only useful insofar as they accurately reflect information about the adequacy of oxygen and energy substrate delivery and metabolic waste removal.

Noninvasive methods of blood pressure monitoring have existed since the early 1800s.[5] Scipione Riva-Rocci, an Italian physician, is credited for creating the first easy-to-use sphygmomanometer in 1896, the important element being a cuff that encircled the circumference of the arm (Fig. P6.1). After visiting Riva-Rocci in Pavia in 1901, Harvey Cushing began using the device intraoperatively, reproducing Riva-Rocci's design with some improvements (such as a wider cuff).

Noninvasive Blood Pressure Measurement

Palpation and Oscillometric Method

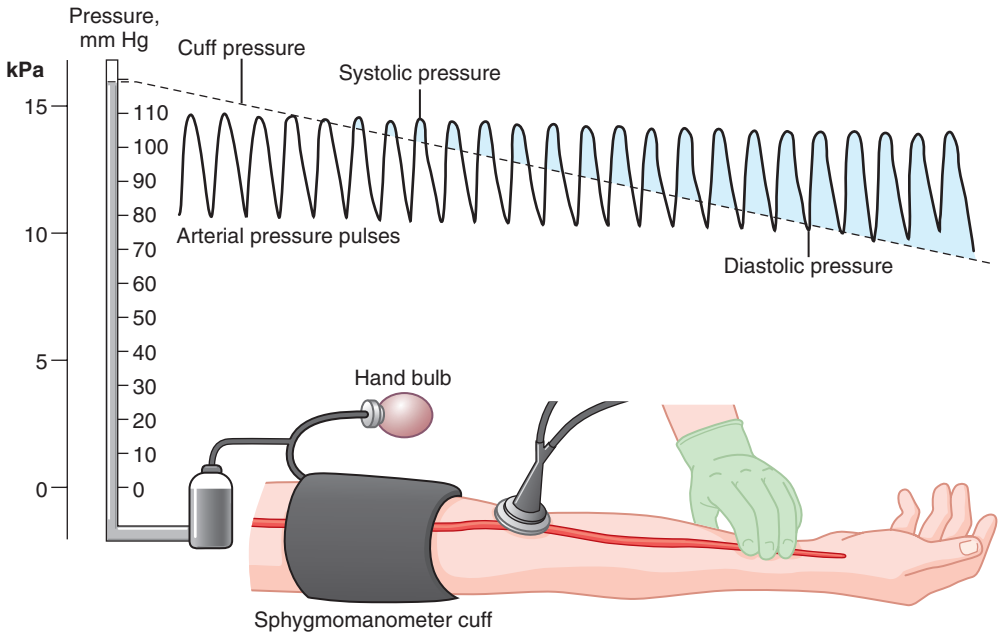
During the early use of sphygmomanometers, the method of determining systolic blood pressure was palpation of the pressure at which a distal pulse appears as the cuff pressure decreases. This gives an accurate systolic pressure but is not useful in determining diastolic or pulse pressure.

The oscillometric method (Fig. P6.2) involves inflating the cuff to a pressure well above systolic pressure and then slowly lowering its pressure. A sensor registers small, fluctuating cuff pressure variations. In the upper extremity, the oscillations are caused by the throbbing brachial artery as it is partially compressed. The oscillations increase, reach a maximum at the mean arterial pressure, and then decrease again. Thus, the largest of these oscillations are thought to occur at the mean arterial pressure. Systolic and diastolic pressures are determined by algorithms proprietary to the manufacturer, that is, at fixed thresholds of the oscillations, for example, at 75% and 60% of maximum oscillations, respectively. Using this method, the mean, systolic, and diastolic pressures—as well as the pulse pressure and heart rate—can be determined. It is critical to recognize that only the mean arterial pressure and heart rate are measured; the systolic and diastolic pressures are calculated.[6]

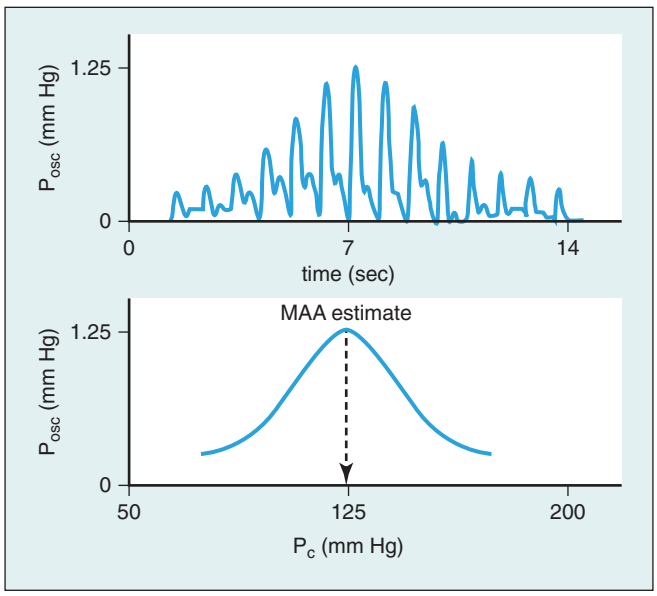
Korotkoff Sounds

After Riva-Rocci invented the sphygmomanometer, Russian surgeon Nikolai Korotkoff discovered and described the auscultatory method of measuring blood pressure that has now been in clinical use for over a century.

When a stethoscope is placed over the brachial artery with no restriction of flow, no sound can be heard. Similarly, when a cuff is inflated over the upper arm and the pressure in the cuff exceeds systolic blood pressure, no sound can be auscultated over the brachial artery. This is because the artery is completely collapsed, with no flow distal to the cuff. When the cuff is then deflated, either continuously or in a stepwise fashion (at a rate of 2–3 mm Hg per second), the five "Korotkoff sounds" appear in series. When the pressure in the cuff decreases to systolic pressure, the first



• **Fig. P6.1** Many noninvasive blood pressure approaches involve inflating the cuff to above systolic pressure and then slowly reducing that pressure. Intersections with systolic and diastolic pressures result in characteristic palpations or sounds. A kPa is a unit of pressure. It is approximately equal to the pressure that a 10-g mass exerts on a 1-cm^2 area. A mm Hg is a manometric unit of pressure, commonly used in medicine, and is equal to the pressure exerted by a column of mercury 1 mm high at 0°C under standard gravity. (From Nara AR, Burns MP, Downs, WG. Blood Pressure. SpaceLabs [Snoqualmie, WA, USA]; 1989 Vol 218. ISBN 0962744905.)



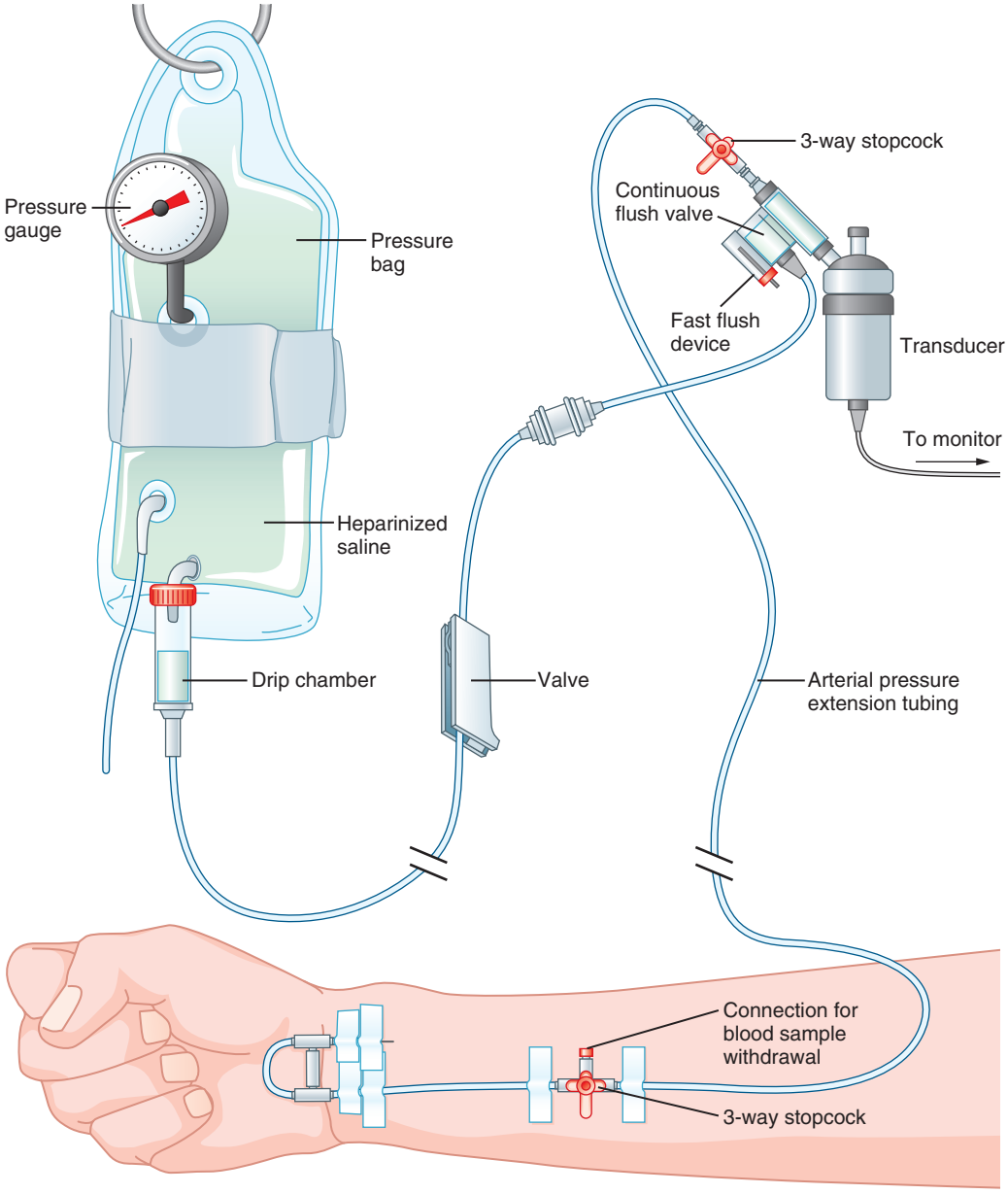
• **Fig. P6.2** The oscillometric method involves inflating the cuff to a pressure well above systolic pressure. The oscillations increase, reach a maximum at the mean arterial pressure and then decrease again *(top)*. P_C is the cuff pressure measured in mm Hg. The cuff pressure at the maximum of the envelope of these oscillations corresponds to the mean arterial pressure according to the maximum amplitude algorithm. P_{OSC} is the oscillatory part of the pressure measured in the cuff expressed here in mm Hg (millimeters mercury). P_C is the nonoscillatory part of the pressure measured in the cuff. (From Baker, PD, Westenskow, DR, Kuck, K. Theoretical analysis of non-invasive oscillometric maximum amplitude algorithm for estimating mean blood pressure. *Med Biol Eng Comput*. 1997 35(3): 271–278.)

Korotkoff sound is heard. As the heart ejects blood, some flow will spurt through the brachial artery during the moments when the peak systolic pressure exceeds the cuff pressure, causing a repetitive tapping sound that can be heard by auscultation. As greater flow is allowed through by further decreasing cuff pressure, phase II and phase III of the Korotkoff sounds can be heard with a softer, swishing quality followed by a return to louder, crisper sounds. These have little clinical significance (i.e., they are not linked to specific physiologic variables). During phase IV, the sounds are softened and muted until they disappear completely in phase V, where there is no restriction in flow caused by the cuff, signaling the diastolic pressure, as Korotkoff described it.

Continuous, Invasive Blood Pressure Monitoring

Invasive arterial blood pressure measurements are considered the gold standard for pressure measurement and give accurate beat-to-beat readings (Fig. P6.3). Even before the noninvasive methods were invented, Stephen Hales recognized the importance of blood pressure and measured it invasively by inserting a brass tube into the artery of a horse and observing the height of the column of blood in the tube.

Invasive monitoring is not without risk, as Hales discovered, but affords numerous advantages. Continuous blood pressure measurement is useful when rapid hemodynamic changes are anticipated or with infusion of vasoactive drugs, among other situations. The arterial waveform can be analyzed for additional information contained in the pulse contour. Arterial catheters are also useful when noninvasive blood pressure measurement is not feasible or accurate, such as with obesity, limited access to extremities



• **Fig. P6.3** The components of an invasive arterial blood pressure monitoring system: Intraarterial cannula, fluid-filled tubing, transducer, infusion/flushing system. Not shown are signal processor, amplifier, and display. (From Nara AR, Burns MP, Downs, WG. Blood Pressure. SpaceLabs (Snoqualmie, WA, USA); 1989 Vol 218. ISBN 0962744905.)

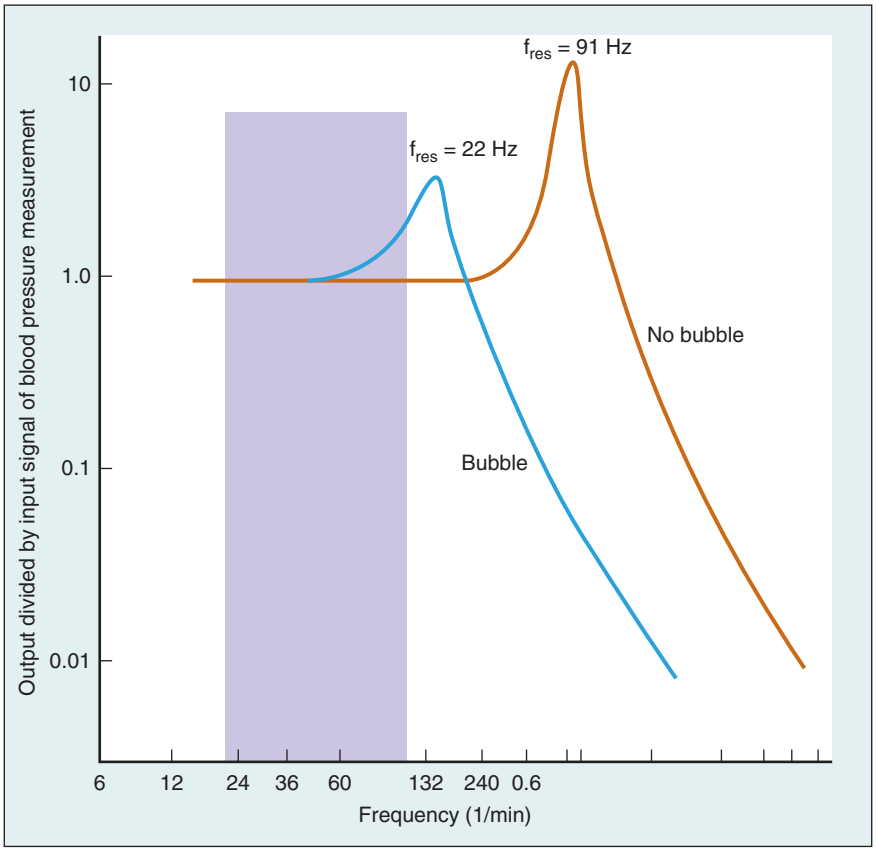
(burn patient), or significant arrhythmias. Arterial cannulation also provides the opportunity for convenient sampling of arterial blood for laboratory testing.

During cardiac systole, the left ventricle generates a pulse as blood is ejected. The waveform of that pulse travels to the artery being monitored, through the intraarterial cannula, through the fluid-filled tubing system, and to the pressure transducer. The transducer converts physical displacement of the transducer membrane into an electrical signal, which is transmitted to the monitor, amplified, and displayed as an analog waveform.

The complex wave of an arterial pressure waveform can be described by a series of sine waves. The periodicity of the wave shows its fundamental frequency, which is the heart rate. In addition, there are other sine waves that are multiples, or harmonics, of the fundamental frequency. The summation of these waves yields an accurate reproduction of the true intraarterial pressure waveform.

Resonant or Natural Frequency

The monitoring system has its own resonant frequency, the natural frequency at which the system tends to vibrate. It is the nature of a resonant system to respond strongly to other vibrations or influences that are close to its resonant frequency, amplifying those influences. It is important that the resonant frequency of the monitoring system does not overlap with the harmonic frequencies present in the arterial pressure waveform (Fig. P6.4). When this



• **Fig. P6.4** Invasive blood pressure measurement system's frequency characteristics. The purple bar in the figure is the range of frequency and harmonics inherent to the patient's blood pressure wave. A bubble in the system will decrease the resonant frequency (f_{Res}) in the system, bringing it closer to overlapping with the patient's blood pressure frequencies and causing resonant artifacts. The resonant frequency indicates the frequency that the system maximally amplifies. Frequencies are measured as number of oscillations per second, expressed in Hertz (Hz). (From Nara AR, Burns MP, Downs, WG. Blood Pressure. SpaceLabs (Snoqualmie, WA, USA); 1989 Vol 218. ISBN 0962744905.)

occurs, the monitoring system will resonate, and the output pressure signal will be distorted and exaggerated.[7]

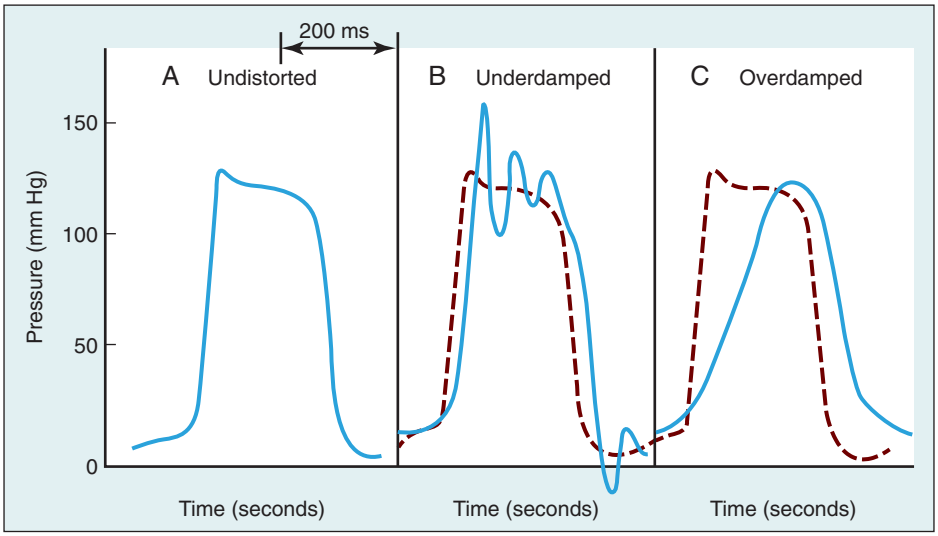
To prevent this artifact, the natural frequency of the system should be high, exceeding the frequencies of the impulses generated by the arterial pressure wave and its harmonics. In general, the harmonic frequencies generated by the arterial pressure waveform are up to 6 to 10 times the heart rate; if heart rate increases to 120 beats per minute, then the resonant frequencies of the cardiovascular system can increase to about 20 Hz. Therefore, the natural resonant frequency of the monitoring system must exceed 20 Hz in order to reconstruct an accurate waveform without significant artifact.[8] Using lengthy extension tubing or excessively soft tubing can decrease the natural frequency of the monitoring system and potentially increase the amount of resonant artifact. These are usually underdamping artifacts that make the blood pressure appear falsely elevated, particularly the systolic pressure.

Damping

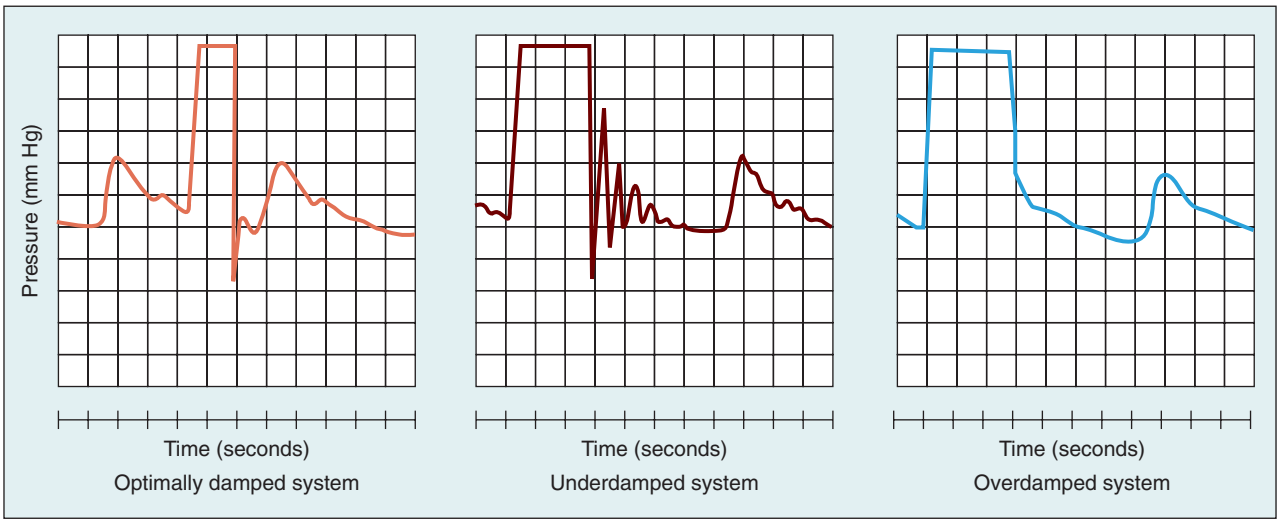
All hemodynamic monitoring systems are damped to some degree, a necessary quality to avoid excessive and uninterpretable wave propagation. Damping refers to the decrease in amplitude of the mechanical pressure wave due to friction or resistance in the system. Since mechanical waves propagate differently in fluid and air, even small air bubbles in the tubing of the monitoring system can overdampen the waveform, making the measured blood pressure appear falsely low. Thus, there is an appropriate level of damping and a damping coefficient that is ideal for the natural frequency of each system (Fig. P6.5).

Fast-Flush Test

The dynamic response of an invasive blood pressure monitoring system is defined by both its resonant frequency and damping coefficient. These parameters dictate whether the system is overdamped, underdamped, or acceptable. In the fast-flush test, the oscillations and their return to baseline can be examined (Fig. P6.6). In general, the period of the wave can be measured as the distance between two successive peaks. The smaller the period (which is inversely related to frequency), the better the dynamic response of the system. If the period is less than 48 seconds, then the natural frequency is at least 21 Hz, which is almost always adequate. The system is overdamped if there are sluggish or no oscillations. An underdamped system is seen when excessive oscillations, or "ringing," occurs. Although mean arterial pressure may be accurate, an underdamped system increases the measured systolic blood pressure and lowers the measured diastolic pressure.



• **Fig. P6.5** All hemodynamic monitoring systems are damped to some degree, a necessary quality to avoid excessive and uninterpretable wave propagation. Damping refers to the decrease in amplitude of the mechanical pressure wave due to friction or resistance in the system. Pressure is expressed in mm Hg (millimeters of mercury); ms refers to milliseconds. (From Nara AR, Burns MP, Downs, WG. Blood Pressure. SpaceLabs (Snoqualmie, WA, USA); 1989 Vol 218. ISBN 0962744905.)



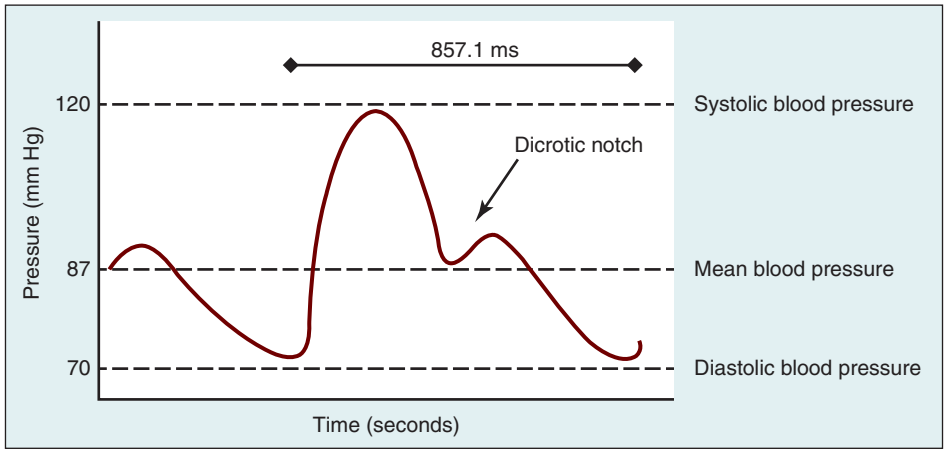
• **Fig. P6.6** The fast-flush test is performed to determine the system's dynamic performance from the oscillations and their return to baseline. (From Nara AR, Burns MP, Downs, WG. Blood Pressure. SpaceLabs (Snoqualmie, WA, USA); 1989 Vol 218. ISBN 0962744905.)

Morphology of the Arterial Waveform

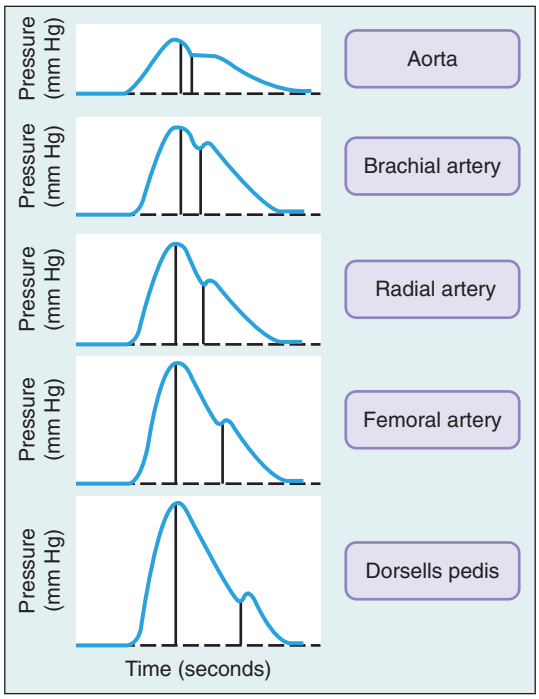
The different phases of the cardiac cycle can be appreciated within the arterial waveform (Fig. P6.7). The steep upstroke begins with left ventricular contraction and systolic ejection. The peak and early decline occurs when the systolic wave reaches the monitored artery and is caused by displacement of flowing blood volume. The dicrotic notch represents aortic valve closure and subsequent retrograde flow. The location of the dicrotic notch on the downslope of the wave varies according to the timing of aortic valve closure and can be seen farther down on the wave in a state of hypovolemia or when measured at more distal sites in the arterial system. Arterial blood pressure further declines during diastole, its nadir occurring at end-diastole. Other factors influence the morphology of the arterial wave, including stiffness and compliance of the arteries, heart failure, valvular heart disease, arrhythmias, and heart rate.

Wave reflection also contributes to the appearance of the measured arterial waveform. Wave reflection is related to the changes in impedance of the narrowing arteries. This leads to retrograde reflections of the pressure waves that are reflected backwards along the arteries, becoming more pronounced for more peripheral vessels (Fig. P6.8). Similar to waves on a beach, the forward waves collide with the retrograde waves. The summation of these waves tends to augment systolic pressure, particularly in the radial and dorsalis pedis arteries, where systolic blood pressure can be up to 25 mm Hg higher than central aortic pressure.[9]

Mean arterial pressure can be estimated as the sum of diastolic pressure plus one-third of the difference between the diastolic and



• **Fig. P6.7** The different parts of the cardiac cycle can be appreciated within the arterial blood pressure waveform. Pressure is expressed in mm Hg (millimeters mercury) and time in ms (milliseconds). The depicted cardiac cycle represents 70 beats per minute.



• **Fig. P6.8** Wave reflection leads to retrograde reflections of the pressure waves that are reflected backwards along the arteries. As a result, waveforms become more pronounced at the more peripheral vessels.

systolic arterial pressure (i.e., the pulse pressure). It can also be calculated by an algorithm as the area under the pressure curve divided by the width of the base of the pressure curve.[10] Although the shape of the arterial waveform changes with different locations of measurement, mean arterial pressure remains relatively constant, decreasing only slightly distally. Mean arterial pressure is also less affected by wave reflection or the dynamic characteristics of the monitoring system.

Leveling and Zeroing

To zero the monitoring system, one should open the air–fluid interface to atmospheric pressure. This establishes for the monitor atmospheric pressure as the zero reference point.

Leveling with the height of the right atrium eliminates effects of hydrostatic pressure (the pressure exerted by a column of fluid). For every 1 cm of distance that the transducer is above or below the height of the right atrium, 0.74 mm Hg of hydrostatic pressure is subtracted or added to the blood pressure. For example, if the transducer is located 10 cm below the level of the right atrium, the recorded pressure will be 7.4 mm Hg higher than the actual central blood pressure. Leveling depends on which vascular bed is the most significant for the clinical scenario. For example, to measure cerebral perfusion pressure with the patient in the sitting position, the level of the transducer is placed at the level of the Circle of Willis and the expected measured blood pressure will be lower than when measured at the level of the heart.

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25

Vasopressors and Inotropes

JOSH ZIMMERMAN, JAMES P. LEE, AND MICHAEL CAHALAN

CHAPTER OUTLINE

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Emerging Developments

This chapter reviews the pharmacology of vasopressors and inotropes used commonly in acute care settings and comparable new drugs with promising clinical potential. It focuses on the pharmacodynamic properties of the drugs to a greater degree than their pharmacokinetic properties because most of these drugs have short half-lives, are administered by continuous infusion, and are titrated to clinical effect.

Relying on landmark studies from the past as well as recent findings, this chapter seeks to build the scientific foundation on which the clinical use of these agents is based. Because their application to human pharmacology is unreliable, data derived exclusively from animal studies are not considered. Even when only human data are considered, the effects of vasopressors and inotropes vary substantially because of patient factors. Clinicians know that when treating patients experiencing severe hypotension or cardiac failure, the effects of vasopressors and cardiotonic drugs depend on many associated factors, including acid-base status, temperature, blood volume, and concomitant drug administration.[1]

Historical Perspective

Vasoactive drugs have an extensive history and have been in clinical use for millennia. The early identification and isolation of vasoactive substances was based on extraction from plants and endocrine glands. For instance, ephedrine has been in clinical use as a diaphoretic and circulatory stimulant for more than 5000 years as the active component of the Chinese drug ma huang. Until the drug was finally isolated in 1887, it was extracted from the plant *Ephedra sinica*.[2]

Similarly, foxglove had been in use for hundreds of years; William Withering published his historic book *An Account of the Foxglove, and Some of Its Medical Uses* in 1785.[3] This text detailed Withering's work with extracts of the plant *Digitalis purpurea* and described effects and side effects of the drugs now known as *digoxin* and *digitoxin*.

In the late 17th century, it was recognized that "an extract of the suprarenal glands caused contraction of the arteries and led to an increase in the beat of the auricles and ventricles," and that an extract of the pituitary gland possessed vasopressor activity. These substances would eventually be named *epinephrine* and *vasopressin*.[4]

While early medicinal chemistry work focused on developing progressively purer isolates of the active substances from natural sources, it eventually shifted to synthesizing drugs chemically. Dopamine was first synthesized in 1910 by Barger and Ewins, who immediately recognized its potency as a vasopressor.[5,6] Vasopressin was the first polypeptide hormone successfully synthesized, for which du Vigneaud won the Nobel Prize in Chemistry in 1955. Work by von Euler confirmed that norepinephrine helped mediate the activity of the sympathetic nervous system and contributed to his 1970 Nobel Prize.[7]

In the modern era, attempts were made to develop drugs with specific characteristics. Dobutamine was synthesized in the early 1970s for the specific purpose of providing a high level of inotropy without the vasodilatory limitations of isoproterenol.[8] Similarly, milrinone was developed in the early 1980s as an alternative to amrinone but without the high incidence of fever and thrombocytopenia that limited the use of amrinone.

The development of novel vasopressors and inotropes continues to this day. Levosimendan, for instance, entered clinical use in Europe as recently as 2000 and numerous drugs are currently under investigation around the world.

Abstract

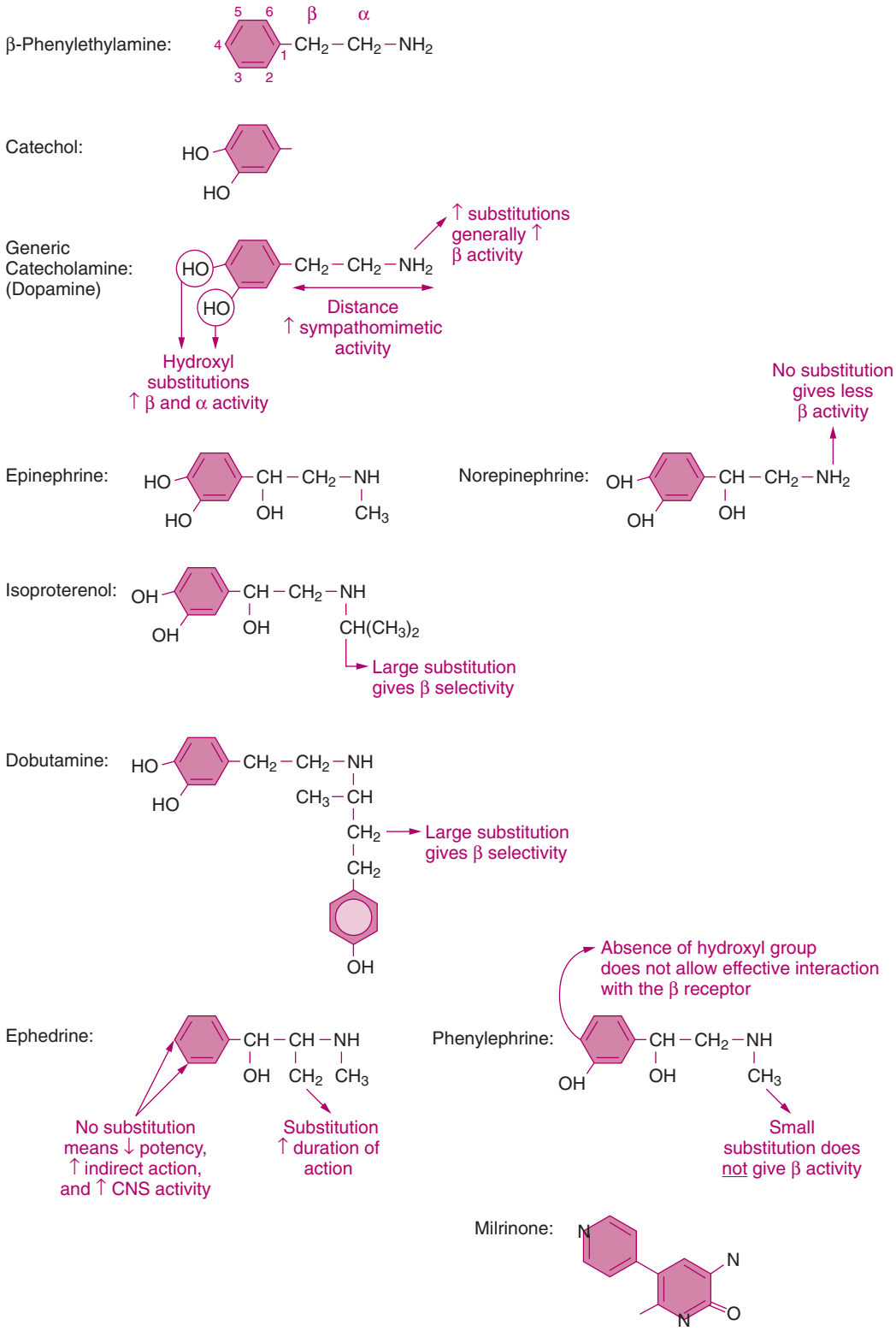
This chapter reviews the pharmacology of vasopressors and inotropes used commonly in acute care settings. It focuses on the pharmacodynamic properties of the drugs to a greater degree than their pharmacokinetic properties as most have short half-lives, are administered by continuous infusion, and are titrated to clinical effect. Clinicians know that when treating patients experiencing severe hypotension or cardiac failure, the effects of vasopressors and cardiotonic drugs depend on many associated factors, including acid-base status, temperature, blood volume, and concomitant drug administration. These factors are reviewed and recommendations are made for the rational selection and application of relevant vasopressors and inotropes.

Keywords

vasopressors
inotropes
vasoactive drugs
pharmacology

Structure-Activity Relationships

Many of the drugs in this chapter share structural similarities that affect their pharmacologic actions, although a few are chemically unrelated (Fig. 25.1). Many sympathomimetics are derived from the parent compound β-phenylethylamine. Many of these drugs are also referred to as *catecholamines* due to the presence of hydroxyl substitutions on carbons 3 and 4 of the benzene ring of β-phenylethylamine. The most basic example of a catecholamine is dopamine, which is the 3,4-hydroxyl substituted form of



• **Fig. 25.1** The chemical structure of selected sympathomimetic agents. Most are chemically related as catecholamines. Milrinone is a notable exception.

βphenylethylamine. It is the metabolic precursor to both norepinephrine and epinephrine as the substrate for dopamine β-hydroxylase. The addition of an N-substitution increases the activity at β-adrenergic receptors. Norepinephrine, like epinephrine, is derived from β-phenylethylamine, but the lack of N-substitution decreases its activity at the β receptors. The impact of the degree of amino substitution on β-receptor activity is further reflected in the structures of isoproterenol and dobutamine. Both of these drugs have bulky side chains and as such have a high degree of β specificity.

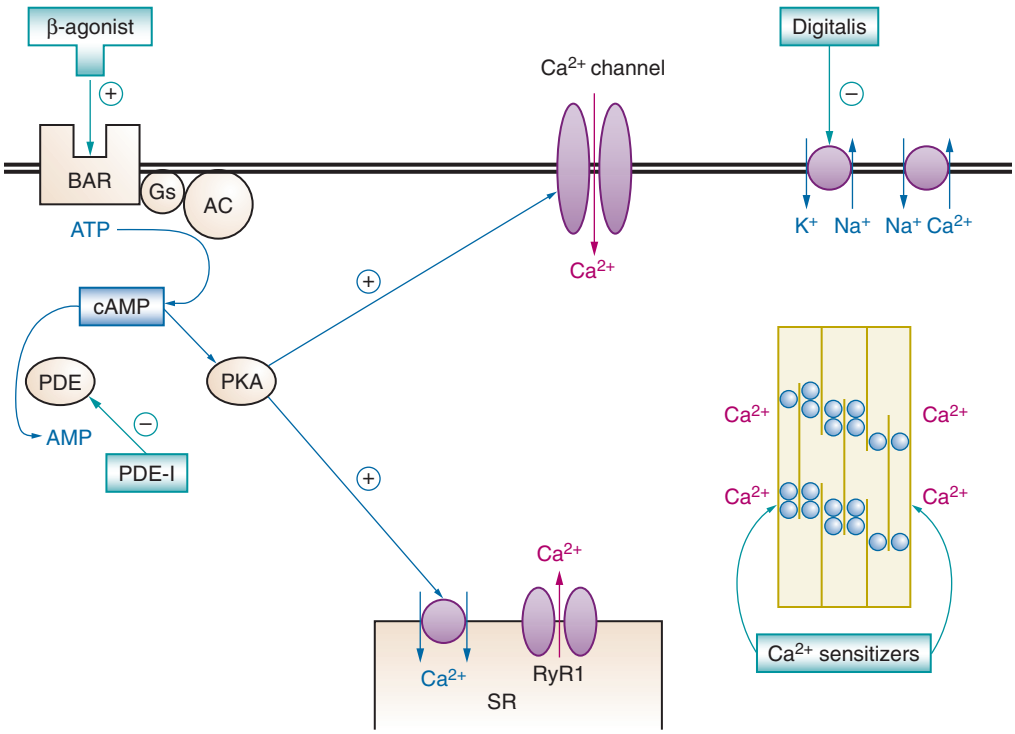
Phenylephrine and ephedrine are not considered catecholamines, in that they are not hydroxylated on both the 3 and 4 carbons of their benzene ring (phenylephrine has a single substitution and ephedrine has none). This lack of hydroxylation prevents phenylephrine from effectively binding the β receptor despite the N-methyl substitution. Ephedrine's lack of hydroxylation substantially decreases its ability to stimulate directly adrenergic receptors. The presence of a methyl group on the α-carbon of ephedrine blocks oxidation by monoamine oxidase and prolongs its action.

Milrinone, vasopressin, and levosimendan neither share structural similarities with the sympathomimetic drugs discussed nor with one another. Milrinone is a bipyridine methyl carbononitrile derivative of amrinone. Vasopressin, as a nonapeptide hormone, consists of a sequence of nine amino acids (Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly), whereas levosimendan is a pyridazone-dinitrile derivative.[9]

Mechanisms

Although the drugs discussed in this chapter are applied in similar clinical settings, they do not all share a pharmacologic class or mechanism. They are perhaps best classified and considered based on their mechanism for increasing inotropy and vasoconstriction (see Chapter 23). Although the drugs that increase inotropy do so by different mechanisms, the common endpoint is positively influencing the interaction of the calcium ion (Ca^{2+}) with actin and myosin in the cardiac myocyte (Fig. 25.2). Each of the β agonists, phosphodiesterase inhibitors, cardiac glycosides, and calcium sensitizers accomplishes this in a different way.

Drugs that act on the β_1 receptor (such as epinephrine, dobutamine, dopamine, isoproterenol, and, to a lesser extent, ephedrine and norepinephrine) begin by stimulating the receptor on the cardiac myocyte sarcolemma with subsequent activation of the G_s protein. This protein activates adenylyl cyclase and enhances the formation of cyclic adenosine monophosphate (cAMP), which activates protein kinase A, thereby phosphorylating and increasing the open probability of voltage-gated Ca^{2+} channels. These channels allow Ca^{2+} influx to increase cytosolic Ca^{2+} concentration, which activates the coupling of actin and myosin in the myocyte. Protein kinase A also activates a Ca^{2+}-adenosine triphosphatase (ATPase) on the sarcoplasmic reticulum, leading to increased Ca^{2+} uptake in diastole and improved lusitropic function.



• **Fig. 25.2** Mechanisms of action of selected positive inotropes indicating where the agents act in a cardiomyocyte. Ultimately cytosolic calcium ion *(Ca^{2+})* and its interaction with the actin-myosin complex cause myocyte contraction. The β agonists and phosphodiesterase inhibitors accomplish this by increasing the activity of protein kinase A *(PKA).* The calcium sensitizers act directly by increasing Ca^{2+} affinity for troponin C at the actin-myosin complex. Digitalis compounds inhibit sodium-potassium adenosine triphosphatase (Na^+,K^+-ATPase [Na^+ pump]) indirectly increasing intracellular Ca^{2+}. *AC,* Adenylyl cyclase; *AMP,* adenosine monophosphate; *BAR,* β-adrenergic receptor; *cAMP,* cyclic adenosine monophosphate; *Gs,* G stimulating α subunit; *PDE,* phosphodiesterase; *PDE-I,* phosphodiesterase inhibitor; *PKA,* protein kinase A; *SR,* sarcoplasmic reticulum.

The inotropic effects of phosphodiesterase inhibitors (e.g., milrinone), like those of the adrenergic agonists, are mediated by cAMP. Unlike adrenergic agonists that increase cAMP by stimulating adenylyl cyclase, milrinone inhibits the breakdown of cAMP by phosphodiesterase type III (PDE3). Increased cAMP enhances Ca^{2+} release from the sarcoplasmic reticulum and increases the force generated by actin-myosin. The vasodilatory action of milrinone is also cAMP mediated. In vascular smooth muscle, cAMP inhibits myosin light chain kinase, the enzyme responsible for phosphorylating myosin light chains and causing smooth muscle contraction. Inhibition of PDE3 increases cAMP, thereby promoting vascular smooth muscle relaxation.

Digoxin increases cytosolic Ca^{2+} by inhibiting the action of a sodium-potassium adenosine triphosphatase (Na^+,K^+-ATPase) on the cell membrane of cardiac myocytes. This leads to an increase in cytosolic sodium ion (Na^+), thereby decreasing the activity of Na^+-Ca^{2+} exchange and indirectly resulting in an increase in intracellular Ca^{2+} available to interact with actin and myosin.

Levosimendan, referred to as a *calcium sensitizer*, has a mechanism that is fundamentally different from the other inotropes discussed herein. Rather than increasing the content of intracellular Ca^{2+}, it acts to modulate the interaction of Ca^{2+}. It first binds the N-terminal lobe of cardiac troponin C (TnC), thereby stabilizing the Ca^{2+}-bound form of the protein. This prolongs the systolic interaction between actin and myosin and increases the force of contraction. Because binding of levosimendan to TnC is dependent on the cytosolic Ca^{2+} concentration, it occurs almost exclusively during systole, leaving diastolic function relatively unaffected. Importantly, unlike other drugs discussed in this chapter, the increased inotropy is achieved without an increase in myocardial oxygen demand.[10]

The majority of drugs discussed in this chapter exert their vasoconstrictive actions via α_1 receptors in the vasculature; the exception is vasopressin that acts on the V1 receptor. Stimulation of α_1 or V1 receptors on vascular smooth muscle act (via separate G proteins) to stimulate phospholipase C (PLC), which hydrolyzes phosphatidylinositol bisphosphate (PIP_2) to generate inositol trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 increases Ca^{2+} release from the sarcoplasmic reticulum, while DAG activates protein kinase C to increase Ca^{2+} influx via voltage-gated Ca^{2+} channels. This increase in cytosolic Ca^{2+} increases vascular smooth muscle tone.[11–13]

Metabolism/Pharmacokinetics

Vasopressors and inotropes generally have short half-lives and are rapidly metabolized, are administered by continuous infusion, and are titrated to clinical effect. This means that for practical purposes these drugs are pharmacokinetic equals; thus pharmacokinetic factors do not typically play an important role in rational drug selection of a specific inotrope or vasopressor. In general, these drugs exert their effects with an ongoing infusion; the effects rapidly decrease once the infusion is terminated. Levosimendan is a notable exception to this general rule.

The catecholamine class of drugs, which includes epinephrine, norepinephrine, dopamine, dobutamine, and isoproterenol, are all rapidly inactivated by methylation of a hydroxyl group of the catechol structure by catechol-*O*-methyltransferase (COMT). In addition, monoamine oxidase (MAO) catalyzes oxidative deamination of this group of compounds (with the exception of dobutamine). Approximately 25% of dopamine is converted to norepinephrine in adrenergic nerve terminals; these nerve terminals also take up norepinephrine. Even though phenylephrine is not a catecholamine, it is nonetheless metabolized by MAO. Ephedrine and milrinone largely resist metabolism and are excreted in the urine, whereas vasopressin is metabolized by specific vasopressinases in the liver and kidney.

Levosimendan is unique in this group of drugs, in that it is metabolized to active compounds that are eliminated slowly. This results in clinical effects for up to a week after discontinuation of an infusion.[14]

Pharmacodynamics and Drug Interactions

The pharmacodynamic profile of specific inotropes and vasopressors is a function of their relative receptor activities and mechanisms; an overview of receptor activities and physiologic effects is presented in Table 25.1. Adrenergic receptors have traditionally been divided into α and β, and have been subdivided into α_1, α_2, β_1, β_2, and β_3. Further subtyping has been performed, and several genetic variations have been described (see "Pharmacogenetics").

The predominant location of α_1 receptors is on peripheral vasculature; stimulation results in vasoconstriction of the skin, muscles, and renal and mesenteric vasculature. There is some contribution of peripheral α_2 receptors to vasoconstriction, but agonism of α_2 receptors is not a major characteristic of drugs discussed here (for pharmacology of α_2 agonists, see Chapter 10).

β_1 Receptors are primarily located in the heart, where their stimulation results in increased inotropy, chronotropy, and lusitropy. β_2 Receptors are widely distributed through the vasculature. Stimulation in peripheral vasculature results in dilation of muscular, splanchnic, and renal vessels. Bronchial smooth muscle has a high concentration of β_2 receptors, the activation of which causes bronchodilation. Additional effects include stimulation of glycogenolysis in the liver and a slowing of peristalsis. The β_3 receptor has been known for years to exist in adipose tissue, where its stimulation results in lipolysis. Its existence in the heart has been more recently recognized, and its role in normal physiology and disease, as well as the pharmacologic implications, is still being investigated. Current thinking suggests that β_3-receptor agonism in the heart causes a decrease in inotropy.

There is a potential interaction between monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants (TCAs) and several inotropes and vasopressors (Table 25.2). Because MAO contributes to the metabolism of norepinephrine and TCAs inhibit its reuptake, patients taking either type of drug can have an exaggerated hypertensive response to norepinephrine, drugs that enhance norepinephrine release (ephedrine and dopamine), and drugs that are metabolized by MAO. This adverse pharmacokinetic drug interaction can have important implications in the perioperative and intensive care settings.

Pharmacogenetics

Although basic knowledge of the α- and β-adrenergic receptors forms the foundation for understanding the pharmacology of inotropes and vasopressors, recent research has unveiled considerable genetic complexity in the receptors.[15] There are at least nine distinct receptor subtypes (three subtypes of each α_1, α_2, and β) that are expressed in a variety of tissues. Many of these receptor subtypes also have well-described genetic variants. For example, 12 single-nucleotide polymorphisms (SNPs) have been identified in the β_1 receptor and 19 in the β_2 receptor.[16,17] These are simple variations in the genetic code, but it is believed that they translate into

TABLE 25.1 Receptor Activity and Physiologic Effects of Vasopressors and Inotropes

Drug	α Receptor	β_1 Receptor	β_2 Receptor	Cardiac Output	Heart Rate	SVR	MAP	PVR
Epinephrine	++	++	++	↑	↑	↑	↑	0
Isoproterenol	0	+++	+++	↑	↑	↓	↓	0
Norepinephrine	+++	++	0	0	0	↑	↑	↑
Dopamine	++	++	0	↑	↑	↑	↑	0
Dobutamine	0	+++	+	↑	↑	↓	↓	↓
Milrinone	0	0	0	↑	0	↓	↓	↓
Phenylephrine	+++	0	0	0	↓	↑	↑	↑
Vasopressin	0	0	0	0	0	↑	↑	0
Ephedrine	+	+	+	↑	↑	↑	↑	0
Levosimendan	0	0	0	↑	0	↓	↓	↓

MAP, Mean arterial pressure; *PVR,* pulmonary vascular resistance; *SVR,* systemic vascular resistance.
Effects vary significantly with dose and between individuals.
Increasing levels of stimulation of adrenergic receptors are represented by +, ++, +++.

TABLE 25.2 Application, Dosing, and Interactions of Vasopressors and Inotropes

Drug	Drug of Choice	Bolus Dose	Infusion Dose	Relevant Drug Interactions
Epinephrine	Anaphylaxis; cardiac arrest	5–10 μg, up to 1 mg for cardiac arrest	0.02–0.3 μg/kg per minute	β-blockers, MAOIs, proarrhythmic medications
Isoproterenol	Refractory bradycardia	No bolus dosing	0.01–0.2 μg/kg/min	No co-infusion with alkaline medications
Norepinephrine	Septic shock	No bolus dosing	0.05–0.5 μ/kg per minute	MAOIs, TCAs
Dopamine	Septic shock with systolic dysfunction	No bolus dosing	1–20 μg/kg per minute	MAOIs, TCAs, butyrophenones, phenothiazines, phenytoin
Dobutamine	Stress echocardiography	No bolus dosing	2–20 μg/kg per minute	Co-administration with alkaline solutions can decrease activity
Milrinone	Weaning from cardiopulmonary bypass	Loading dose: 20–50 μg/kg over 10 min	0.2–0.75 μg/kg per minute	Can precipitate with furosemide
Phenylephrine	Mild hypotension from general or regional anesthesia	50–200 μg	20–200 μg/min	MAOIs, TCAs
Vasopressin	Post–cardiopulmonary bypass vasoplegia	0.5–2 units for mild hypotension, 20 units	0.01–0.04 μ/min	Carbamazepine, TCAs, norepinephrine, lithium, heparin
Ephedrine	Mild hypotension from general or regional anesthesia	5–10 mg	No infusion dosing	MAOIs, TCAs
Levosimendan	Unclear at this time	Loading dose: 12 μg/kg over 10 min	0.05–0.2 μg/kg per minute	None yet identified

MAOIs, Monoamine oxidase inhibitors, *TCAs,* tricyclic antidepressants.

clinically significant phenotypes. Polymorphisms have also been identified in the α_1 and α_2 receptors. There appears to be an association between some of these genotypes and the development of hypertension and heart failure.[18]

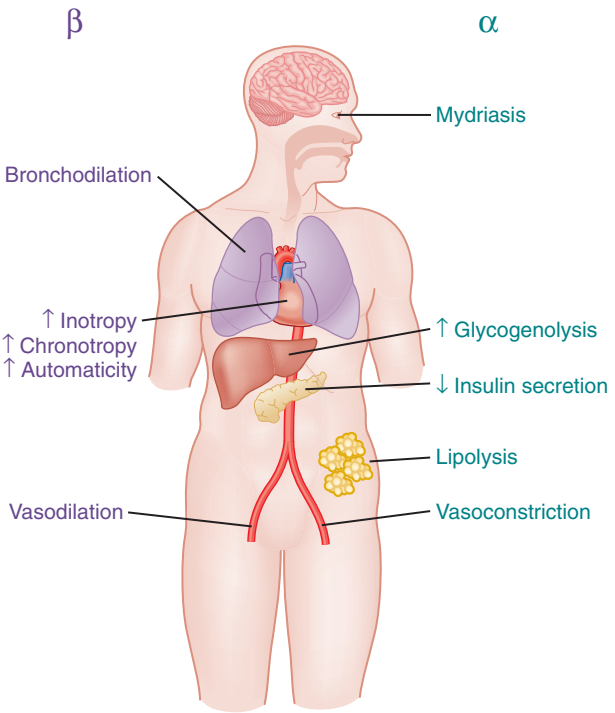
The majority of research on the impact of adrenergic receptor genetic variation has focused on its implications on the development and treatment of cardiovascular disease, as well as on the clinical outcomes after certain cardiac diagnoses (e.g., myocardial infarction). Little work has focused on the effects of vasopressors and inotropes in these different genotypes. It is reasonable to expect, however, that clinically significant differences seen in the response to receptor antagonists (e.g., β blockers) might also be observed for receptor agonists. Indeed, a polymorphism in the β_1 receptor affects the response to dobutamine, with a significantly greater heart rate and inotropic response.[19] Even though much work remains to be done in this area, it is likely that at least some of the large interindividual variability seen in the response to these drugs is a function of genetic variation.

Individual Drugs

Epinephrine

Epinephrine is a naturally occurring sympathomimetic with nonselective adrenergic agonist activity. It is synthesized, stored, and released by the chromaffin cells of the adrenal medulla in response to physiologic stress. It binds to α, β_1 (the predominant β receptor in the heart), and β_2 (the predominant ββ receptor in the lungs and vasculature) receptors. Action at the β_3 receptor is not currently a target of clinical application of epinephrine.

Epinephrine is the drug of choice in two extreme clinical conditions: anaphylactic shock and cardiac arrest (Fig. 25.3). In anaphylaxis, α-receptor–mediated vasoconstriction of small arterioles and precapillary sphincters increases mean arterial pressure (MAP) and decreases mucosal edema. Its β-receptor–mediated effects cause bronchodilation and stabilization of mast cells. The latter decreases the release of histamine, tryptase, and other inflammatory mediators that perpetuate the pathophysiology of anaphylaxis. In cardiac arrest, epinephrine is given in large doses (1 mg every 3–5 minutes) to increase MAP, thereby increasing cerebral perfusion pressure during chest compressions. The value and safety of its β-receptor–mediated effects during cardiac arrest are controversial because they increase myocardial oxygen consumption. However, studies demonstrate better survival with epinephrine than without it.[20]



• **Fig. 25.3** Summary of the effects of epinephrine mediated by α- and β-adrenergic receptor stimulation.

Other indications for epinephrine take advantage of specific subsets of its nonselective adrenergic agonism profile. Epinephrine is used to treat asthma (β_2-mediated bronchodilation), severe hypotension associated with bradycardia (β_1-mediated chronotropy) and/or low cardiac output (β_1-mediated inotropy), and to prolong the effects of local anesthetics (α-mediated vasoconstriction). Low doses of epinephrine (0.02–0.05 μg/kg per minute) are used to increase depressed cardiac output after cardiopulmonary bypass; other catecholamines and inotropes have similar effects, but none has proven superior to epinephrine in terms of patient outcome. Epinephrine has also been studied as an alternative to other vasopressors in the treatment of vasodilatory shock from sepsis, even though the data do not yet support its use as a first-line therapy.[21]

Epinephrine's effects are route, time, and dose dependent. At low doses (0.01–0.05 μg/kg per minute), the β-receptor effects of epinephrine predominate, while at higher doses, α effects predominate (see Table 25.1). An intravenous bolus of epinephrine (5–15 μg) causes an initial increase in heart rate, systolic blood pressure, and systemic vascular resistance (SVR, from stimulation of α and β receptors), and a subsequent decrease in systolic and diastolic blood pressure and vascular resistance (from continued stimulation of β receptors with peripheral vasodilation.)[22]

In healthy subjects, increasing rates of epinephrine infusion (0.01–0.2 μg/kg per minute) progressively increase heart rate and systemic blood pressure. In general, at progressively higher continuous infusion rates, heart rate, blood pressure, SVR, and cardiac output increase while pulmonary artery pressure, central venous pressure, and pulmonary artery occlusion pressure remain unchanged.

Mast cell stabilization and bronchodilation via stimulation of β_2 receptors are the two most important nonhemodynamic, therapeutic effects of epinephrine. Epinephrine has numerous other nonhemodynamic effects that are potentially adverse. At doses typically administered for vasopressor and/or inotropic effects, these potentially adverse effects include the following:

- Hyperglycemia—due to increased liver glycogenolysis, reduced tissue uptake of glucose, and inhibition of pancreatic secretion of insulin
- Hypokalemia—due to increased uptake of K+ in skeletal muscle secondary to stimulation of β_2 receptors. Infusion of epinephrine at a rate of 0.1 μg/kg per minute reduces plasma K^+ concentration by about 0.8 mEq/L.[23]
- Lactic acidosis—in theory due to inhibition of pyruvate dehydrogenase, causing pyruvate to be shunted to lactate.[24] Although the mechanism is not fully elucidated, epinephrine infusion results in lactic acidosis even in the absence of tissue hypoxia and may not necessarily signify a poor prognosis.[24,25]
- Myocardial ischemia—due to hypertension, tachycardia, and increased inotropy that increase myocardial oxygen demand.

Epinephrine is administered by continuous infusion, bolus, infiltration, or inhalation. Usual intravenous infusion doses are

0.02 to 0.3 μg/kg per minutes. Intravenous bolus doses range from 5 to 10 μg for moderate hypotension (MAP 40–60 mm Hg) unresponsive to other vasopressors up to 1 mg as recommended by the American Heart Association guidelines for cardiac arrest.[26] The usual intramuscular dose is 0.3 mg administered into the lateral thigh *(vastus lateralis),* which produces significantly higher plasma concentrations than administration into the deltoid or subcutaneously. Subcutaneous administration results in delayed absorption and lower peak plasma concentrations than other routes. This is generally reserved for treatment of severe asthma in doses of 0.3 to 0.5 mg for adults or 0.01 mg/kg for children, when inhaled selective β_2 agonists cannot be administered.[27] In addition, epinephrine can be administered via an endotracheal tube during cardiac arrest if other routes are not available; the recommended dose is double the intravenous dose diluted with 10 mL of normal saline solution. Epinephrine is not effective orally owing to rapid metabolism and does not cross the blood-brain barrier in sufficient amounts to directly affect the central nervous system.

Epinephrine should not be used in patients with acute cocaine intoxication because of the potential for exacerbation of myocardial ischemia and stroke. In patients with dynamic obstructions to ventricular outflow (e.g., tetralogy of Fallot and hypertrophic obstructive cardiomyopathy), epinephrine can worsen outflow obstruction and lower cardiac output. Administration of epinephrine with a β blocker can lead to significant α-receptor stimulation without opposing β-receptor–mediated vasodilation, which can result in severe vasoconstriction, hypertension, and heart failure. Care should also be taken when administering epinephrine with medications that predispose the heart to arrhythmia, particularly digitalis and halothane.

Isoproterenol

Isoproterenol was approved by the U.S. Food and Drug Administration (FDA) in 1947 and was used initially to treat asthma. Interestingly, it was the first drug for which the FDA required a package insert beginning in 1968. As the isopropyl derivative of norepinephrine, isoproterenol is a synthetic sympathomimetic with nonselective β-adrenergic activity.

Stimulation of cardiac β_1 receptors by isoproterenol increases heart rate, inotropy, and lusitropy, resulting in an increase in cardiac output and systolic blood pressure. Stimulation of β_2 receptors results in vasodilation of the muscle, kidney, skin, and splanchnic circulations, thereby decreasing total peripheral vascular resistance and mean and diastolic blood pressure. The decrease in systemic blood pressure combined with increases in myocardial contractility and heart rate can precipitate myocardial ischemia in patients with significant coronary artery disease. At higher doses, palpitations, headache, and flushing can occur.

Isoproterenol was used initially via inhaler to treat asthma and bronchospasm but has been replaced by β_2-selective bronchodilators. Currently isoproterenol is indicated in hemodynamically significant bradycardia until cardiac pacing can be established. In prior years, it was used immediately following cardiac transplantation to enhance inotropy and chronotropy without concomitantly increasing systematic vascular resistance. Currently other drugs are used in this setting more commonly (e.g., epinephrine, milrinone, and vasopressin with cardiac pacing as necessary). Isoproterenol is also being used during electrophysiology procedures to stimulate the underlying arrhythmia for better mapping and increases the likelihood of a successful ablation.

Norepinephrine

Norepinephrine is a naturally occurring sympathomimetic with both α- and β_1-receptor affinity. Its effects are comparable to epinephrine on β_1 receptors, but because of its greater affinity for α receptors and its near-total inactivity at β_2 receptors, it is an intense vasoconstrictor. As the primary neurotransmitter of the sympathetic nervous system, it is released from postganglionic sympathetic nerve endings and represents 10% to 20% of the catecholamine content of the adrenal medulla.

Norepinephrine causes an increase in systolic and diastolic blood pressures owing primarily to an increase in SVR (see Table 25.1). Cardiac output does not increase and can decrease owing to increased resistance to ventricular ejection. Heart rate remains unchanged or decreases from compensatory baroreceptor-mediated vagal activity. Blood flow decreases in renal, mesenteric, splanchnic, and hepatic beds. Norepinephrine increases pulmonary vascular resistance (PVR), probably by α_1-mediated vasoconstriction.[28]

Norepinephrine is the drug of choice for septic shock when MAP is less than 65 mm Hg despite adequate volume resuscitation.[29] Compared with dopamine in sepsis, norepinephrine is more likely to improve hypotension with fewer arrhythmias and tachycardia.[30–32] Norepinephrine is also used to treat hypotension following cardiopulmonary bypass. However, when used to treat hypotension associated with milrinone administration, norepinephrine is less effective than vasopressin in preserving a beneficial ratio of systemic and PVR.[33] Although norepinephrine increases PVR, its ability to substantially increase right ventricular perfusion pressure can make it a useful vasopressor in right heart failure.[34]

With regard to adverse effects, norepinephrine can cause severe hypertension with increased myocardial workload and cardiac ischemia. Systemic vasoconstriction can impair perfusion of the gut and other organs, resulting in organ dysfunction and metabolic acidosis. Clinical studies, however, have not consistently shown a decrease in splanchnic perfusion or worsening organ function when patients with sepsis are treated with norepinephrine.[35] In some cases a decrease in splanchnic perfusion is associated with improved gastrointestinal perfusion, suggesting a redistribution of blood flow in the gut.[36,37]

Dopamine

Dopamine is a naturally occurring catecholamine that stimulates β_1-and α_1-adrenergic receptors, as well as vascular D_1-dopamine receptors (primarily in mesenteric and renal vasculature). It is synthesized in the kidney and has both diuretic and natriuretic effects. In addition to its peripheral actions, it is an important neurotransmitter in the central nervous system (see Chapters 8 and 12).

At low plasma concentrations, dopamine acts primarily on the D_1 receptor in renal, mesenteric, and coronary vasculature (see Table 25.1) to produce vasodilation of these beds with a resultant increase in glomerular filtration rate, renal blood flow, Na^+ excretion, and urine output.[38] Low doses can also decrease SVR. Higher doses directly stimulate β_1 receptors and enhance release of norepinephrine from sympathetic nerve terminals to increase myocardial contractility, heart rate, systolic blood pressure, and pulse pressure. Diastolic blood pressure is minimally affected but PVR can increase.[39] At high doses, stimulation of α_1 receptors predominates, resulting in generalized peripheral vasoconstriction.

It is commonly stated that doses of 0.5 to 3 μg/kg per minute stimulate primarily DA1 receptors, 3 to 10 μg/kg per minute

stimulate primarily β_1 receptors, and greater than 10 μg/kg per minute primarily stimulate α receptors, but clinically the hemodynamic effects of dopamine are difficult to predict based on these empirical dosing guidelines.[40] In healthy male volunteers, weight-based dopamine administration resulted in up to 75-fold intersubject variability in plasma concentrations.[41] However, no study has yet compared plasma concentrations of dopamine with its effects. Therefore dosing should be titrated to physiologic effect, rather than being based on rigid concepts of relative receptor activity for a given dosage.

Dopamine had previously been recommended as a first-line treatment for septic shock with systolic dysfunction. Recent studies showing worse outcomes with dopamine have resulted in a change in recommendations and it is now suggested only in patients at low risk for arrhythmia or those with bradycardia.[29,42] Comparison of dopamine with norepinephrine for treatment of shock showed a higher incidence of arrhythmias in all patients and higher mortality in patients with cardiogenic shock treated with dopamine.[32] Compared with dobutamine after cardiac surgery and in patients with chronic heart failure, dopamine resulted in less hemodynamic improvement.[43,44] When compared with dopexamine, it resulted in significantly more adverse cardiac events.[45]

Renal dose dopamine refers to an infusion of dopamine in low doses (usually 1–3 μg/kg per minute) for treatment or prevention of acute renal failure with a goal of selective stimulation of D_1 receptors. It is a misleading phrase and outdated concept, as the effects of dopamine even in low doses are not exclusively limited to the kidneys. Even though low doses of dopamine increase renal blood flow, glomerular filtration, and urine output, numerous studies have failed to show a decreased incidence of renal failure with its use.[46]

Dopamine can cause tachycardia, tachyarrhythmias, and myocardial ischemia, and at high doses causes decreased splanchnic perfusion and gut ischemia.[35,47] In addition to its hemodynamic effects, dopamine reduces the ventilatory response to hypoxemia, consistent with its role of as a neurotransmitter in the carotid bodies.[48] Dopamine infusions alter endocrine and immune function, including decreased secretion of growth hormone, prolactin, and thyroid stimulating hormone.[49] Like other vasoconstrictors, dopamine can cause skin necrosis and sloughing if extravasation occurs.

The renal and mesenteric vasodilating properties of low-dose dopamine are suppressed by dopamine receptor antagonists such as butyrophenones and phenothiazines.[50,51] There are reports of dopamine causing hypotension and bradycardia in patients taking phenytoin.[52]

Dobutamine

Dobutamine is a direct-acting synthetic catecholamine and is the drug of choice for the noninvasive assessment of coronary disease (dobutamine stress echocardiography). Dobutamine is also used for short-term treatment of congestive heart failure and for low cardiac output after cardiopulmonary bypass. In patients with chronic low output cardiac failure, dobutamine was superior to dopamine in its ability to increase cardiac output without untoward side effects.[44] Similarly, it is superior to dopamine in managing hemodynamically unstable patients after cardiac surgery, reducing cardiac filling pressures and PVR with less trachycardia.[39,43] Compared with milrinone after cardiac surgery, dobutamine was "comparable," producing a greater increase in cardiac output, blood pressure, and heart rate but with a higher incidence of arrhythmias.[53]

In patients with congestive heart failure, the principal effect of dobutamine is an increase in myocardial contractility and ventricular ejection mediated by its β_1 effects. In contrast to epinephrine or dopamine, dobutamine generally reduces SVR by a combination of direct vasodilation and a reflex decrease in sympathetic vascular tone. This might be offset by the increase in cardiac output, leading to no change or a decrease in MAP. Dobutamine generally decreases cardiac filling pressures and PVR. Dobutamine has a variable effect on heart rate, but it can significantly increase heart rate (particularly at the higher concentrations used in stress echocardiography).[8,54] After cardiopulmonary bypass the primary mechanism of increased cardiac output by dobutamine is an increase in heart rate (approximately 1.4 beats/min per microgram per kilogram per minute) with an increase in SVR.[55] The contrasting results of these studies reflect dobutamine's complex mechanisms of action, particularly with regard to the balance of α_1 stimulation and inhibition by its isomers, as well as patient factors.

Dobutamine can produce tachycardia, arrhythmias, and hypertension. Dobutamine can exacerbate myocardial ischemia in susceptible patients by increases in heart rate and contractility.

Milrinone

Milrinone is a phosphodiesterase type III inhibitor, and as such is a synthetic noncatecholamine inodilator. Milrinone increases cardiac index with reductions in arterial pressure, left ventricular end-diastolic pressure, and PVR. Heart rate can increase, although this is not a consistent response and bradycardia can also occur. Compared with dobutamine, milrinone produces less tachycardia with more pulmonary and systemic vasodilation.[56]

Milrinone significantly increases success in the first attempt at weaning from cardiopulmonary bypass with less need for catecholamine support but with a greater requirement for additional vasoconstrictors.[57,58] Milrinone might be preferable to adrenergic agonists in patients with chronic heart failure undergoing cardiopulmonary bypass as downregulation of adrenergic receptors in this population can lead to decreased responsiveness to catecholamines. In addition, milrinone improves flow in grafted internal mammary artery and saphenous vein grafts.[59,60] Intravenous milrinone has also been used to reverse cerebral vasospasm after subarachnoid hemorrhage, while inhaled milrinone has been used to treat severe pulmonary hypertension and acute lung injury.[61–64]

Milrinone is attractive for use in right heart failure by increasing ventricular contractility and decreasing PVR. However, milrinone-induced decreases in SVR and arterial blood pressure might offset these benefits and worsen supply-demand balance in the failing right heart. For this reason, milrinone is often combined with norepinephrine or vasopressin in an attempt to offset peripheral vasodilation. Comparing these two combinations, adding low-dose vasopressin to milrinone might be superior to adding norepinephrine in improving the ratio of systemic to PVRs.[33]

Inhaled milrinone offers the potential advantage of decreased PVR and increased ventricular contractility while maintaining SVR and MAP. Its use has been shown to improve the ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FIO_2) as well as decrease the intrapulmonary shunt fraction (Qs/Qt).[65] When administered during cardiopulmonary bypass, inhaled milrinone may be superior to intravenous administration in reducing pulmonary reperfusion syndrome by preventing endothelial dysfunction in the pulmonary arterial system.[66]

The most common adverse effect of milrinone is arterial hypotension, though this is often a desired effect. Milrinone use is an

independent risk factor for the development of atrial fibrillation after cardiac surgery, but the incidence is less than with dobutamine.[53,67] About 12% of patients given milrinone in phase II and III trials developed ventricular arrhythmias (primarily premature ventricular contractions).

Milrinone is typically given intravenously, but it can also be nebulized. Intravenous dosing of milrinone is initiated with a loading dose of 20 to 50 μg/kg over 10 minutes, followed by an infusion of 0.2 to 0.75 μg/kg per minute. Owing to the high degree of renal clearance, the dose should be reduced in patients with reduced creatinine clearance. Inhaled milrinone is nebulized in a concentration of 1 mg/mL. The most common administration regimen has been a single dose of 5 mg, though longer infusions have been studied as well.

Phenylephrine

Phenylephrine is a synthetic noncatecholamine α_1 agonist and produces dose-dependent vasoconstriction of cutaneous, muscular, mesenteric, splanchnic, and renal vasculature (see Table 25.1). Systemic arterial vasoconstriction increases systolic, diastolic, and MAPs, with reflex bradycardia. Phenylephrine can also cause pulmonary vasoconstriction and pulmonary hypertension.

Phenylephrine is the drug of choice for initial treatment of mild hypotension with normal or increased heart rate in the setting of general or regional anesthesia. The use of phenylephrine to support blood pressure during spinal anesthesia for cesarean section has long been discouraged because of concerns that vasoconstriction could have a deleterious effect on placental blood flow. Several studies have strongly contradicted this traditional teaching by documenting that phenylephrine does not worsen fetal outcome and might in fact be superior to ephedrine.[68,69] The use of phenylephrine in the management of septic shock is generally not recommended. Exceptions to this include cases in which norepinephrine causes significant arrhythmia or when vasodilation is refractory to other thrapy.[29] Phenylephrine has been used to increase right ventricular perfusion in pulmonary hypertension and right heart failure, though it can worsen right ventricular function and raise pulmonary artery diastolic pressures; norepinephrine appears to be more effective in this setting.[70,71] Phenylephrine is used topically as a nasal decongestant; as a mydriatic; and in ear, nose, and throat surgeries to constrict mucosa or control bleeding.

Severe bradycardia or even brief asystole can occur with higher doses of phenylephrine. With left ventricular dysfunction, the combination of bradycardia and increased afterload can significantly reduce cardiac output. Case reports document the risk of pulmonary edema, arrhythmias, cardiac arrest, and death when phenylephrine is used topically in excessive doses during head and neck surgery to control bleeding.[72] Topical doses should be limited to no more than 0.5 mg in adults, and blood pressure and heart rate should be monitored. Severe hypertension can require treatment with an α_1 antagonist such as phentolamine or with a direct vasodilator such as hydralazine. β Blockers or calcium channel blockers should not be administered in this setting because their cardiac depressant effects can result in acute heart failure.[72]

Vasopressin

Arginine vasopressin (AVP, vasopressin, also known as antidiuretic hormone) is a nonapeptide hormone synthesized in the magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus (see Chapter 36). It is stored and released from neurosecretory vesicles in the posterior pituitary gland (neurohypophysis).[13]

Vasopressin is given typically by continuous intravenous infusion. Previously recommended infusion rates for hypotension were from 0.01 to 0.04 units/min based on a study that suggested increased cardiac complications with doses above 0.04 units/min.[73] While some evidence suggests that a dose of 0.067 units/min results in better cardiovascular function with no increase in side effects, the surviving sepsis campaign recommends a maximal dose of 0.03 units/min in patients with sepsis and suggests that any further increase should be done only as salvage therapy.[74,75] Further study is required to identify the optimal doses for different clinical settings. Vasopressin can be given as a bolus of 1 to 2 units to treat intraoperative hypotension, though its effects are short-lived.

The hemodynamic effects of vasopressin are complex and vary depending on the presence or absence of intact sympathetic and renin-angiotensin systems. Interestingly, the effect of vasopressin infusions in healthy volunteers appears to be minimal even at high plasma concentrations.[76] This paradoxical finding can be explained by the action of vasopressin on the area postrema of the central nervous system. The expected vasoconstrictive effect is effectively counterbalanced by an augmented baroreflex inhibition of efferent sympathetic activity.[77] In patients with septic shock, low-dose vasopressin increases systemic arterial blood pressure and vascular resistance, but it does not alter pulmonary vascular resistance and pressures, cardiac filling pressures, or cardiac index.[78] Heart rate can decrease, though this finding is not consistent.

Even though it is not considered a first-line therapy, vasopressin is used as an adjunct to catecholamines in the treatment of septic shock. Patients with septic shock have much lower plasma vasopressin concentrations than those with cardiogenic shock. This has been interpreted as a relative vasopressin deficiency caused by early depletion of hypothalamic stores or inhibition of vasopressin release.[79] The Vasopressin and Septic Shock Trial (VASST) compared norepinephrine with low-dose vasopressin to norepinephrine alone. There was no difference in overall mortality or adverse events, but mortality was reduced in patients with less severe sepsis who were given vasopressin.[80]

Guidelines on the use of vasopressin in cardiopulmonary resuscitation are evolving. Endogenous vasopressin levels are higher in patients who are successfully resuscitated.[81] Studies have compared the use of vasopressin and epinephrine in cardiac arrest with variable outcomes.[82–85] It does not appear that vasopressin confers a significant benefit compared with epinephrine, and the most recent American Heart Association guidelines have removed vasopressin as a single agent to replace a dose of epinephrine.[26]

Cardiopulmonary bypass is normally associated with a substantial increase in circulating vasopressin.[86] In some cases of postbypass hypotension, plasma vasopressin concentrations are inappropriately low.[87] These patients frequently respond to low doses of vasopressin, as do some patients with vasodilatory shock after cardiac transplantation or left ventricular assist device placement.

Although not supported by specific studies, vasopressin is also used to treat intraoperative hypotension during general or epidural anesthesia. Clinical experience suggests that it might be useful in treating hypotension refractory to catecholamines in patients receiving long-term treatment with drugs that inhibit the renin-angiotensin system (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers).[88]

In patients with septic shock, vasopressin reduces gastrointestinal mucosal perfusion and increases liver enzymes and total bilirubin concentrations.[89,90] In addition, it decreases platelet count (likely

due to increased platelet aggregation) but does not significantly alter coagulation.[91]

Numerous drugs interact with vasopressin. Potentiation of its antidiuretic effect can be seen with carbamazepine, chlorpropamide, clofibrate, fludrocortisone, and TCAs. Inhibition of the antidiuretic effect can be seen with demeclocycline, norepinephrine, lithium, heparin, and alcohol.

Ephedrine

Ephedrine is a synthetic noncatecholamine agonist at α, β_1, and β_2 receptors with both direct and indirect actions. Ephedrine is given as an intravenous bolus of 5 to 10 mg. It is effective in the same dose range when administered intramuscularly, albeit with slower onset and longer duration. When given in repeated doses, tachyphylaxis occurs, probably because of depleted norepinephrine stores. Ephedrine causes an increase in systolic, diastolic, and MAPs. It increases myocardial contractility, heart rate, and cardiac output (see Table 25.1).

In the acute care setting, ephedrine is used primarily to treat mild hypotension and bradycardia associated with general or regional anesthesia. Previously, ephedrine was the first-line therapy for parturients with hypotension secondary to spinal or epidural anesthesia based on studies in pregnant ewes suggesting that ephedrine preserved uterine blood flow compared with other vasopressors.[92] These data have been challenged recently; phenylephrine appears to be as good or better in preserving uterine blood flow and does not cause or worsen maternal tachycardia.[93,94]

At higher doses, ephedrine causes hypertension and tachycardia. Because it crosses the blood-brain barrier, ephedrine can cause agitation and insomnia. In patients with prostatic hypertrophy, ephedrine can produce urinary retention. Because ephedrine causes release of norepinephrine, patients taking MAOIs can have an exaggerated hypertensive effect.

Digoxin

Digoxin, a cardiac glycoside, exerts its positive inotropic effects by inhibiting the plasma membrane Na^+,K^+-ATPase of cardiac myocytes. This leads to an increase in available Ca^{2+} as described earlier. Although digoxin has been in clinical use for hundreds of years as an inotrope and to control heart rate in atrial fibrillation, it has largely been replaced by more effective medications with fewer side effects.

Digoxin is currently indicated (as a second- or third-line therapy) for ventricular rate control in atrial fibrillation and in the treatment of systolic heart failure.[95,96] Although it is effective in providing symptomatic relief for heart failure, it does so with a significant increase in mortality and its use should essentially be considered palliative.[97] It is likewise associated with increased mortality in patients with atrial fibrillation, and although it is effective in decreasing ventricular rate at rest, it does not prevent exercise induced tachycardia, does not aid in conversion to sinus rhythm, and may be associated with conversion from sinus rhythm back to atrial fibrillation.[98]

In addition to concerns about increased mortality with the use of digoxin, its use is significantly limited by the high incidence of side effects. The therapeutic index of digoxin is very small and requires plasma concentration monitoring, and its use is frequently associated with a wide variety of cardiac arrhythmias, including sinus bradycardia, sinus arrest, atrioventricular conduction delays, second- or third-degree heart block, and malignant ventricular arrhythmias. Digitalis toxicity is generally treated with digitalis binding antibody, as well as lidocaine, magnesium, phenytoin, and correction of hypokalemia.

Rational Drug Selection

Rational selection of vasopressors and inotropes in clinical practice is founded on numerous factors, including the targeted therapeutic goals and the adverse effects most critical to avoid. Because in most clinical scenarios there is not a clearly established evidence-based approach supported by outcome data, institutional protocols and physician experience often figure prominently in the formulation of a therapeutic plan. Once formulated, the plan is instituted as a therapeutic trial; the complexity and dynamic nature of circulatory physiology might necessitate a change in the initial regimen if the results are unsatisfactory or if conditions change.

In situations in which a variety of different drugs could potentially achieve the hemodynamic goals (and given the lack of class I evidence supporting the use of a particular drug), using a drug with which the practitioner has considerable experience is a reasonable approach. On the other hand, there are some clinical situations for which a particular drug might be preferable (see later text). The overarching principle is that rational drug selection must match the physiologic state of the patient with the anticipated effects of the drugs under consideration; the clinician must periodically reassess both the patient's physiology and the drug choice to determine whether changes are necessary.

Septic Shock

The pharmacologic management of septic shock has been the target of a large amount of research as well as the topic of published guidelines.[29] Norepinephrine is considered the drug of choice in the septic shock patient when the MAP is below 65 mm Hg despite volume resuscitation.

Cardiac Arrest

The use of large doses of epinephrine (up to 1 mg every 3–5 minutes) is the treatment of choice in the pulseless patient while a definitive diagnosis is being sought.

Mild, Intraoperative Hypotension

Anesthesiologists are frequently faced with mild hypotension during the course of routine general and neuraxial anesthetics. As in all cases of hypotension, it is of paramount importance to identify the etiology to institute appropriate therapy. While the cause is being investigated, however, it is reasonable to administer small doses of ephedrine. Phenylephrine can also be used if low afterload is suspected and the patient has an adequate heart rate to tolerate the bradycardia associated with phenylephrine. It should be recognized, though, that the use of a vasoconstrictor can compromise cardiac output and organ perfusion in some cases.

Hypotension in the Parturient

Until recently, the conventional wisdom has been that phenylephrine is contraindicated in the hypotensive pregnant patient and that ephedrine is the drug of choice. Recent literature, however, has contradicted that traditional teaching. In most routine circumstances, both ephedrine and phenylephrine are reasonable choices depending on the heart rate.

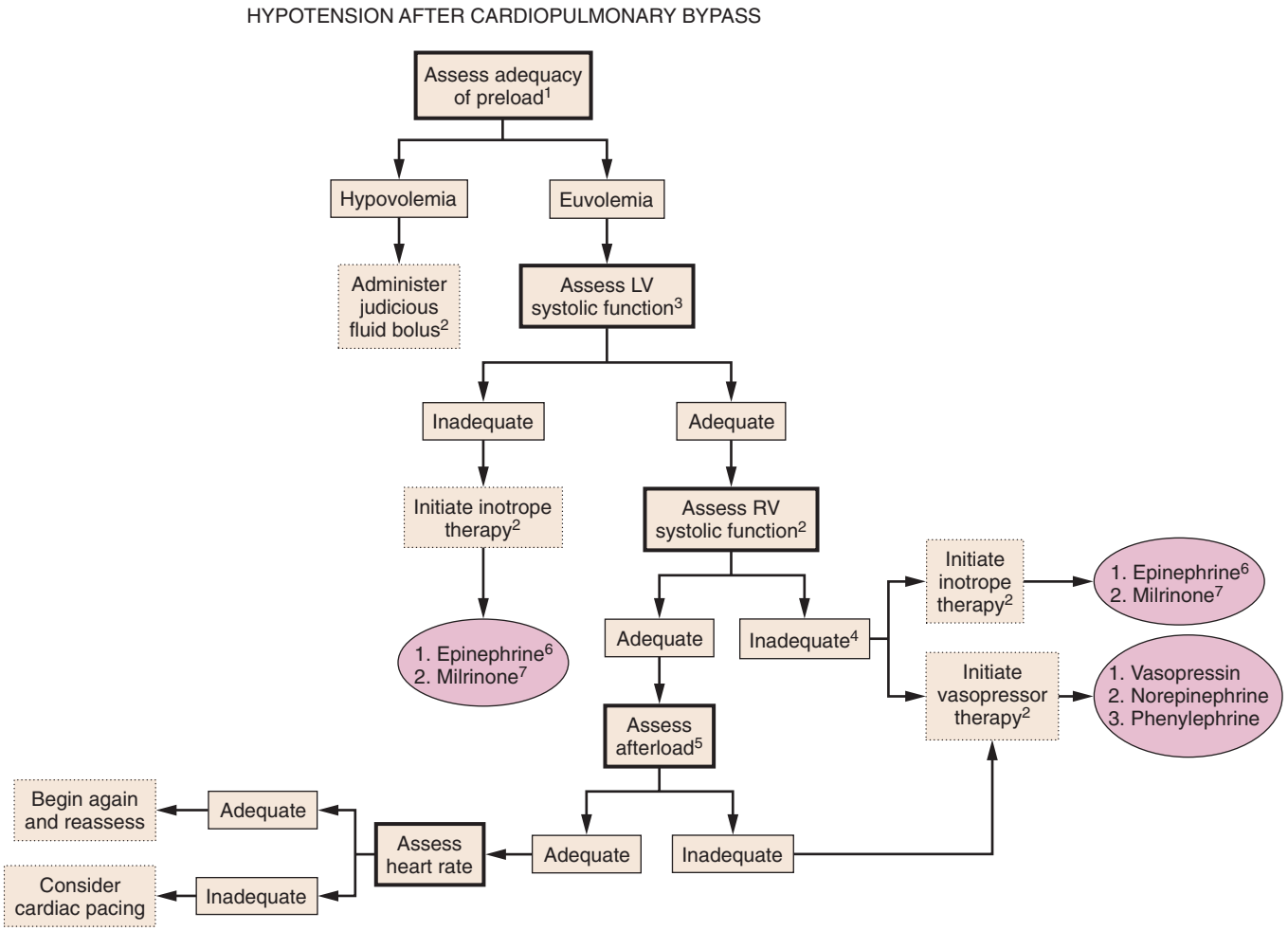
Right Heart Failure

In addition to identifying and treating reversible causes of elevated PVR, pharmacologic management is crucial in the critically ill patient with right heart failure. Guiding principles are to support myocardial contractility as well as perfusion of the ventricle. The combination of milrinone with vasopressin is an excellent choice in this situation. Milrinone provides inotropy and pulmonary vasodilation, whereas vasopressin supports perfusion of the right ventricle by increasing the SVR. When milrinone proves inadequate to increase contractility adequately, the addition of epinephrine might be successful.

Postbypass Hypotension

Hypotension in the patient being weaned from cardiopulmonary bypass represents an extremely complex interplay of physiologic factors; no single drug or protocol can reasonably be expected to prove universally efficacious. A comprehensive discussion of this topic is beyond the scope of this chapter, but basic concepts guiding the therapeutic decisions are summarized in Fig. 25.4.

Before treatment is initiated, the first step is to reach an underlying diagnosis. In contemporary anesthesia practice, transesophageal echocardiography is unparalleled as a diagnostic tool in this setting.



1. Generally utilizing a combination of echocardiography and invasive pressure measurements.

2. After each intervention, the clinical scenario should be reassessed to determine if patient has stabilized.

3. LV and RV systolic functions are best evaluated with transesophageal echocardiography.

4. Causes of pulmonary vasoconstriction should be sought and corrected, and consideration should be given to instituting a pulmonary vasodilator such as nitric oxide or inhaled prostacyclin.

5. Low afterload (SVR) is indicated by adequate ventricular filling, a hyperdynamic ventricle, elevated cardiac output, and a low calculated SVR.

6. Dopamine could be considered in place of epinephrine, although epinephrine is usually considered the first-line drug.

7. The use of milrinone to support ventricular function in these patients will generally result in an increase in cardiac output, but to avoid worsening hypotension, it should be accompanied by the addition of vasopressin.

• **Fig. 25.4** An approach to management of post–cardiopulmonary bypass hypotension. *LV,* Left ventricular; *RV,* right ventricular; *SVR,* systemic vascular resistance.

A broad differential diagnosis in this situation often includes left and/or right ventricular systolic dysfunction, inappropriate vasodilation, hypovolemia, and inadequate heart rate, each of which alone and in combination requires a different pharmacologic approach.

The only drug that has been shown to improve ability to wean from cardiopulmonary bypass is milrinone. It provides excellent inotropic support, particularly in heart failure patients with downregulated autonomic receptors. Because its use is commonly associated with peripheral vasodilation and worsening hypotension, however, milrinone should generally be combined with vasopressin in this population. Epinephrine is also a common and appropriate choice in the hypotensive patient with decreased contractility of the right and/or left ventricle; its use is associated with an increase in cardiac output and blood pressure.

When pure vasodilation is the cause of post–cardiopulmonary bypass hypotension, vasopressin is an excellent choice as it acts independently of the adrenergic receptors and as such can be expected to be additive with catecholamines. However, its use in this setting is a relatively new approach. In contrast, dopamine, epinephrine, and to a somewhat lesser extent, norepinephrine have a long history of successful use in supporting hemodynamics following cardiopulmonary bypass.

Emerging Developments

Understanding the pharmacogenetic basis of the variability in response to vasopressors and cardiotonic drugs is a primary focus of contemporary research in this area. In the future, it is conceivable that vasopressor and inotropic therapy will be personalized to an individual's genotype based on pretreatment testing. Combined with functional hemodynamic data allowing goal-directed therapy, it might eventually be possible to predict with accuracy and precision how an individual patient will respond to these drugs (see Chapter 4).[99]

Work continues as well in the area of drug development. Terlipressin, for example, is a recently developed long-acting synthetic analog of vasopressin with a half-life of 6 hours. In a small subset of patients with catecholamine-resistant septic shock, those receiving a single bolus of terlipressin had significantly less rebound hypotension during the reduction or cessation of norepinephrine.[100]

The calcium sensitizer subclass of drugs has also recently emerged in clinical practice and is being compared to more conventional therapies. Levosimendan is currently the only clinically available calcium sensitizing inodilator. In patients with heart failure, it has been shown to cause an increase in stroke volume and cardiac output with little change in heart rate (see Table 25.1). Cardiac filling pressures and pulmonary artery pressure decrease as well.[14] Levosimendan is used in the treatment of acute decompensated heart failure, pulmonary hypertension, postpartum cardiomyopathy, and ventricular dysfunction after cardiac surgery. Several studies have compared levosimendan with dobutamine in acute decompensated heart failure with mixed results.[101–104] Nonetheless, it represents a major advance in the development of new vasoactive drugs and exemplifies the continuing need for further research in the field.

Key Points

- Vasoactive drugs have an extensive history and have been used clinically for more than 5000 years.
- Many inotropes and vasopressors are derivatives of β phenylethylamine; the nature and extent of the ethylamine side chain substitution determines their receptor specificity.
- Although various inotropes and vasopressors exert their effects via different receptors and mechanisms, they generally increase the availability of calcium to interact with actin and myosin in either the cardiac myocyte or vascular smooth muscle.
- Catecholamines are primarily metabolized by catechol-*O*-methyl transferase and monoamine oxidase.
- Despite well-established profiles in selected populations, the effects of vasopressors and inotropes are difficult to predict in an individual, and thus these drugs should be titrated to effect rather than administered by empiric dosage schemes.
- A bolus of epinephrine can result in a transient increase in blood pressure from α-receptor stimulation, followed by a drop below the previous baseline from unopposed β-receptor stimulation. This serves as an example of the variable physiologic response to a given plasma concentration of a vasoactive agent.
- The use of low-dose dopamine as a means to preserve or improve renal function in critically ill patients is not supported by evidence despite extensive study and cannot be recommended.
- Phosphodiesterase inhibitors such as milrinone enhance cardiac function by inotropic and vasodilator actions. Their use can facilitate restoration of acceptable hemodynamic parameters following cardiopulmonary bypass.
- Contrary to long-standing dogma, either phenylephrine, an α-adrenergic agonist, or ephedrine, a mixed α- and β-adrenergic agonist, is an acceptable agent to treat hypotension in obstetric patients.
- Although once a mainstay inotrope in the treatment of heart failure, because of its low therapeutic index and frequent incidence of serious dysrhythmias, digoxin is no longer a first-line therapy.
- Treating an overdose of phenylephrine with β blockers or calcium channel blockers is contraindicated and can result in acute heart failure and death as the result of acute pulmonary edema.
- Description of the phenotypes associated with genetic variations in adrenergic receptors and development of calcium sensitizers are among important emerging developments in the field.

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26

Antihypertensive Drugs and Vasodilators

JOHN W. SEAR

CHAPTER OUTLINE

Historical Perspective

Sites and Mechanisms of Antihypertensive and Vasodilator Drugs

Basic Pharmacology and Mechanisms of Action of Individual Drug Classes
- Calcium Channel Blockers
- β Blockers
  - *Action of β Blockers at the Adrenergic Receptor*
- Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Antagonists
- Diuretics
- Centrally Acting Agents
- α_2 Adrenoreceptor Agonists
- α_1 Adrenoreceptor Antagonists
- Nitrovasodilators
- Other Vasodilators

Pharmacokinetics, Pharmacodynamics, and Adverse Effects
- Calcium Channel Blockers
  - *Adverse Drug Interactions*
  - *New Calcium Channel Blockers*
- β Blockers
  - *Antihypertensive Effect of β Blockers*
  - *New β Blockers*
  - *Adverse Effects of β Blockers*
- Angiotensin-Converting Enzyme Inhibitors
- Angiotensin II Receptor Antagonists
  - *Adverse Effects and Drug Interactions*
- Diuretics
  - *Adverse Effects and Drug Interactions*
- α_2 Adrenoreceptor Agonists
- α_1 Adrenoreceptor Antagonists
  - *Phentolamine and Phenoxybenzamine*
- Vasodilators
  - *Hydralazine*
  - *Nicorandil*
  - *Minoxidil*
  - *Nitrates*
  - *Phosphodiesterase Inhibitors*

Pharmacotherapy of Hypertension

Hypertension and Anesthesia

Pulmonary Vasodilators
- Phosphodiesterase Inhibitors
- Novel Pulmonary Vasodilators

Emerging Developments
- New Management Guidelines for Hypertension
- Direct Renin Inhibitors
- Natriuretic Peptides
- Endothelin and Endothelin Blockade

There are probably more than 1 billion people worldwide with raised blood pressure.[1] It is one of the most common chronic medical conditions internationally (US National Center for Health Statistics, 2005), and occurs almost twice as often in African-Americans than in whites. The incidence of hypertension increases with age, with a slightly greater incidence in men than in women.[2] In the United States, hypertension affects about 25% of all adults older than 40 years of age. More importantly, the prevalence of undiagnosed hypertension is about 1 in 15. In the United Kingdom, there are about 7.5 million patients suffering from raised blood pressure; 80% to 85% of these patients are either not treated or are being inadequately treated.

Blood pressure has been classified into four categories in the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, 7th Report (JNC 7 Report) based on systolic (left) and diastolic (right) pressures[3]:

- Normotension less than 120 and less than 80 mm Hg
- Prehypertension 120 to 139 or 80 to 89 mm Hg
- Stage I hypertension 140 to 159 or 90 to 99 mm Hg
- Stage II hypertension greater than 160 or greater than or equal to 100 mm Hg

In addition, patients with isolated systolic hypertension (ISH) are classified into ISH 1 (140–159/< 90 mm Hg) and ISH 2 (> 160/< 90 mm Hg). In 2014, JNC 8 recommended treatment of systolic blood pressure over 150 mm Hg or diastolic blood pressure over 90 mm Hg to a goal of less than these values for patents aged > 60 years, and treatment for systolic blood pressure over 140 mm Hg or diastolic blood pressure over 90 mm Hg for patients aged <60 years.[3a]

Abstract

Hypertension is a prevalent chronic disease associated with significant morbidity; early treatment is indicated to reduce end-organ damage and associated morbidity and mortality. First line treatments include diuretics, calcium channel blockers, and antagonists of the adrenergic system; other important classes of antihypertensive drugs include antagonists of the renin-angiotensin system and vasodilators. These drugs have distinct mechanisms of action, and are frequently used in combination. All have side effects, largely cardiovascular, and important drug interactions that must be considered in the perioperative period.

Keywords

hypertension
cardiovascular risk
beta blockers
calcium channel blockers
diuretics
renin-angiotensin system
nitric oxide

Many patients with hypertension have associated metabolic disorders (decreased high-density lipoproteins, increased triglycerides, increased urates, and reduced glucose tolerance). These of all contribute to the increased cardiovascular risk associated with high blood pressure and to the possible development of type 2 diabetes mellitus. These additional comorbidities influence the choice of drug therapy for treatment of raised blood pressure.

In the United States, strategies for treatment have included initiation of treatment if blood pressure is more than 20 mm Hg systolic or 10 mm Hg diastolic above the target pressure, but this has been modified by the JNC 8 criteria to include specific thresholds. Many studies have shown monotherapy to be generally inadequate and to be associated with an increased incidence of cardiovascular events occurring early after starting treatment. The use of combination therapy is not new; it originates from the mid-1960s when studies showed the efficacy of fixed doses of reserpine, hydrochlorothiazide, and hydralazine.

Historical Perspective

The causes of arterial hypertension are multiple but can be divided into 3 distinct subgroups (Table 26.1). There are various ways of reducing blood pressure and hence of treating hypertension. The history of the treatment of raised blood pressure shows how different drugs have been used to act on different effector sites or receptors. The dates of introduction of some of these early antihypertensive therapies are listed in Table 26.2.

One of the earliest treatments for hypertension was that described by Pauli using the sedative and hypotensive properties of sodium thiocyanate to obtain relief from the subjective symptoms of hypertension.[4] Another drug used for the treatment of malignant hypertension was sodium nitroprusside.[5,6] In the 1930s, the beneficial effects of extracts of *Rauwolfia serpentina* were first described with its first clinical use in 1955.[7,8] In the 1940s, sympathectomy was used to treat high blood pressure, often preceded by use of tetraethylammonium as a prognosticator to judge the likely success of the surgery, but was associated with a fairly high surgical mortality.

Real advances in management came with the introduction of ganglion blocking drugs (e.g., mecamylamine, pempidine, hexamethonium, and pentolinium) in the 1950s. Other drugs introduced over the next decade included reserpine (a rauwolfia alkaloid) and hydralazine.[9] The combination of a ganglion blocker and general anesthesia resulted in the development of significant bradycardias and hypotension. Diuretics were also introduced for treatment of hypertension (initially chlorothiazide). The reduction in circulating fluid volume produced by natriuresis enhanced the hypotensive effect of ganglion blocking agents and reduced some side effects of drugs such as reserpine. These synergistic interactions between drugs allowed a smaller dose of each drug and hence a less severe side-effect profile.

In the late 1950s and 1960s, two new important classes of drugs were introduced—adrenergic neuron blockers and the first generation of β-adrenoceptor blockers (see Chapter 14).

The antihypertensive effect of adrenergic neuron blockers (bretylium being the first) depends on inhibition of transmitter release from adrenergic nerve terminals in response to sympathetic nerve impulses. This results in a decrease in cardiac output, decrease in peripheral vascular resistance, and increase in venous capacitance. The main side effects of neuron blockade was postural hypotension, exertional hypotension, and hypotension in hot environments (all due to a failure of sympathetically mediated circulatory control).

α-Methyl DOPA (a false transmitter), introduced in 1961, reduces blood pressure by inhibition of norepinephrine synthesis. A slowly developing antihypertensive effect develops after repeated administration of small doses that do not exert a significant pressor effect. It is not established whether its hypotensive action is due to a peripheral effect (from impaired neuroeffector transmission)

TABLE 26.1 Causes of Hypertension

Essential

Secondary

Chronic kidney disease
Coarctation of the aorta
Cushing disease and other conditions leading to excess levels of glucocorticoid (including steroid therapy)
Obstructive uropathy
Pheochromocytoma
Primary aldosteronism and other mineralocorticoid excess states
Renovascular hypertension
Sleep apnea
Thyroid/parathyroid disease

Drugs

Secondary to Na^+ and water retention, sodium salts of drugs, steroid treatment (mineralocorticoids, glucocorticoids, oral contraceptive pill); NSAIDs
Vasoconstrictor drugs, such as sympathomimetics
Monoamine oxidase inhibitors through interaction with amines, including dietary tyramine
Rebound hypertension following acute withdrawal of clonidine, α-methyl DOPA, and β blockers

NSAIDs, Nonsteroidal antiinflammatory drugs.

TABLE 26.2 Drugs Used in Treatment of Hypertension from the Mid-1930s to 1966

1930s—Sedative drugs (barbiturates, bromides, cannabis preparations)
1940s—Surgical sympathectomy (bilateral thoracolumbar ganglionectomy)
1944—Salt-free diet (rice and fruit)
1945—Nitroprusside and thiocyanate salts
1950—Hexamethonium (the first of a series of improved ganglion-blocking drugs)
1952—Phenoxybenzamine and phentolamine (both used for treatment of hypertension, although introduced primarily for treatment of pheochromocytoma)
1953—Benefit of combination therapy recognized: pentolinium (ganglion blocker), hydralazine (vasodilator), reserpine and other rauwolfia alkaloids
1957—Mecamylamine (ganglion blocker) and chlorothiazide. Although chlorothiazide had only weak antihypertensive effects, its use was associated with a marked potentiation of the effect of other antihypertensive drugs.
1959—Bretylium, the first adrenergic neuron blocker
1960—Guanethidine
1961—α-Methyl DOPA (the first of the drugs that act through production of "false transmitters")
1962—Diazoxide (vasodilator)
1963—Monoamine oxidase inhibitors
1965—Propranolol, followed by oxprenolol and practolol; also, bethanidine (second-generation adrenergic neuron blocker)
1966—Clonidine (centrally acting antihypertensive agent); debrisoquine

or to a central effect (involving the norepinephrine synapses in the medulla oblongata).

First-generation monoamine oxidase inhibitors (MAOIs), such as pargyline, were introduced in 1963. The antihypertensive effect of MAOIs has a slow onset that persists for a considerable period after cessation of treatment. In time, tolerance develops, probably due to fluid accumulation. The underlying mechanism for their antihypertensive effect is probably due to a change in composition of the monoamine stores of adrenergic neurons with a relative increase in amines other than norepinephrine (in particular, dopamine).

Other centrally acting drugs introduced in the 1960s include the α_2-adrenoceptor agonist clonidine and the second generation of adrenergic neuron blockers typified by bethanidine and debrisoquine. One of the first β-adrenergic blocking drugs introduced into clinical practice was pronethalol in 1962, followed by propranolol in 1965, alprenolol in 1967, and oxprenolol and practolol in 1968.

At the same time, a major controversy and debate developed regarding whether antihypertensive drugs should be withdrawn from patients before anesthesia and surgery because of their effects in obtunding the normal mechanisms of cardiovascular control. The value of maintaining therapy was emphasized in a series of controlled studies of treated and untreated hypertensive patients.[10] Patients with well-controlled hypertension maintained on their drugs up to and including the morning of surgery experienced less cardiovascular instability than their untreated counterparts, especially in the postoperative period. Recent evidence suggests that withholding angiotensin converting enzyme inhibitors or angiotensin II receptor blockers before major noncardiac surgery reduces intraoperative hypotension and risk of death.[4a]

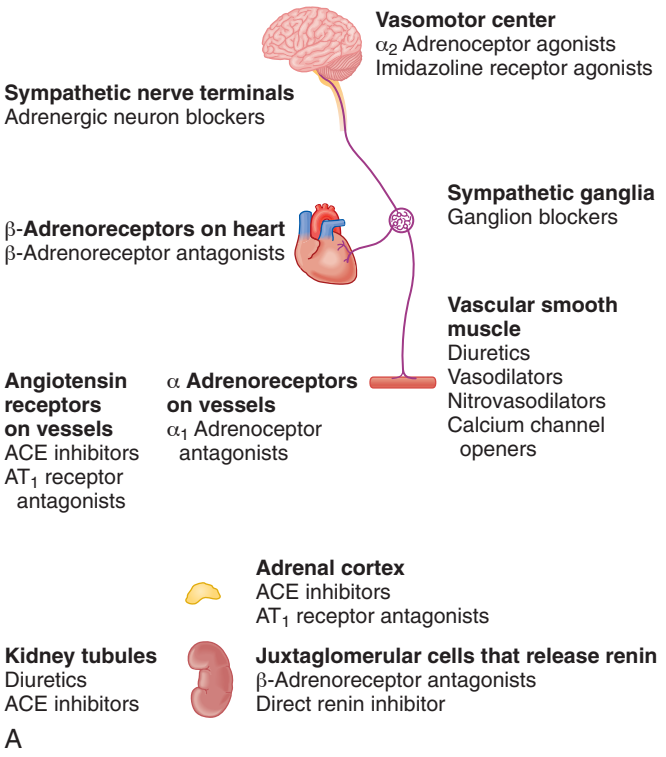
Sites and Mechanisms of Antihypertensive and Vasodilator Drugs

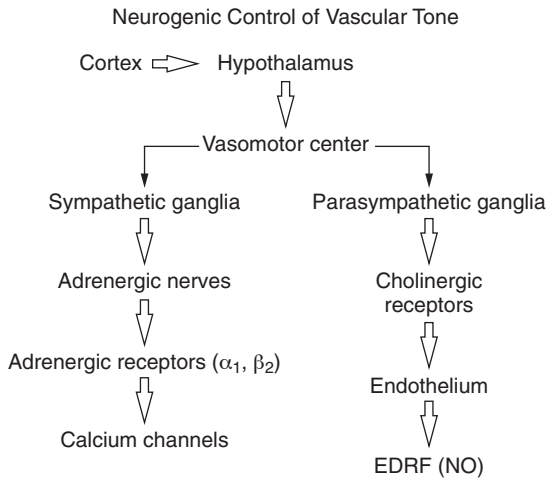
The main center for neurogenic control of vascular tone and hence blood pressure is the vasomotor center in the midbrain. This affects both the sympathetic ganglia and parasympathetic nerves (Fig. 26.1). There are 2 different central neural control systems involved in blood pressure regulation: neurogenic control (as outlined previously) and arterial baroreceptor reflexes.

Other humoral and endocrine control systems include the renin-angiotensin-aldosterone system, atrial natriuretic peptides, renal control of Na^+ and water excretion, eicosanoids, the kallikrein-kinin system, adrenal steroids (both glucocorticoids and mineralocorticoids), the endothelin system, and medullipin in patients with hypertension secondary to uremia and renal failure.

There are 3 main mechanisms by which drugs act in treatment of high blood pressure: (1) effects on the autonomic nervous system, (2) inhibition of the renin-angiotensin-aldosterone system, and (3) peripheral vasodilation. Based on these mechanisms, there are a number of potential sites of action for antihypertensive agents (Table 26.3).

Based on the 3 main antihypertensive mechanisms and the multiple sites at which drugs can act, there are different physiologic approaches to the reduction of blood pressure (Table 26.4).[11] Most drugs currently available do not act via a single mechanism. Within this physiologic approach to lowering blood pressure by vasodilation, the drugs available can be divided into 3 main subgroups (Table 26.5). Most of these vasodilator drugs act either on the arterial or venous circulations, with very few acting on both (Table 26.6).





• **Fig. 26.1** (A) Sites of action within the body of drugs that can be used for the treatment of high blood pressure. (B) Mechanisms of the neurogenic control of vascular tone via the vasomotor center. *EDRF,* Endothelial-derived relaxing factor; *NO,* nitric oxide.

TABLE 26.3 Sites of Action of Antihypertensive Agents

Vasomotor center
Sympathetic nerve terminals
β Adrenoceptor on heart
Sympathetic ganglia
Angiotensin receptors on vessels
α Adrenoceptors on vessels
Vascular smooth muscle
Adrenal cortex
Kidney tubules
Juxtaglomerular cells that release renin

TABLE 26.4 Physiologic Strategies for Reduction of Blood Pressure

Decrease Systemic Vascular Resistance

Decreased sympathetic vascular motor tone
- Decreased central sympathetic activity
- Blockade of ganglionic transmission
- Impairment of vascular neuroeffector transmission

Decreased vascular reactivity
- Relaxation of vascular smooth muscle
- Decrease of Na^+ content of vascular tissue

Decreased humorally mediated vasoconstriction
- Inhibition of vasoconstrictor release
- Blockade of action of vasoconstrictors

Decrease Cardiac Output

Decreased sympathetic cardiac tone
- Decreased central sympathetic activity
- Blockade of sympathetic ganglionic transmission
- Impairment of cardiac neuroeffector transmission

Decreased cardiac reactivity
- Increased vagal activity
- Depression of myocardial reactivity directly

Decreased cardiac return
- Decreased venomotor tone (and thereby increased venous capacitance)
- Decreased circulating fluid volume

Adapted from Bowman WC, Rand MJ. *Textbook of Pharmacology.* 2nd ed. Oxford: Blackwell Scientific; 1980:23.26-23.58.

TABLE 26.5 Drugs and Their Physiologic Mechanisms for Lowering Blood Pressure

Neurogenically Acting Hypotensive Agents

Central depression of catecholamines—rauwolfia alkaloids, α-methyl DOPA, α_2 agonists, monoxidine
Ganglion blockers—pentolinium, hexamethonium, trimetaphan
Adrenergic nerve blockers—guanethidine, bethanidine, bretylium, monoamine oxidase inhibitors

Neurogenically Acting Vasodilators Acting on Adrenergic Receptors

α_1 blockers—prazosin, indoramin, doxazosin, and related compounds
α_1, α_2 blockers—phentolamine, phenoxybenzamine
α_1, β_1 blockers—labetalol, carvedilol, nebivolol
β_2 agonists—isoproterenol

Other Vasodilators

Renin–angiotensin system antagonists—angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, direct renin inhibitors
Nitrovasodilators—nitric oxide, sodium nitroprusside, nitroglycerin, isosorbide dinitrate, isosorbide mononitrate
Other vasodilators—hydralazine, minoxidil

Basic Pharmacology and Mechanisms of Action of Individual Drug Classes

Calcium Channel Blockers

These drugs have a direct dose-related effect on three separate functions of the heart (conduction, contraction, and inotropy), and on peripheral and coronary vascular tone. When used to treat high blood pressure, the major effect of these drugs is arterial vasodilation by blockade of Ca^{2+} influx through L-type voltage-gated Ca^{2+} channels in the smooth muscle cells of resistance vessels. They also reduce the increase in intracellular Ca^{2+} in response to membrane depolarization and the secondary Ca^{2+}-induced Ca^{2+} release from intracellular stores. Some calcium channel blockers also reduce heart rate and myocardial contractility, which leads to decreased cardiac output and blood pressure.

TABLE 26.6 Sites of Action of Vasodilator Drugs

Arteriolar	Both	Venodilators
Prazosin	Nitroprusside	Nitroglycerin
Phentolamine		
Phenoxybenzamine		
Tolazoline		
Hydralazine		
Diazoxide		
Calcium channel blockers		
Angiotensin-converting enzyme inhibitors		

There are 3 classes of calcium channel blockers. Difference in subunit structure of Ca^{2+} channels in vascular and cardiac tissues might explain the different selectivity of the drugs. The dihydropyridines act mainly on vascular smooth muscle of resistance vessels, while the nondihydropyridines act on the myocardium. All 3 classes act on voltage-gated Ca^{2+} channels that are made up of 5 subunits (α_1, α_2, β, γ, and δ). The α_2 and δ subunit dimer and γ subunit are transmembrane, while the β unit is located intracellularly. The α_1 subunit forms the transmembrane ion channel.

Dihydropyridines (e.g., nifedipine and nicardipine) bind to the extracellular domain of the L-type voltage-gated Ca^{2+} channel (Ca_V1) in the cell membrane, thus inhibiting Ca^{2+} influx.[10] These drugs primarily affect resistance vessels with minimal effects on veins owing to the low density of L-type Ca^{2+} channels in capacitance vessels.

Phenylalkylamines (e.g., verapamil) act mainly on the heart, where inhibition of voltage-gated Ca^{2+} channels is frequency dependent. The phenylalkylamines probably enter the cell and bind internally to produce their effects.[12]

Benzothiazepines (e.g., diltiazem) bind on the extracellular side of the L-type channel.[13] Their effects are greater on vascular compared with cardiac smooth muscle.

β Blockers

There are at least 3 distinct subtypes of β receptors (β_1, β_2, and β_3), each of which has different tissue distributions. Both β_1 and β_2 agonists mediate their cellular effects through increases in cyclic adenosine monophosphate (cAMP). β receptors are G protein–coupled receptors that traverse the lipid cell membrane 7 times. The N-terminal end of the protein is extracellular and the C-terminal end is intracellular. The region conferring β-receptor coupling is thought to lie in the third cytoplasmic loop between the fifth and sixth transmembrane segments (for further details on this receptor, see Chapter 1).

β_1 receptors are present mainly in heart muscle. The ligand–receptor complex is coupled to a Gs protein, which, in turn, activates adenylyl cyclase to produce cAMP. The cAMP activates protein

kinase A, leading to enhanced influx of Ca^{2+} and, in turn, muscle contraction.

β_2 receptors exist in heart muscle (hence the rationale for use of salbutamol in some patients with low-output states). However, they are more abundant in bronchial and peripheral vascular smooth muscle, where they lead to bronchodilation and vasodilation, respectively (see Chapter 30).

β_3 receptors are present in adipose tissue and heart muscle. In contrast to β_1 and β_2 adrenoceptors, activation of β_3 leads to a *decrease* in inotropic state of the myocardium via a Gi protein–dependent pathway. Thus, as well as having an effect on thermogenesis, β_3 activation can lead to cardiodepressant effects.[14]

Action of β Blockers at Adrenergic Receptors

Administration of some β blockers restores receptor responsiveness to catecholamines after β receptor desensitization, leading to normal GRK2 activity (G protein–coupled receptor kinase 2; also known as BARK1, or β adrenoceptor kinase 1) and receptor protein subunit $G_{\alpha 1}$ levels. Other β blockers allow intracellular signaling to return toward normal despite concurrent catecholamine stimulation. A third class of β blockers (including metoprolol and carvedilol) have an additional property in reversing the effects of cardiac remodeling. These differences in action could explain why some β blockers protect myocytes more effectively than others and why all are not equally effective in reducing perioperative ischemia, myocardial infarction, and cardiac mortality.[15,16]

β receptors can exist in 3 distinct activation states: stabilized and inactivated, nonstabilized and inactivated, or stabilized and activated. Normally, there is a dynamic equilibrium between the activated and the 2 inactivated states. Drugs that stabilize the receptor in the activated state are either partial or full agonists; drugs that push the equilibrium toward the inactivated state are either full or partial agonists; drugs that block access to the receptor binding site without affecting the state of equilibrium are termed *neutral* (competitive) *antagonists* (see Chapter 1).

At the molecular level, some β blockers incompletely stabilize the activated state of the receptor, leading to a coupling of the receptor to the G protein (these are therefore partial agonists—bucindolol, xamoterol). They block the effects of potent agonists while generating low-level β adrenoceptor stimulation on their own. Other β blockers stabilize the receptor in the inactivated state, thus leading to receptor upregulation rather than the desensitization and downregulation seen with xamoterol. Such drugs are inverse agonists (metoprolol, nebivolol, sotalol). However, most of the β blockers are neutral or competitive antagonists in that they bind to the β receptor without affecting its activation state.

These different molecular actions give rise to drugs with different clinical profiles. Thus, the β_1 selective blockers (acebutolol, atenolol, bisoprolol, celiprolol, esmolol, xamoterol) diminish detrimental cardiac remodeling while preserving the protective effects of β_2 activation. The β_1, β_2, and α_1 blockers (e.g., bucinodolol, carvedilol, labetalol) decrease arterial vascular tone and serve as effective afterload-reducing drugs; they also block the deleterious effects of sympathetic hyperactivity. The partial inverse agonists (metoprolol and nebivolol) might reduce β receptor desensitization while maintaining functional β receptor responsiveness.

β adrenoceptor blocking drugs act by competitive antagonism. Their action to reduce blood pressure is by both decreasing cardiac output (through their effects on contractility and heart rate) and by inhibiting renin release from the kidneys. There are several ways of classifying the pharmacologic effects of β adrenoceptor blockers, depending on their receptor specificity: the presence of either intrinsic sympathomimetic or vasodilator activity and their lipophilicity or hydrophilicity (Table 26.7).

TABLE 26.7 Classification and Relative Potency of β Blockers Used for Treatment of Hypertension

Antagonists*	Partial Agonists (ISA)*
Selective	
Atenolol (1)	Acebutolol
Metoprolol (3)	Practolol
Esmolol (0.02), landiolol	
Bisoprolol	
Nonselective	
Propranolol (1)	Oxprenolol (1)
Timolol (10)	Alprenolol
Nadolol	Pindolol (20)
Sotalol (0.1)	

Vasodilators: labetalol (0.25), celiprolol, carvedilol, nebivolol.
ISA, Intrinsic sympathomimetic activity.
*Number enclosed in parentheses indicates potency relative to propranolol at the β_1 receptor.

The *β_1 selective agents*—such as atenolol, bisoprolol, and metoprolol—are cardioselective, although this selectivity is reduced at higher doses. The pure β adrenoceptor blocking drugs do not cause vasodilation. These agents diminish the detrimental effects of myocardial remodeling while preserving the protective effects of β_2 activity.[17,18]

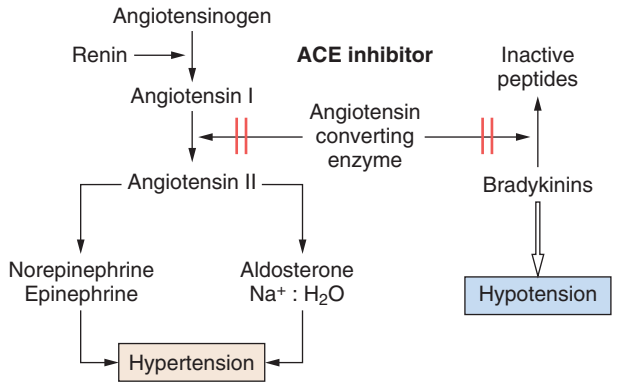
Nonselective (β_1 and β_2) agents have similar effects to the selective agents on blood pressure.

Partial agonists (pindolol) result in less resting bradycardia and some peripheral vasodilation.

Vasodilator activity is also produced by drugs with antagonist action at α receptors (labetalol, celiprolol, carvedilol) or by agents that promote endothelial nitric oxide production via the L-arginine-NO (nitric oxide) pathway (nebivolol).[19] The use of these drugs with vasodilatory properties can be advantageous when treating hypertension. One of the first drugs of this type (celiprolol) is formulated as a racemic mixture, is hydrophilic, and acts as a β_1 antagonist, mild β_2 agonist, and weak vasodilator.[20] Celiprolol also causes an increase in myocardial inducible NO synthase activity.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Antagonists

Renin is a protease synthesized in the kidney that catalyzes the production of angiotensin I from angiotensinogen (a 225 amino acid prohormone). Angiotensin-converting enzyme (ACE) then biotransforms angiotensin I to angiotensin II—the latter being a vasoconstrictor through action at angiotensin receptors. The molecular mechanism of action for angiotensin II is through coupling to the phospholipase C Gq protein–IP_3 transduction pathway. Angiotensin II also affects norepinephrine kinetics through facilitation of its release and prevention of its reuptake at sympathetic nerve terminals. The renin–angiotensin pathway can therefore be interrupted at two separate sites (both leading to vasodilation):



• **Fig. 26.2** Mechanisms of action of angiotensin-converting enzyme inhibitors with inhibition of conversion of angiotensin I to angiotensin II, and inhibition of the breakdown of bradykinin to inactive peptides.

direct inhibition of ACE and angiotensin receptor antagonism (Fig. 26.2).

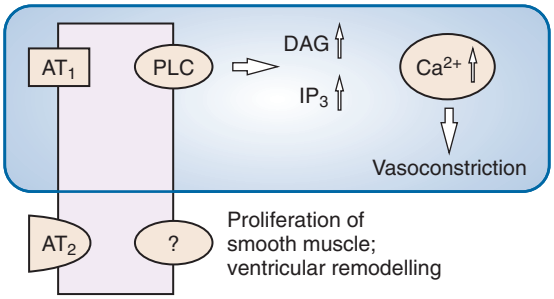
ACE inhibition occurs both in plasma and in the vascular endothelium. Inhibition also reverses arteriolar hypertrophy that occurs in hypertension and reduces left ventricular hypertrophy. ACE inhibitors decrease conversion of angiotensin I to angiotensin II, thereby reducing vasoconstrictor effects, aldosterone secretion, and sympathetic activation (see Chapter 40). Angiotensin II acts on AT_1 receptors via Gq to activate phospholipase C. This has the effect of increasing intracellular diacyl glycerol (DAG) and IP_3, which increase Ca^{2+} release from the sarcoplasmic reticulum (SR) to cause vasoconstriction of the efferent arteriole.[21] Stimulation of the AT_2 receptor leads to smooth muscle proliferation and ventricular remodeling (Fig. 26.3).

Both ACE inhibitors and AT receptor antagonists produce arterial vasodilation by limiting the direct effects of angiotensin II on vascular smooth muscle and minimizing its ability to increase sympathetic vascular tone. Their action is accompanied by an increase in parasympathetic tone. They also decrease the effect of aldosterone on the distal convoluted tubule of the nephron, thus promoting salt and water loss. They also block breakdown of bradykinin, which, in turn, contributes to the vasodilator effects of the drugs.

ACE inhibitors prevent the breakdown of kinins; the increased concentration of bradykinin is probably responsible for the unwanted side effects of cough and allergic reactions. Other side effects of ACE inhibitors include diarrhea. On the other hand, the angiotensin receptor antagonists prevent the vasoconstrictor effects of angiotensin II without affecting ACE activity.[10] Thus, in contrast to ACE inhibitors, they do not affect kinin production (hence, cough is not a prominent side effect of these drugs). These drugs act as selective blockers at the AT_1 receptors, with no effect on AT_2 receptors.

Diuretics

The action of diuretics to reduce blood pressure is twofold. First, they cause an initial decrease in intravascular volume, although compensatory mechanisms are activated and this effect is reduced over time. They have a secondary mechanism to reduce blood pressure by direct arterial vasodilation. The exact mechanism involved is not clear but might be through a decrease in Ca^{2+} entry into smooth muscle cells and through stimulating local vasodilator prostaglandin formation. Although the decrease in intravascular



• **Fig. 26.3** Mechanism of action of angiotensin II receptor blockers (at the AT_1 and AT_2 angiotensin receptors). *DAG,* Diacylglycerol; *IP_3,* inositol trisphosphate; *PLC,* phospholipase C.

volume and total body Na^+ occurs within weeks of the start of diuretic therapy, an increase in renin release causes them to return to normal. The antihypertensive effects of diuretics are not just related to their effects on Na^+ and water balance, because more effective diuretic agents (e.g., furosemide) are not very effective hypotensive agents.

There are 3 main classes of diuretics (see Chapter 42):

1. *Thiazides* inhibit Na^+/Cl^- co-transporters in the proximal diluting segment of the distal collecting tubule and early collecting duct. The diuretic effect of the thiazides (except metolazone and indapamide) is less effective in patients with renal impairment.[22] If used long term, thiazides inhibit maximal reabsorption of Na^+ to about 3% to 5% of the filtered load.
2. *Loop diuretics* have a short duration of action and hence are rarely used as first-line drugs for treatment of hypertension. They act on the medullary and cortical thick ascending limb segments of the nephron to prevent Na^+, Cl^-, and water reabsorption. There is some debate as to whether they also have other actions, such as systemic vasodilation and a reduction in left ventricular filling pressure secondary to preload reduction due to venodilation. However, they are useful if volume expansion contributes in part to the etiology of the hypertension (in patients with renal failure or from use of vasodilator drugs).
3. Of the *potassium-sparing diuretics,* both amiloride and triamterene have weak antihypertensive effects. However, spironolactone (an aldosterone antagonist) can be useful as an antihypertensive treatment in primary or secondary hyperaldosteronism or if the hypertension is treatment resistant. This class of diuretics has relatively weak natriuretic effects, with a maximal excretion of only about 1% to 2% of filtered Na^+ load.[23]

Centrally Acting Agents

Most centrally acting antihypertensive drugs are no longer widely used. However, identifying their sites of action illustrates the diversity of approaches used to reduce blood pressure.

Reserpine acts to deplete neuronal stores of catecholamines both centrally and peripherally at the postganglionic neuron. Its mechanism of action is related to inhibition of norepinephrine and dopamine uptake into terminal synaptic vesicles, leading to increased breakdown of norepinephrine and reduced conversion of dopamine to norepinephrine. Although reserpine crosses the blood-brain barrier, this is probably not the site of its antihypertensive effect.

Bethanidine, guanethidine, and debrisoquin are selective postganglionic neuron blockers that act to inhibit release of norepinephrine from peripheral sympathetic nerve terminals.

Although the exact mechanism of action of these drugs is not clear, there is evidence that the drugs must be actively taken up into neurons, where they accumulate in synaptic vesicles, causing norepinephrine depletion. Their antihypertensive effects are through reduced adrenergic synaptic transmission.

α_2 Adrenoreceptor Agonists

α_2 Receptor agonists have several distinct pharmacologic effects—sedation, analgesia, and hypotension. The α_2 adrenoceptor is coupled to a Gi protein complex, which inhibits adenylyl cyclase and Ca^{2+} and K^+ ion channels. The net result of α_2 agonist binding is reduced cAMP production, hyperpolarization, and decreased intracellular Ca^{2+}. α_2 Receptors occur both presynaptically and postsynaptically. Stimulation of presynaptic α_2 receptor decreases central sympathetic outflow. Agonist stimulation of postsynaptic α_2 receptors mediates the sedative and analgesic effects.[24]

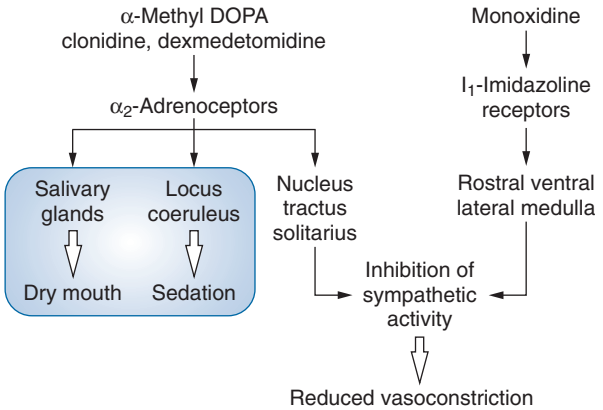
Some of the earliest antihypertensive therapies were based on drugs acting on the control mechanisms in the central nervous system (CNS). There are α_2 adrenoceptors in the locus coeruleus in the floor of the fourth ventricle, where α_2 agonists act to cause sedation. The locus coeruleus also has afferent connections from the rostral ventrolateral medullary nuclei and efferent connections to noradrenergic fibers connecting to the thalamus and elsewhere. The α_2 agonists also block salivary gland secretion. Effects in the nucleus tractus solitarius lead to inhibition of sympathetic activity and reduce peripheral vasoconstriction. These drugs are no longer widely used in the treatment of hypertension, with the exception of α-methyl DOPA for treatment of preeclampsia of pregnancy.

Excessive hypotension secondary to α_2 agonist therapy can be reversed by vasopressors and inotropes. The use of ephedrine, phenylephrine, and dobutamine, but not norepinephrine, can be accompanied by an enhanced pressor response due to the β effects of these agents.

There are three main classes of α_2 agonists: (1) the phenylethylates (α-methyl DOPA, guanabenz), (2) the imidazolines (clonidine, dexmedetomidine, mivazerol), and (3) the oxaloazepines.

α-Methyl DOPA is converted in noradrenergic neurons to the false transmitter α-methyl norepinephrine, which is a potent α_2 agonist. It stimulates brainstem postsynaptic α_2 receptors to decrease sympathetic tone and systemic vascular resistance.

Clonidine acts as a presynaptic α_2 agonist on receptors in the brainstem, leading to reduction in sympathetic outflow and an increase in vagal activity. After intravenous dosing, there can be an initial transient hypertensive response due to peripheral vasoconstriction through α_1 and α_{2B} interactions. In contrast to α_2 agonists, such as α-methyl DOPA, imidazoline compounds produce hypotension following direct intramedullary injection. This led to the proposal of the presence of nonadrenergic receptors in the lateral reticular nuclei of the ventrolateral medulla (VLM). Two types of nonadrenergic imidazoline receptors have been identified: I_1 receptors in the brain and I_2 receptors in the brain, pancreas, and kidney. A number of the α_2 agonists also have activity at I_1 receptors. It is likely that they mediate their effects through a G protein–coupled mechanism that results in an increase in arachidonic acid and the subsequent release of prostaglandins. This led to the development of two specific I_2 receptor agonists with more ideal hemodynamic profiles: monoxidine and rilmenidine. Both drugs have a weaker affinity for central α adrenoreceptors than α-methyl DOPA and clonidine. Other α_2 agonists include dexmedetomidine, which has a greater selectivity and specificity for α_2 receptors than clonidine (α_2 : α_1 1620:1 compared with 200:1); and mivazerol (119:1; Fig. 26.4). This latter sympatholytic drug has been examined for a role in myocardial protection, but there are no published studies examining its use in the treatment of perioperative hypertension.[25]



• **Fig. 26.4** Mechanisms of action of α_2 adrenoreceptor agonists and I_1 imidazoline receptor agonists.

Monoxidine is a selective imidazoline receptor agonist that stimulates I_1 receptors in the VLM, thereby decreasing sympathetic outflow and lowering blood pressure. In contrast to some other drugs, its use is not associated with a reflex tachycardia.

α_1 Adrenoreceptor Antagonists

Agonists of the α_1 adrenoreceptor leads to an increased intracellular Ca^{2+}. The α_1 agonist–receptor interaction leads to activation of phospholipase C (linked to Gq), which increases hydrolysis of phosphatidylinositol bisphosphate (PIP_2) and increases synthesis of the second messengers DAG and 1,4,5-inositol trisphosphate (IP_3). DAG activates protein kinase C while IP_3 increases the intracellular Ca^{2+} concentration by releasing Ca^{2+} from the SR. There is also evidence that IP_3 causes an increase in the Ca^{2+} sensitivity of the contractile proteins. The phosphorylated product of IP_3 (IP_4—1,3,4,5-inositol tetraphosphate) has been suggested as the messenger that enhances Ca^{2+} flux across the cell membrane, causing vasoconstriction.

The α_1 selective antagonists block α_1 receptors to prevent Ca^{2+} increases, thus leading to smooth muscle relaxation in arterioles and venous capacitance vessels.

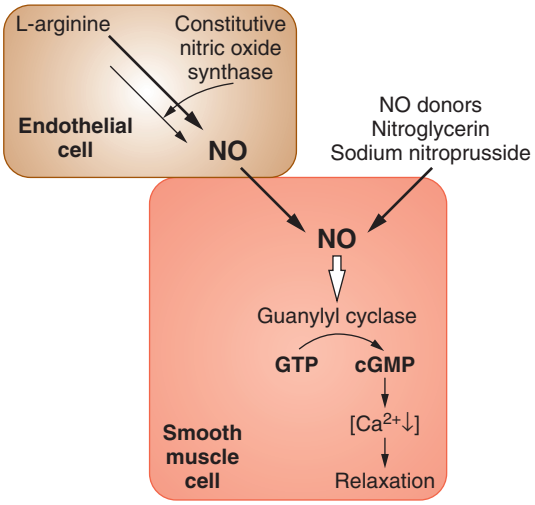
There are two types of α_1 antagonists:

1. Selective α_1 antagonists: doxazosin, terazosin, prazosin, and indoramin
2. Nonselective α_1 antagonists: phentolamine and phenoxybenzamine

While the selective antagonists act in a competitive manner, phenoxybenzamine combines irreversibly with the α_1 receptors and so has a prolonged duration of effect. Phentolamine is a short-acting, reversible antagonist.

Nitrovasodilators

NO was identified as the "endothelium-dependent relaxing factor" by Furchgott and Zawadski in 1980[26] and its mechanism was defined by Palmer and colleagues.[27] NO is an endogenous vasodilator that causes renal vasodilatation, leading to a diuresis and natriuresis and resulting in reduced blood pressure. There is some suggestion that deficiency in NO could contribute to the etiology of high blood pressure.



• **Fig. 26.5** Mechanism of action of nitric oxide and nitric oxide donors on vascular smooth muscle. *cGMP,* Cyclic guanosine monophosphate; *GMP,* guanine monophosphate; *GTP,* guanine triphosphate; *NO,* nitric oxide.

NO stimulates guanylyl cyclase to produce cyclic guanosine monophosphate (cGMP), which activates cGMP-dependent protein kinase (PKG). PKG then activates myosin light chain phosphatase (MLCP) to dephosphorylate myosin light chains and hence produce vascular relaxation.[28] NO also activates sarcoplasmic and endoplasmic reticular Ca^{2+}-ATPase to enhance reuptake of Ca^{2+}, an effect that is cGMP independent. NO might also activate K^+ channels, resulting in membrane hyperpolarization, thus closing voltage-gated Ca^{2+} channels (Fig. 26.5).

There are a number of NO donors. Some vasodilators release NO spontaneously (sodium nitroprusside) while others (organic nitrates such as nitroglycerin) need active reduction of the nitrate radical by intracellular sulfhydryl groups. All NO donors are potentiated by phosphodiesterase-5 inhibitors that reduce hydrolysis of cGMP (see later discussion).[29]

Nitrites act as both arterial and venous dilators. They are usually associated with a reflex increase in heart rate; hence they are often coadministered with β blockers.

Sodium nitroprusside (SNP) is broken down in red cells with liberation of cyanide and NO. SNP has a rapid onset of action and is of short duration (1–2 minutes). While breaking down to form NO, SNP interacts with oxyhemoglobin to form cyanmethemoglobin and cyanide.[30] The latter is converted to thiocyanate through transsulfation by the liver enzyme rhodanase, with thiosulfate acting as the sulphur donor. There are still issues over the total safe dose of SNP. Prolonged administration leads to accumulation of thiocyanate and cyanide, with the development of venous hyperoxemia and metabolic acidosis.

Nitrates undergo denitration to produce NO, their active component. Denitration can involve reaction with sulfhydryl groups or depends on the action of glutathione-S-transferase, cytochrome P450, and xanthine oxidoreductase. A stepwise increase in the dose of infused nitrate leads to a reduction in venous tone and central venous pressure. This is accompanied by a gradual decrease in systemic pressure. Administration of bolus doses of nitrates causes significant and immediate decreases in arterial pressure.

Glyceryl trinitrate (GTN), or nitroglycerin, acts as an NO donor, with a greater action on venous rather than arteriolar vessels. Its use can lead to tachyphylaxis due to a decrease in NO formation through generation of superoxide and peroxynitrite free radicals that inhibit aldehyde dehydrogenase. Without this enzyme, the conversion of organic nitrates and nitroglycerin to NO is impaired. In addition to decreasing blood pressure, nitroglycerin also reduces preload and myocardial oxygen demand. Nitroglycerin is a coronary vasodilator (including relaxation of stenosed vessels) and brings about an increased collateral coronary flow, improved subendocardial perfusion, and improved diastolic function. Because nitroglycerin undergoes extensive first-pass metabolism after oral dosing, nitrates are administered orally as isosorbide dinitrate (ISDN) and its metabolite isosorbide mononitrate (ISMN). Although the main use of nitroglycerin, ISDN, and ISMN is for antiangina therapy, they can also be used by titration for the control of blood pressure in the cardiac patient.

Adenosine stimulates purinergic receptors (P_1 and P_2) on endothelial cells to stimulate NO production. Adenosine also has direct effects on smooth muscle via a G protein–coupled pathway and activates ATP-sensitive K^+ channels, leading to membrane hyperpolarization and relaxation.[31,32] Adenosine receptor blockers prevent Ca^{2+} entry during phase 1 of the action potential, thus causing vascular relaxation. Although predominantly a coronary vasodilator, it can decrease blood pressure. It is not absorbed from the gut; thus, it is given by the intravenous route. The half-life after intravenous dosing is less than 10 seconds. It is intracellularly phosphorylated to AMP and then deaminated to inosine, hypoxanthine, xanthine, and uric acid. Both theophylline and other xanthines are antagonists at both P_1 and P_2 receptors; hence, their concurrent use increases dose requirements for adenosine. The uptake of adenosine into coronary endothelial cells is inhibited by dipyridamole.

Other Vasodilators

Minoxidil opens ATP-sensitive K^+ channels in vascular smooth muscle, hyperpolarizes the cell membrane, and closes voltage-gated Ca^{2+} channels, leading to smooth muscle relaxation and vasodilation.[33]

Hydralazine acts by promoting the influx of K^+ into vascular smooth muscle cells, thereby causing hyperpolarization and muscle relaxation.[34] It can also cause arterial vasodilation by promoting smooth muscle relaxation through activation of guanylyl cyclase, leading to an increase in cGMP. Other mechanisms of action include inhibition of Ca^{2+} release from the SR, reduction in Ca^{2+} stores in the SR, and stimulation of NO formation by the vascular endothelium.

Diazoxide is chemically similar to thiazide diuretics but causes Na^+ retention. It is a powerful antihypertensive agent due to peripheral vasodilation secondary to opening K^+ channels.

Nicorandil promotes vasodilation of both systemic and coronary arteries by opening ATP-sensitive K^+ channels, hyperpolarization of the membrane, and reduced opening of voltage-gated Ca^{2+} channels and therefore vascular smooth muscle relaxation. This is enhanced by the local production of NO from a nitrate-like action that also causes venodilation.[35]

Ganglionic blockers formerly played a significant role in the modulation of blood pressure. Now, only trimethaphan is used (rarely) in hypertensive emergencies or for the production of controlled hypotension during surgery. Ganglionic blockers act by inhibiting autonomic activity at both sympathetic and parasympathetic ganglia. The decrease in sympathetic outflow causes vasodilation.

Magnesium affects vascular tone by diverse mechanisms; it acts as a Ca^{2+} channel antagonist, stimulates production of vasodilator

prostaglandins and NO, and alters the response of vascular endothelium to vasoactive agonists.[36]

Endothelin receptor antagonists reduce blood pressure by blocking the actions of endothelins. Endothelins act on both ET_A and ET_B receptors. Endothelin 1 (ET-1) causes vasoconstriction through activation of both types of receptor on vascular smooth muscle cells. The receptors are coupled to Gq, with activation leading to increased synthesis and release of IP_3 and Ca^{2+} release from the SR.[37,38] ET-1 synthesis and release is stimulated by a number of mediators: angiotensin II, arginine vasopressin, thrombin, cytokines, reactive oxygen species, and shear forces on the endothelium. Mixed ET receptor antagonists lower arterial blood pressure and prevent vascular and myocardial hypertrophy. Use of these drugs has also been studied in the treatment of pulmonary hypertension.

Peripheral dopamine (DA) agonists cause selective vasodilation of a number of vascular beds (splanchnic, cerebral, and coronary circulations) and can therefore be used in the treatment of hypertension. There are two subtypes of peripheral DA receptors. DA_1 receptors are postsynaptic Gs protein–coupled receptors and cause vasodilation following increased intracellular cAMP and reduced intracellular calcium. DA_2 receptors are presynaptic and coupled to Gi protein, leading to reduced cAMP, with membrane hyperpolarization and reduced norepinephrine release. The effects of dopamine on various catecholamine receptors are dose dependent: DA_1 interactions occur at low doses, β_1 at moderate doses, and α_1 with high doses (see Chapter 25).

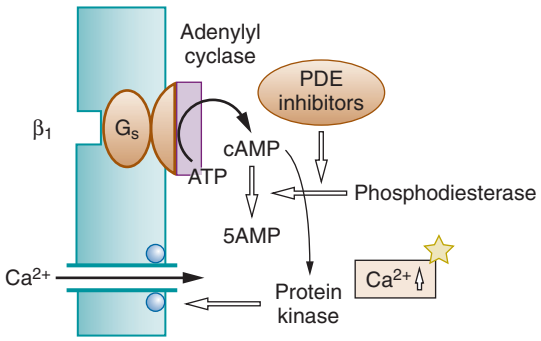
Fenoldopam is a selective DA_1 receptor agonist without adrenergic receptor agonist properties. It is more potent than dopamine at DA_1 receptors and is useful for control of blood pressure. It also has no agonist effects at the DA_2 receptor. As such, it causes a decrease in blood pressure without increases in heart rate or contractility due to adrenergic effects. An advantage of the drug is that it does not cross the blood-brain barrier. It is available in the United States and some European countries, where it is recommended for acute or emergency control of blood pressure in the perioperative period.[39]

Phosphodiesterases catalyze the hydrolysis of cyclic nucleotides. Phosphodiesterase inhibitors (PDEIs) block the hydrolysis of cAMP or cGMP, prolonging the effects on smooth muscle of signaling pathways involving these second messengers.[40,41] An increase in cAMP (or cGMP) leads to phosphorylation of myosin light chain kinase, leading to a reduction of its activity due to reduced affinity for the Ca^{2+}-calmodulin complex. The resulting reduced phosphorylation of myosin light chains leads to smooth muscle relaxation and vasodilatation. There are five subtypes of phosphodiesterase; PDE3 is inhibited by milrinone and enoximone, and PDE5 is inhibited by sildenafil and related compounds (see later discussion).

PDE3 inhibition prevents the breakdown of cAMP. Specific phosphodiesterases also hydrolyze cGMP, which might contribute to the vasodilator effect of PDE5 inhibitors. As a result of the inhibition of cyclic nucleotide breakdown, PDEIs cause a decrease in systemic vascular resistance and a small but significant fall in arterial pressure (Fig. 26.6).

Prostaglandins PGE_1 and PGI_2 (prostacyclin) have direct vasodilator actions via prostanoid receptors on vascular smooth muscle involving stimulation of cAMP. Although they decrease systemic vascular resistance (and, therefore, blood pressure), their main effect is on pulmonary vascular resistance (see later discussion).

A number of other drugs are also vasodilators. These include ganglion-blocking neuromuscular blocking drugs (tubocurarine derivatives), general anesthetics, and histamine.



• **Fig. 26.6** Mechanism of action of phosphodiesterase (PDE) inhibitors. *β_1,* β_1 Adrenoceptor; *cAMP,* cyclic adenosine monophosphate; *5AMP,* 5′ adenosine monophosphate; *Gs,* stimulatory subunit of the G protein complex.

Pharmacokinetics, Pharmacodynamics, and Adverse Effects

Calcium Channel Blockers

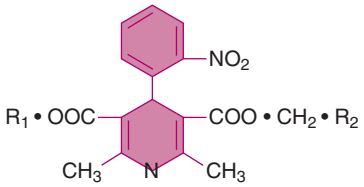
All calcium channel blockers are effective in reducing blood pressure, although there is some controversy over the adverse effects of short-acting drugs.[42] In general, they are all well tolerated and are becoming the first-line treatment for patients older than 55 years. The actions of the three classes of calcium channel blocking drugs differ. The relationship between vasodilation and negative inotropy is about 1:1 for both diltiazem and verapamil, 10:1 for nifedipine, and up to 1000:1 for the newer dihydropyridines.[43] In the same way, the side effects of calcium channel blockers differ according to the class of drug.

Verapamil (a phenylalkylamine) is a racemic mixture that is well absorbed orally and has high presystemic metabolism (about 85%; L-enantiomer > D-enantiomer). Metabolism is extensive by O-demethylation (25%) and N-dealkylation (40%) followed by conjugation. Some of the metabolites are active, especially norverapamil, which has about one-fifth to one-tenth the activity of the parent drug. Verapamil has a half-life of about 5 hours (range, 2–7 hours), which can be prolonged in patients with liver disease. The clearance of L-verapamil is greater than that of the D-enantiomer, although the half-lives of the 2 enantiomers are similar. There is greater free fraction of L-verapamil; hence, it has a greater volume of distribution. Verapamil is excreted in the urine (70%; as metabolites and unchanged drug) and feces.

Diltiazem (a benzothiazepine) is well absorbed orally (> 90%), but has a smaller fraction undergoing presystemic metabolism (about 50%). Diltiazem is extensively metabolized, and some of these metabolites are active.

All dihydropyridines (nifedipine, amlodipine, felodipine, isradipine, nicardipine, lacidipine, lercanidipine, nisoldipine) are well absorbed by the oral route (> 90%), but because of their significant presystemic metabolism, sublingual dosing is preferable for some (e.g., nifedipine). Presystemic metabolism of nifedipine results in inactive metabolites with half-lives of about 9 hours, while that of the parent drug is about 2 to 6 hours, with plasma protein binding of more than 90% and a small volume of distribution (0.3–1.2 L/kg). Metabolites are excreted in both the urine (80%) and feces.

Chemical substitutions in nifedipine at the R1 position, with introduction of long side chains (as amlodipine), produce drugs with a longer duration of action and a half-life of up to 30 to 40 hours (felodipine 12–36 hours; isradipine 2–8 hours; nicardipine



• **Fig. 26.7** Structure of the dihydropyridine calcium entry blockers. R_1 and R_2 are side chains at the 1 and 4 positions of the pyridine ring.

3–12 hours; amlodipine 35–60 hours; Fig. 26.7). The dihydropyridines are metabolized by hepatic cytochrome P450 (mainly CYP 3A4). Hence, there are many examples of drug–drug interactions either with CYP 3A4 inhibitors (the -azoles, -avirs, erythromycin, clarithromycin) or with other drugs competing for metabolism by the same isoform (e.g., midazolam, alfentanil, cyclosporin). Nifedipine shows a bimodal polymorphism of metabolism by CYP 3A4/5.

The calcium channel blockers all demonstrate age-related kinetics due to reduction in cardiac output (and liver blood flow), leading to increased bioavailability and decreased systemic clearance. Other side effects of dihydropyridine include vasodilation with flushing, headaches, ankle edema, and reflex tachycardia. The use of calcium channel blockers is contraindicated in patients with heart failure owing to their negative inotropic effects (especially the nondihydropyridines) and slowing of sinoatrial and atrioventricular node conduction, leading to bradycardia and heart block. Pronounced antihypertensive effects are mainly observed with the dihydropyridines. The decrease in blood pressure is accompanied by reflex tachycardia and increased myocardial oxygen utilization.

Adverse Drug Interactions

Dihydropyridines increase plasma digoxin concentrations by inhibiting their tubular secretion by interaction with P-glycoprotein.

Verapamil can worsen cardiac failure in affected patients, causing hypotension due to both vasodilation and negative inotropy. If verapamil is given in combination with a β blocker, patients can develop hypotension, asystole, and an increased incidence of arrhythmias.

Diltiazem reduces cardiac output and hepatic clearance of flow-limited drugs, such as propranolol and cyclosporin A. Both nondihydropyridines (diltiazem and verapamil) can cause bradycardia and heart block when administered in conjunction with β blockers. They can also exacerbate congestive heart failure through negative inotropic effects.

Newer Calcium Channel Blockers

Clevidipine (an intravenous dihydropyridine) is characterized by rapid onset of action, vascular selectivity, and unique pharmacokinetics. Unlike other drugs in this class, it is not metabolized in the liver but rather undergoes breakdown of an ester-linkage in blood and extravascular tissues to produce inactive carboxylic acid metabolites. This leads to a rapid onset of effect (within 60 seconds) and short duration of action. It is highly protein bound (> 99.5%) with a small volume of distribution (0.5–0.6 L/kg) and high clearance (0.105 L/kg/min). The rapid offset relates partly to its short elimination half-life (about 15 minutes). After infusions of up to 12 hours, the context-sensitive half-time of the drug is less than 2 minutes. Drug metabolism does not involve CYP enzymes; hence, its elimination is not affected by hepatic or renal disease and there are no significant drug–drug interactions documented to date.[44] Clevidipine might be useful for emergency control of blood pressure by careful titration of an intravenous infusion.[45,46]

β Blockers

There are two main chemical structural types of β blockers: (1) amino-oxypropanol derivatives (propranolol, timolol, pindolol, metoprolol, atenolol, esmolol, and carvedilol) and hydroxyaminoethyl compounds (sotalol and labetalol). Although described in Table 26.7 as β1 selective blocking drugs, metoprolol, celiprolol, and bisoprolol all show β2 antagonism at high doses. Most β blockers are well absorbed when given orally, although atenolol and sotalol, being more polar, have lower oral absorption (about 50%). Carvedilol, metoprolol, and propranolol all undergo extensive presystemic metabolism; bisoprolol shows no presystemic metabolism and is metabolized by only about 50%. Both atenolol and sotalol are eliminated in urine mostly unchanged. The principal kinetics and dynamics of some commonly used β blocking agents for treatment of hypertension are summarized in Table 26.8.

Propranolol is a nonselective β-blocking drug (although β_1 activity is greater than β_2 activity), with some membrane-stabilizing activity (MSA). It is highly lipid soluble and can therefore cross the blood-brain barrier, which can result in drug-induced depression. Propranolol undergoes extensive hepatic metabolism with less than 4% of the drug excreted unchanged in the urine and feces.

Oxprenolol is a β_1-selective blocker with intrinsic sympathomimetic activity (ISA) and MSA. Like propranolol, it is extensively metabolized, with less than 5% excreted unchanged in the urine.

Metoprolol is a highly selective β_1 drug with no MSA and no ISA. Metoprolol shows polymorphism with regard to its metabolism; some of the metabolites (especially α-OH-metoprolol and *O*-desmethyl-metoprolol) are active at the β_1 receptor. There can also be extrahepatic metabolism.

Pindolol is excreted in the urine as both unchanged drug (40%) and metabolites following oxidation and glucuronide conjugation.

Atenolol has properties similar to those of metoprolol. It is eliminated by renal excretion (90%) as unchanged drug. Being hydrophilic, there are few CNS side effects due to minimal blood-brain barrier transfer.

Bisoprolol is a β_1-selective blocker that is well absorbed orally. Elimination is via the kidney (50% unchanged and 50% as an active metabolite) following hepatic biotransformation.

Nadolol is a β_1-selective blocker that is eliminated solely by the kidney. Hence, its use is contraindicated in patients with renal impairment.

Timolol is a nonselective β blocker that is eliminated by both hepatic metabolism and renal excretion (20% as unchanged drug).

Bextalol is a cardioselective blocker that is well absorbed and undergoes minimal presystemic metabolism. It has a half-life of 13 to 24 hours and is metabolized by hepatic hydroxylation with little conjugation. The hydroxyl-metabolite is excreted in the urine, together with 10% to 17% unchanged drug.

Acebutolol, carteolol, penbutolol, and pindolol are all nonselective agents with some ISA. Acebutolol is biotransformed by hydrolysis and N-acetylation in the liver to an active metabolite, diacetolol, which has a long half-life of 10 to 14 hours. There can also be some drug metabolism in the gut following oral dosing.

Celiprolol is a third-generation selective β_1 blocker with no MSA. This agent has some ISA at the β_2 receptor, manifest as weak bronchodilation and vasodilation.

TABLE 26.8 Pharmacokinetics and Pharmacodynamics of Common β Blockers

	Oral ABSN (%)	Bioavail-ability (%)	$T_{1/2}$ (hr)	Plasma Protein (%)	Metabolic Route	β_1 selectivity	ISA	MSA	Vasodilation	Other
Acebutolol	>50	30–50	3–6	26	100% H	Yes	Yes	Yes	No	Nil
Atenolol	40–50	>90	6–7	<3	10% H	Yes	No	No	No	Nil
Bisoprolol	>95	80–90	9–13	30	50% H	Yes	No	No	No	Nil
Carvedilol	25	R30; S15	7–10	98	H	No	No	Yes	Yes	Yes[1]
Celiprolol	30–70	>85	4–6	30	Minimal	Yes	No	No	Yes	Yes[2]
Labetalol	>95	15–90	3–4	50	90% H	Yes	No	No	Yes	Yes[3]
Metoprolol*	50–70	40–50	3–7*	5–10	90% H, gut	Yes	No	No	No	Nil
Nadolol	30–40	>95	17–24	30	Minimal	No	No	No	No	Nil
Nebivolol*	?	12–96	12–19*	?	Extensive H	Yes	No	No	Yes	Yes[4]
Oxprenolol	90	20–70	1–2	80	Extensive H	No	Yes	Yes	No	Nil
Pindolol	>95	85–90	3–4	40	H	No	Yes	Yes	No	Nil
Propranolol	>95	5–50	3–6	80–95	100% H	No	No	Yes	No	Nil
Timolol*	>95	50	2–5	80	80%H	No	No	No	No	Nil
Esmolol	N/A	N/A	0.14–0.18	55	Rbc–esterase	Yes	No	No	No	Nil

*, Drug showing polymorphism; *ABSN,* absorption; *H,* hepatic; *ISA,* intrinsic sympathomimetic activity; *MSA,* membrane stabilizing activity; *plasma protein (%),* plasma protein binding; *Yes* [1], α_1, β_2 antagonism; *Yes* [2], β_2 agonism; *Yes* [3], β_1 and β_2 antagonism, some ISA at β_2; *Yes* [4], nitric oxide-potentiating vasodilatory effect.

Antihypertensive Effect of β Blockers

The exact mechanism by which β blockers reduce blood pressure is unclear. They could act through reduction in cardiac output that is not compensated for by baroreflex mechanisms and where there might be a resetting of the reflex. Some of the drugs (those that are lipophilic) can also have a central effect to reduce sympathetic outflow. Another antihypertensive effect can be through inhibition of renin release from the kidney.

Newer β Blockers

Carvedilol (α_1, β_1, β_2 blocker) has a unique carbazole moiety. It is a nonselective agent that also blocks the α_1 receptor. Carvedilol has some MSA but no ISA. It exerts a greater clinical effect than other β blockers in the management of congestive cardiac failure and postmyocardial infarction. It is also an antioxidant with antiarrhythmic, antiapoptotic, and antiproliferative properties that influence carbohydrate and lipid metabolism.[47] Carvedilol is metabolized by CYP 2D6 to an active metabolite (a 4-hydroxyphenol). Drug elimination is via the biliary route and excretion in the feces. Carvedilol has an elimination half-life of 7 to 10 hours.

Nebivolol is formulated as a racemic mixture. It is highly lipophilic and rapidly absorbed, with a peak effect of 0.5 to 2 hours. It has vasodilating properties that are mediated by stimulation of the L-arginine-NO pathway. It is available only as an oral preparation and undergoes extensive metabolism by glucuronidation and N-dealkylation and oxidation by CYP P450 2D6 with less than 0.5% excreted unchanged. Because of genetic polymorphism of CYP 2D6, bioavailability varies from about 12% in fast metabolizers to 96% in poor metabolizers, and the terminal half- life varies from 11 hours to 30+ hours, respectively.[19,48,49] Both carvedilol and nebivolol reduce blood pressure through a decrease in systemic vascular resistance rather than the proposed decrease in cardiac output (see later discussion).[47,49]

Adverse Effects of β Blockers

Because of differences in pharmacologic profiles, different β adrenoceptor blockers have varied *side-effect profiles,* but there are some common features:

- All β blockers have negative inotropic effects and can cause acute left ventricular failure when given in large doses to patients with impaired left ventricular function.
- All β blockers can exacerbate intermittent claudication and the Raynaud phenomenon in patients with coexisting peripheral vascular disease.
- Large doses of β blockers can cause bradycardia, leading to syncope.
- Nonselective β blockers that interact with β_2 receptors can result in bronchospasm in patients with asthma or chronic obstructive pulmonary disease owing to blockade of β_2 receptors.
- β Blockade can cause significant blood lipid effects, leading to increased triglycerides and decreased high-density lipoprotein cholesterol.
- Lipophilic β blockers that can cross the blood-brain barrier can cause CNS effects, leading to depression, sleep disturbances, vivid dreams, and hallucinations.
- Sudden withdrawal of β blockers results in increased catecholamine sensitivity; this upregulation can produce tachycardia, acute hypertension, and palpitations.

There are also important *drug interactions* involving β blockers:

- Cimetidine (a CYP inhibitor) decreases hepatic first-pass metabolism of propranolol and metoprolol and decreases the hepatic metabolism of bisoprolol.
- Carvedilol increases plasma concentrations of digoxin and the risk of toxicity.
- Concurrent administration of β blockers and verapamil increases risk of bradyarrhythmias and heart failure.
- Avoid use of sotalol in conjunction with other drugs that prolong the QT interval (e.g., amiodarone, disopyramide, procainamide, quinidine).
- All β blockers can potentiate the effects of insulin and other oral hypoglycemic drugs and can block the normal sympathetic responses to hypoglycemia. Some evidence suggests that this effect is more pronounced with nonselective β blockers.

Angiotensin-Converting Enzyme Inhibitors

Both captopril and enalapril are well absorbed orally, but absorption is decreased to 50% if taken in the presence of food. Captopril has limited presystemic metabolism (3%–14%), has a half-life of 1 to 2 hours, and has plasma protein binding of 30%. It undergoes both hepatic and renal elimination, with 50% excreted unchanged and 50% transformed to inactive metabolites.

Enalapril is the orally administered prodrug of the active compound enalaprilat (available for intravenous use), which is formed when enalapril undergoes extensive presystemic metabolism. Enalapril has a half-life of less than 1 hour, but enalaprilat has a long half-life of 35 hours. Enalaprilat is excreted unchanged in urine.

Lisinopril shows slow and poor oral absorption (< 25%) and is eliminated unchanged in the urine. It has a half-life of about 12 hours and low protein binding (3%–10%).

Ramipril is modestly well absorbed (about 60%) and undergoes some presystemic metabolism. Like enalapril, it is metabolized to the active form ramiprilat, which, in turn, undergoes partial excretion in the bile.

Other ACE inhibitor prodrugs include quinalopril and perindopril. The long half-lives of all the ACE inhibitors relate to their extensive binding to ACE in the plasma.

Angiotensin II Receptor Antagonists

Angiotensin II receptor antagonists act as competitive antagonists at the AT-1 receptor: currently, they are formulated only as oral medications. Candesartan is rapidly and completely de-esterified during absorption of candesartan axetil. It is highly protein bound, and undergoes part metabolism and part excretion in the bile. Unchanged drug is excreted in the urine. Candesartan has a half-life of about 10 hours, with a peak concentration at 3 to 4 hours.

Irbesartan is also rapidly and completely absorbed after oral dosing and undergoes minimal presystemic metabolism. The drug is 90% bound to plasma proteins. It is metabolized by oxidation (CYP 2C9) and glucuronidation, with a half-life of 12 hours. There are interactions between candesartan and other drugs metabolized by CYP 2CP in vitro, although no significant changes in disposition have been reported in vivo.

Losartan is well absorbed after oral administration but undergoes extensive presystemic metabolism by CYP 2C9 and 3A4. The parent drug has a half-life of 2 hours, but there is an active metabolite (with a half-life of about 8 hours). Peak concentrations of drug and metabolite occur at about 1 and 4 hours, respectively. Losartan is inactivated by further metabolism with two inactive metabolites excreted in the bile. Systemic bioavailability is double in patients with liver disease, but there is no change after oral dosing in patients with renal dysfunction.

Valsartan has a low systemic bioavailability (25%), reduced even further (to 15%) if administered with food. The drug is extensively protein bound (95%), mostly excreted in the bile and feces (83%), with 13% eliminated in the urine. There is no effect of renal failure on valsartan disposition. It has a half-life of about 6 hours.

Other drugs of this class are mainly longer acting (owing to longer elimination half-lives): eprosartan (5–9 hours), olmesartan (about 13 hours), and telmisartan (16–23 hours).

Adverse Effects and Drug Interactions

Hypotension is associated with intravascular volume depletion due to accompanying diuretic therapy.

ACE inhibitors can cause renal impairment and hyperkalemia, especially in patients with renal artery stenosis, as perfusion of the affected kidney depends on the local production of angiotensin. Rashes are seen in about 10% of patients and can be accompanied by fever and eosinophilia. Rarely, this is associated with episodes of angioneurotic edema.

Coadministration of nonsteroidal antiinflammatory drugs (NSAIDs [cyclooxygenase inhibitors]) can reduce the hypotensive effects of ACE inhibitors. ACE inhibitors can inhibit the excretion of lithium and can result in lithium toxicity. Angiotensin II receptor antagonists can cause hypotension if coadministered with diuretics. They should be used with caution in patients with renal failure, because they rarely lead to hyperkalemia.

Because these drugs do not affect the breakdown of kinins (as is seen with the ACE inhibitors), patients do not develop episodes of coughing and rarely develop angioneurotic edema.

Diuretics

Diuretics are discussed in more detail in Chapter 42.

Thiazides are all absorbed when given orally and are excreted unchanged by the kidney. Half- lives range between 3 and 90 hours. Chlorthalidone is well absorbed (60%–70%), with negligible presystemic metabolism. Unlike some other thiazides, it has a long half-life (50–90 hours), with protein binding of 75%.

Loop diuretics act by inhibiting Na^+ and K^+ reabsorption in the ascending loop of Henle by inhibiting $Na^+/K^+/Cl^-$ co-transport. *Furosemide* is poorly absorbed (50%–65%), with poorer absorption in the presence of heart failure, is excreted mainly unchanged in the urine, has a plasma half-life of about 1 hour, and high protein binding (96%–98%). *Bumetanide* drug is well absorbed following oral administration (65%–95%). About 60% is excreted unchanged in the urine, with the rest being metabolized by the liver and excreted in urine and bile. Bumetamide has a half-life of 1.5 hours, volume of distribution of 9.5 to 35 L, and high protein binding (95%). As is seen with furosemide and the thiazides, bumetamide, in the presence of hypokalemia, potentiates the effects of glycosides and other antiarrhythmic drugs, thus increasing the incidence of arrhythmias.

Diazoxide is well absorbed orally (85%–95%) and has a long half-life (20–40 hours) and high protein binding (90%).

Amiloride shows poor oral absorption, with no presystemic metabolism. It has low protein binding, with a large volume of distribution (5 L/kg). Amiloride is almost completely excreted unchanged in urine and has a plasma half-life of 6 to 9 hours.

Spironolactone is an aldosterone antagonist that is well absorbed orally, with a short half-life of 10 minutes. It is metabolized in

the liver to the active compound canrenone, which has a half-life of 16 hours and is excreted by the kidney. Protein binding is high (98%). Because of the long half-life of its metabolite, spironolactone has a long duration of action, with the maximum effect of the drug taking some days to be reached.

Triamterene undergoes incomplete (30%–83%), although rapid, absorption from the gut. There is some presystemic metabolism, and it is extensively biotransformed in the liver before urinary excretion and variable biliary excretion. The elimination half-life is about 2 hours, with protein binding of 45% to 70%.

Adverse Effects and Drug Interactions

There are important side effects of all diuretics. Prolonged use of thiazides (especially in older adults) can lead to hyponatremia and hypokalemia and an increased plasma uric acid concentration. Prolonged hypokalemia, in turn, leads to impaired glucose tolerance due to inhibition of insulin release and enhancing digitalis toxicity. Whereas thiazides cause a reduction in Ca^{2+} excretion, the loop diuretics increase Ca^{2+} excretion.

Both groups of diuretics reduce clearance of lithium by the kidney (which increases the risk of toxicity, as the latter has a narrow therapeutic range). Hypokalemia potentiates the effects of cardiac glycosides and alters the effects of antiarrhythmic drugs, leading to ventricular arrhythmias (torsade de pointes).

All potassium-sparing diuretics (amilioride, spironolactone, and triamterene) potentiate additively the potassium-sparing effects of ACE inhibitors; therefore, their coadministration can lead to dangerous hyperkalemia. In addition, the potassium-sparing diuretics can lead to hyperkalemia in patients also receiving potassium supplements or in patients with renal failure. These diuretics can also cause renal failure when coadministered to patients receiving NSAIDs. Spironolactone interferes with the assay of digitalis. Triamterene inhibits the urinary excretion of the antiparkinsonian drug amantadine.

α_2 Adrenoreceptor Agonists

There are no available data to suggest that α_2 agonists are useful for the rapid control of blood pressure in the perioperative period. They are used in special circumstances for treatment of chronic hypertension.

Clonidine is the archetypal drug of this group. It is moderately lipid soluble, shows complete absorption after oral dosing, but undergoes limited presystemic metabolism (up to 25%). Clonidine has a peak effect at 1 to 1.5 hours and peak plasma concentration at 1 to 3 hours. Clonidine has a long half-life (12–24 hours), protein binding of 20% to 40%, and a large volume of distribution (2–4 L/kg). It is eliminated by both hepatic metabolism and renal excretion.

Dexmedetomidine was introduced into clinical practice principally as a sedative rather than antihypertensive. It is the D-enantiomer of medetomidine. Dexmedetomidine has a volume of distribution of 100 L and clearance of about 40 L/hr. There is high protein binding to albumin and α_1 glycoprotein, and it undergoes extensive hepatic biotransformation. Dexmedetomidine also has a weak inhibitory effect on CYP 2D6–mediated metabolism in vitro.

α-Methyl DOPA is incompletely absorbed following oral dosing and has variable (10%–60%) bioavailability. It has low protein binding (10%–15%), a half-life of 6 to 12 hours, and is eliminated through both the biliary tract and the kidney.

An important issue with these drugs is that all α_2 agonists have significant side-effect profiles. Central α_2 agonists (e.g., clonidine) cause decreased sympathetic activity, leading to postural or exertional hypotension. Other side effects include ejaculation failure and an effect on CNS-mediated sedation and drowsiness. Significant side effects of α-methyl DOPA include orthostatic hypotension, dizziness, sedation, dryness of the mouth, nasal congestion, headaches, and impotence. Rebound hypertension can occur on withdrawal but occurs less frequently than after cessation of clonidine. It can also cause a reversible positive Coombs test hemolytic anemia. I_1 receptor agonists (monoxidine) can cause dry mouth, nausea, fatigue, dizziness, and headaches.

α_1 Adrenoreceptor Antagonists

Phentolamine and Phenoxybenzamine

Phentolamine is a competitive nonselective antagonist of α_1 receptors, with a half-life of 3 to 13 hours and protein binding of 54%. Little more is known about its pharmacokinetics or metabolism, although it is excreted mainly unchanged by the kidney. Phentolamine has equal efficacy at α_1 and α_2 receptors and is a 5-hydroxytryptamine (serotonin) antagonist.

Phenoxybenzamine is a haloalkylamine that acts as a noncompetitive, irreversible antagonist. The half-life is 18 to 24 hours, but the duration of effect depends on the cellular turnover of receptors—with evidence of drug action for 3 to 4 days. It is biotransformed probably in the liver. The slow onset of effect is due to the need for initial conversion of its ring structure to a reactive carbonium ion, which covalently binds to the α_1 receptor.

There are common adverse effects for both drugs (similar to those of other drugs that decrease sympathetic outflow): vasodilation leading to a reflex tachycardia, orthostatic hypotension secondary to venous pooling, nasal congestion, and ejaculatory failure. Headaches, lethargy, dizziness, nausea, and urinary frequency also occur.

Although labetalol is normally classified as a β-receptor antagonist, it also shows nonspecific α-receptor antagonist properties.

Prazocin, doxazocin, and *terazocin* are all absorbed orally (up to 65% for doxazocin), undergo some presystemic hepatic metabolism, and are then mostly broken down in the liver by dealkylation followed by conjugation. All three drugs have high protein binding (90% to 98%).

Although the half-lives of the drugs vary (prazocin, 2–4 hours; doxazocin, 9–12 hours; terazocin, 11 hours), their therapeutic effects lasts longer (prazocin about 10 hours; doxazocin about 30 hours). Terazocin is eliminated unchanged in the urine and feces. There is need to reduce dosage of all 3 agents in patients with renal failure. This is not owing to drug or metabolite accumulation but rather to increased drug sensitivity. The exact mechanism is unclear but may be due to increased absorption, decreased first-pass metabolism, altered drug binding, or decreased volume of drug distribution.

Indoramin is also well orally absorbed (> 90%) but undergoes almost complete metabolism by presystemic metabolism. Indoramin has variable protein binding (72%–92%), a half-life of 2 to 10 hours, and might have active metabolites.

The antihypertensive effects of α_1 blocking drugs are enhanced by coadministration with other antihypertensive agents, especially diuretics and β blockers. α_1 Blockers should not be given in conjunction with MAOIs.

Vasodilators

Hydralazine

Hydralazine is well absorbed orally, undergoes presystemic metabolism, and shows extensive metabolism (65%–90%) by acetylation

(with a bimodal distribution). The half-life of hydralazine is 3 to 7 hours; because acetylation by NAT-2 occurs mainly during presystemic metabolism, the subsequent rate of drug clearance is not directly related to the rate of acetylation. There is a bimodal distribution of clearance; slow acetylators are at risk of developing a lupus-type condition. However, acetylator status does not appear to affect the half-life. Hydralazine has high protein binding (87%) and a large volume of distribution (3.6 L/kg).

The ratio of fast : slow acetylators in the population is racially determined. In Europe, the ratio is about 40:60, in Japan 85:15, and in the Inuit population 95:5. The consequences of this bimodal metabolic profile are twofold: first, slow acetylators can have an enhanced response to treatment; second, they can also have an increased risk of drug toxicity. The difference between fast and slow acetylators is not dependent on kinetic properties but rather on the amount of the NAT-2 isoform expressed. A reduced dose of hydralazine is indicated in the presence of renal and hepatic disease, regardless of the metabolic phenotype.

Nicorandil

Nicorandil acts as a mixed vasodilator with part nitrate-like action and part K^+ channel opening effect.[50] After oral twice-daily dosing, steady-state concentrations are reached by 96 to 120 hours, although there is an onset of effect by 30 minutes after dosing. Nicorandil undergoes extensive hepatic metabolism to an inactive denitrated metabolite that is excreted in the urine and has a short half-life (1 hour) and high clearance (about 1.1 L/min).

Side effects associated with the use of nicorandil include headache in 25% to 50% of patients on starting the drug and dizziness, nausea, and vomiting.

Minoxidil

Another arterial vasodilator (like hydralazine), *minoxidil* is well absorbed orally and has an elimination half-life of 3 to 4 hours. The duration of effect of a single dose is 8 to 12 hours. It is mainly prescribed in patients with resistant hypertension but is often accompanied by significant side effects. These include hirsutism (therefore, the drug is usually prescribed only in males) and peripheral edema due to fluid retention. Because it is a powerful vasodilator, other adverse effects include skin flushing, headache, reflex tachycardia, and associated palpitations. To overcome the edema and tachycardia, the drug is often coadministered with a β blocker and diuretic.

Nitrates

Glyceryl trinitrate (or nitroglycerin) undergoes extensive hepatic presystemic metabolism when given orally. Therefore, it is usually given by the sublingual route, by which it is well absorbed and rapidly taken up into the circulation. Buccal administration has a similar effect; this route is used for more prolonged action over a few hours. When given intravenously, there is drug breakdown by the cells of the vascular endothelium. Nitroglycerin is broken down (bioactivated) to 1,2 glyceryl nitrate and NO by hepatic mitochondrial aldehyde dehydrogenase. Tolerance develops over time, as the enzyme is depleted by continuous exposure.

Isosorbide dinitrate (ISDN) is absorbed in the gut and extensively metabolized to active metabolites, especially the mononitrate ISMN, which also shows good oral absorption but, in contrast to ISDN, has low presystemic metabolism. The half-lives of these nitrates are a few minutes for nitroglycerin, 1 hour for ISDN, and 4 hours for ISMN. Protein binding differs for the three agents (ISMN < 5%, for ISDN 30%, and nitroglycerin 60%). There are also differences in their volumes of distribution (ISMN 3 L/kg; ISDN 1–8 L/kg; nitroglycerin 0.7 L/kg).

Sodium nitroprusside is effective within 30 to 40 seconds of infusion, and offset is similarly rapid. It is broken down in the liver to cyanide and thiocyanate; together with the parent drug, both are excreted in the urine. Dose reduction is indicated for all nitrates in patients with renal or hepatic disease. There may be tolerance to vasodilatory effects of nitrates with prolonged dosing, especially when given transdermally. The safe doses of nitroprusside are less than 1.5 μg/kg/min during hypotensive anesthesia and up to 8 μg/kg/min to treat hypertensive crises.

Phosphodiesterase Inhibitors

The peripheral actions of the PDEIs are mediated by PDE3. There are two main chemical classes of inhibitors—the bipyridines (amrinone and milrinone) and the imidazolones (enoximone). These drugs cause vasodilation by increasing the intracellular cAMP in vascular smooth muscle, leading to activated outward Ca^{2+} transport and, hence, a decrease in intracellular Ca^{2+} concentration.

Amrinone has an elimination half-life of 2 to 4 hours, clearance of 4 to 9 mL/kg/min, and a small volume of distribution (1.3 L/kg). It has low protein binding (20%) and its elimination is not affected by renal disease. On the other hand, *milrinone* in healthy patients has an intermediate protein binding of 70%, terminal half-life of 2 hours, clearance of 2 to 3 mL/kg/min, and volume of distribution of 0.4 to 0.5 L/kg; its terminal half-life is increased in patients with renal dysfunction. Enoximone has a higher clearance (10 mL/kg/min), protein binding (70%–85%), and longer terminal half-life of 6 to 7 hours. The action of enoximone is increased in renal failure owing to the accumulation of the active sulfoxide metabolite.[51]

Other nonspecific PDEIs include the methylxanthines (e.g., theophylline and aminophylline) and the benzylisoquinoline, papaverine.

Pharmacotherapy of Hypertension

Treatment of hypertension is indicated to prevent or reduce end organ damage and subsequent morbidity. Current first-line drugs for the treatment of high blood pressure are diuretics, ACE inhibitors and angiotensin II receptor blockers, and calcium channel blockers; the latter three groups of drugs potentiate the effect of the diuretics. The JNC 7 and 8 guidelines indicate that thiazides are the first choice for treatment of uncomplicated hypertension, while combination therapy has greater efficacy than doubling of single-drug dosage.[52] However, calcium channel blockers are an effective treatment in hypertensive patients for the prevention of stroke but have little effect on the incidence of heart failure, major cardiovascular events, and cardiovascular and total mortality.[53]

β Blockers for the treatment of hypertension should be reserved for patients with associated coronary artery disease or tachycardia/tachyarrhythmias including secondary prevention after myocardial infarction.[54–56] In comparisons with other treatments, β blockers show a greater ability to reduce the incidence of stroke (29% vs. 17%) but no difference in prevention of coronary events and heart failure.[57] In patients with associated heart failure, thiazides, ACE inhibitors, aldosterone receptor blockers (spironolactone), and low-dose-titrated β blockers are indicated. In patients with renal impairment, ACE inhibitors and angiotensin II receptor antagonists are the drugs of choice.[58]

A Cochrane Review of randomized trials of at least 1-year duration compared thiazides, β blockers, calcium channel blockers, ACE inhibitors, α_1 blockers, and angiotensin II receptor blockers as first-line

therapies for patients with uncomplicated hypertension. The review concluded, "Low-dose thiazides reduced all cause mortality and morbidity (as stroke, coronary heart disease, cardiovascular events); ACE inhibitors and calcium channel blockers might be similarly effective but the evidence is less robust; and high-dose thiazides and β blockers are inferior to low-dose thiazides."[59]

Hypertension and Anesthesia

Hypertensive patients exhibit greater intraoperative cardiovascular lability, including hypertension with tracheal intubation and post-induction and intraoperative hypotension that is associated with adverse outcomes.[59a] Present anesthetic practice dictates that antihypertensive therapies (with the possible exception of high-dose ACE inhibitors and angiotensin II receptor antagonists[4a]) are maintained up to the time of surgery. Not all investigators agree that ACE inhibitors and angiotensin II receptor antagonists should be withheld.[60,61] However, preoperative evaluation for patients with hypertension should include the measurement of plasma K^+ concentrations, especially in patients receiving diuretics or renin-angiotensin system antagonists.

One of the present controversies concerns which groups of patients (if any) should not undergo surgery because of raised blood pressure. There are few data on the influence of coexisting hypertension on cardiovascular outcome following noncardiac surgery. Mild to moderate preoperative hypertension is not a major risk factor for complications.[61a,61b] None of the scoring systems used to categorize patient risk include hypertension as a factor. However, a study of outcome from Switzerland identified an increased incidence of cardiovascular complications: 11.2% vs. 4.6% (adjusted odds ratio [AOR], 1.38; 95% confidence interval [CI], 1.27–1.49) in the hypertensive subgroup.[62] These results are in keeping with the meta-analysis of Howell and colleagues[63] (AOR, 1.35; 95% CI, 1.17–1.56) for perioperative cardiovascular complications of cardiac mortality, myocardial infarction and heart failure, and arrhythmias.

The 2014 American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology/European Society of Anaesthesiology guidelines offer recommendations for management.[61a,61b] Observational data agree that stage 1 or 2 hypertension is not an independent risk factor for perioperative cardiovascular complications; hence, there is no scientific evidence to support postponing these patients' surgery in the absence of target organ damage. However, the case for stage 3 (SAP ≥ 180 and/or DAP ≥ 110 m Hg) hypertension is less clear. The guidelines recommend control of blood pressure before surgery, but this is not supported by a large body of data relating exclusively to patients with these levels of blood pressure. An analysis of a large UK primary care database showed an association between elevated diastolic blood pressure and postoperative mortality.[64]

Based on clinical studies and practice, there is no evidence to cancel and treat hypertensive patients other than those with documented target organ damage. Blood pressure control should be optimized before surgery in patients in whom hypertension is associated with accompanying significant risk factors such as diabetes mellitus, coronary artery disease, peripheral vascular disease, impaired renal function, smoking, or hypercholesterolemia.[65,66]

Isolated systolic hypertension (ISH) is frequent in older adults. It is characterized by increased systolic pressure as well as pulse pressure due to increased large artery stiffness secondary to aging. There are also often associations with obesity and reduced physical activity. In nonsurgical patients with ISH, there is a clear association with increased prevalence of silent myocardial ischemia. The influence of ISH on perioperative outcomes has not been well studied, although a recent study (PROMISE—Perioperative Myocardial Ischemia in Isolated Systolic Hypertension) showed no increased incidence of myocardial ischemia in ISH patients.[67]

In patients with "white coat" hypertension, as many repeat blood pressure readings as possible should be obtained to inform clinical decisions. Starting a normally normotensive patient with white coat hypertension on inappropriate therapy can be dangerous. If surgery is to be deferred to allow white coat hypertension to be treated, it is unclear how long treatment should be given before surgery.

Pulmonary Vasodilators

The pulmonary circulation is normally a low-pressure, low-resistance circuit (see Chapters 29 and 30). Pulmonary hypertension is defined as mean pulmonary artery pressure greater than 20 mm Hg or systolic pulmonary artery pressure greater than 30 mm Hg.

The causes of pulmonary hypertension are idiopathic (50%) with the remaining 50% associated with connective tissue disorders; congenital heart disease; portal hypertension; infection with human immunodeficiency virus; or intake of appetite-suppressant drugs, such as fenfluramine or dexfenfluamine. The hypertension can be aggravated by hypoxic vasoconstriction; hence, these patients should receive supplemental oxygen while avoiding causative drugs.

Hypoxic pulmonary vasoconstriction (HPV; see Chapter 29) is mediated by the endothelium. The exact mechanism is not well defined, but the "redox theory" proposes the coordinated action of a redox sensor (within the proximal mitochondrial electron transport chain) that generates a diffusible mediator (probably a reactive oxygen species, such as hydrogen peroxide) that regulates an effector protein (either a voltage-gated K^+ or Ca^{2+} channel). The subsequent inhibition of oxygen-sensitive K^+ $K_V1.5$ and K_V 2.1 channels depolarizes pulmonary artery smooth muscle and activates voltage-gated Ca^{2+} channels. This leads to an influx of Ca^{2+}, causing vasoconstriction.[68]

Hypoxic pulmonary vasoconstriction can be modulated by a number of variables. The reflex activity decreases with increases in pulmonary artery pressure, cardiac output, left atrial pressure, and central blood volume. Drugs also modulate the reflex and interfere with ventilation/perfusion matching (Table 26.9). Other perioperative conditions that impair the response include hypocapnia and hypothermia. When hypoxic pulmonary vasoconstriction is inhibited, there is an increase in alveolar–arterial oxygen gradient.

Until recently, the prognosis for patients with pulmonary hypertension was poor (with a survival of 5–6 years) even with treatment, and the only useful treatment was chronic calcium channel blockers. This has changed with the introduction of NO, prostacyclin analogs, PDEIs, and lung transplantation. Other useful therapies include inotropic drugs that can cause some right ventricular adaptation secondary to an increase in systolic function. Conversely, these patients tolerate β adrenoceptor blockade poorly. Diuretics can also help by decreasing pericardial and pleural effusions and by improving right ventricular volumes and left ventricular diastolic function.

A classification of pulmonary vasodilators is shown in Table 26.10. There is no vasodilator that acts solely on the pulmonary vasculature. Adenosine, acetylcholine, nitroglycerin, and prostacyclin have the best ratio of pulmonary to systemic effects. Most drugs used to attempt a reduction in pulmonary blood pressure are not without significant side effects: systemic hypotension, pulmonary hypertension (drug-induced decrease in systemic blood pressure can increase pulmonary artery pressure by increasing cardiac output and sympathetic tone), decreased myocardial contractility, and

TABLE 26.9 Effect of Vasoactive and Other Drugs on the Hypoxic Pulmonary Vasoconstrictor Reflex

Drug	Effect
Hydralazine	None
Nifedipine	Inhibition
Verapamil	Inhibition
Nitroglycerin	Inhibition
Sodium nitroprusside	Inhibition
Nicardipine	None
Labetalol	None
Inhaled anesthetics	None to slight inhibition
Intravenous anesthetics ketamine and propofol	None
Thoracic epidural	No direct effect; but changes likely attributable to alterations in cardiac function

TABLE 26.10 Classification of Pulmonary Vasodilators

Direct-acting: inhaled nitric oxide, hydralazine, nitroglycerin, sodium nitroprusside (through activation of guanylyl cyclase)
α Adrenoceptor antagonists: tolazoline, phentolamine
β Adrenoceptor agonists: isoproterenol (isoprenaline; activation of adenylyl cyclase)
Calcium channel blockers: nifedipine, diltiazem
Prostaglandins: PGE_1 and prostacyclin
Adenosine
Endothelin receptor antagonists
Indirect-acting vasodilators: such as acetylcholine, that causes the release of nitric oxide
Phosphodiesterase inhibitors

hypoxemia. Because of these side effects, there have been a number of new treatments assessed since the mid-1990s.

Inhaled nitric oxide (iNO) readily diffuses from the alveoli to the vascular smooth muscle, where it activates guanylyl cyclase to increase cGMP, causing pulmonary vasodilation. NO has little effect on the systemic circulation. It can be administered in doses ranging from 5 to 80 ppm. About 33% of patients with pulmonary hypertension show little or no response to iNO owing to a nonreactive pulmonary circulation, rapid NO inactivation, abnormalities of the guanylyl cyclase system, or rapid breakdown of cGMP (although this can be inhibited by addition of dipyridamole). The main adverse effects of iNO are inhibition of platelet function and rebound hypoxemia and pulmonary hypertension.

Prostanoid pulmonary vasodilators can be administered by a variety of different routes—intravenous (epoprostenol, treprostinil, iloprost), subcutaneous (treprostinil), inhalation (iloprost), and oral (beraprost). Prostacyclin (PGI_2) is endogenously synthesized, predominantly by endothelial cells, including the pulmonary vascular endothelium. Prostacyclin produces vasodilation in low-resistance beds, such as the pulmonary circulation.[69] It not only stimulates the endothelial release of NO but, in turn, NO enhances PGI_2 synthesis in smooth muscle cells of the pulmonary artery. PGI_2 is spontaneously broken down by plasma hydrolysis to an inactive 6-keto metabolite, with a half-life of about 6 minutes. Animal studies show PGI_2 to have a high clearance (90–100 mL/kg/min), a volume of distribution of 357 mL/kg, and a half-life of 2.7 minutes.[70] Delivery of PGI_2 by aerosol causes minimal systemic effects, but achieves a dramatic and rapid improvement in arterial oxygenation and lowering of pulmonary artery pressure.

Phosphodiesterase Inhibitors

Both NO and atrial natriuretic peptide (ANP) activate smooth muscle cell guanylyl cyclase to decrease intracellular Ca^{2+} with muscle relaxation, inhibition of cell proliferation, and activation of apoptosis. There is evidence that phosphodiesterase (PDE) is overexpressed in pulmonary hypertension, leading to an increased degradation of cGMP. There is also decreased expression of NO synthase. Hence, therapy has focused on the efficacy of PDE5 inhibitors, which cause pulmonary vasodilation. PDE5 is located in the corpus cavernosus, vascular smooth muscle, and platelets.

Sildenafil reduces pulmonary vascular resistance. It has high oral bioavailability, with onset of effect within 15 minutes and peak hemodynamic effect at 2 hours. Sildenafil has a half-life of about 4 hours and is metabolized by two separate routes involving CYP 3A4 (major) and 2C9 (minor). Both pathways are influenced by CYP inhibitors and inducers. The drug is effective in reducing pulmonary artery pressure in both adults and children.

Tadalafil has a longer half-life; hence, it is viewed as a once-per-day drug.

For the effective treatment of pulmonary hypertension, combination therapies are often the most efficacious.

Novel Pulmonary Vasodilators

A number of therapies are under evaluation in vitro and in animal models—these include potassium channel openers, antiproliferative drugs, rapamycin, and statins.

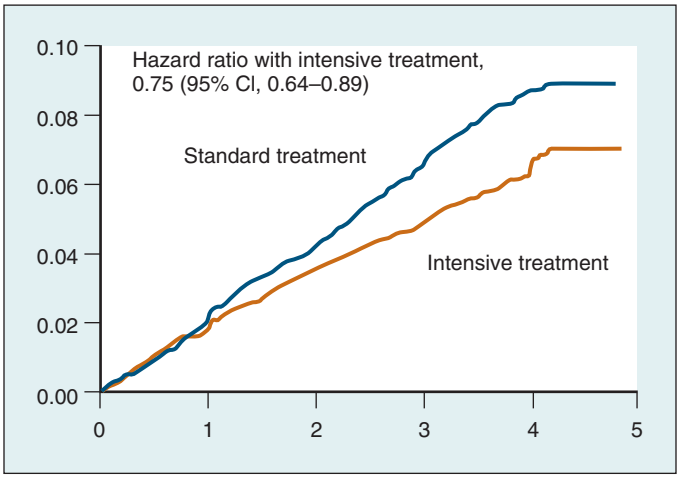
Emerging Developments

New Management Guidelines for Hypertension

New guidelines for the prevention, diagnosis, and treatment of hypertension were released in 2017 by a task force of professional societies.[70a] Guidelines for the care of pediatric hypertensive patients have also been revised.[70b] Experts expect these revamped guidelines to have a major impact on physician behavior and public health as it relates to cardiovascular disease.[70c,70d]

A major motivation to update the existing guidelines was a large, randomized, controlled trial commonly referred to as the SPRINT study (Systolic Blood Pressure Intervention Trial).[70e] As presented in Figure 26.8, SPRINT confirmed the hypothesis that a lower systolic blood pressure target (i.e., ≥ 120 mm Hg instead of the traditional target of ≥ 140 mm Hg) reduces adverse cardiovascular outcomes such as myocardial infarction, acute coronary syndrome, stroke, congestive heart failure, and cardiovascular death in more than 9000 hypertensive patients randomized to standard and more intensive treatment groups. An adverse consequence of the more intensive treatment was a higher risk of hypotensive episodes, syncope, and acute kidney injury, among others.

Key components of the new guidelines include confirming the diagnosis of hypertension with multiple "out-of-office" measurements (avoiding false, "white coat" hypertension diagnoses), instituting non-pharmacologic interventions (e.g., weight loss, exercise, healthy diet), and targeting a systolic blood pressure of



• **Fig. 26.8** Cumulative hazard ratios for the primary outcome (a composite of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes) from the SPRINT study comparing standard antihypertensive therapy with more intensive treatment.[5] See text for details.

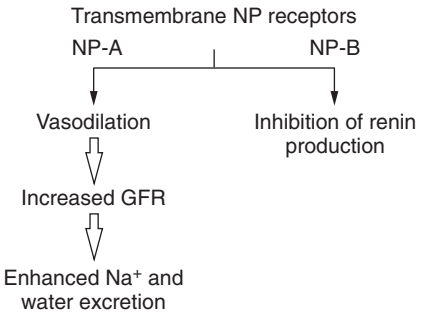
≥ 130/80 mm Hg.[70a,70f] Patients with a high risk of adverse cardiovascular outcomes because of other risk factors warrant special attention. The guidelines recommend thiazide diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers as first line antihypertensive agents, noting that combination therapy might be necessary to achieve the lower blood pressure targets.

Applying these guidelines into everyday clinical care will be challenging.[70g] The updated guidelines call for an additional 31 million patients in the USA to be treated (and 55 million more will need more intense treatment). The revamped guidelines will change the typical clinical profile of the treated hypertensive patient presenting for anesthesia and surgery.

Direct Renin Inhibitors

Direct renin inhibitors are a new class of drugs that act as non–peptide renin inhibitors by binding competitively to renin and blocking the generation of angiotensin I from angiotensinogen. Direct renin inhibitors act on the juxtaglomerular cells of the kidney, where the hormone is produced. They cause arterial and venous dilatation by blocking formation of angiotensin and cause downregulation of sympathetic adrenergic activity and promotion of Na^+ and water excretion by the kidneys. Aliskiren can be used in patients when ACE inhibitors or angiotensin receptor antagonists (ARAs) are not tolerated. It has additive antihypertensive effects when combined with ARAs. Unlike ACE inhibitors and ARAs, they do not appear to cause a compensatory rise in plasma renin and produce a more complete block of the pathway.[71,72] They appear to possess fewer side effects than either ACE inhibitors or ARAs and are recommended as a third-line treatment for hypertension (especially where resistant to other therapies).[73]

There are few kinetic data available for the two currently available direct renin inhibitors, aliskiren and remikiren. Both drugs are formulated for oral use only. *Aliskiren* is a piperidine derivative that is poorly absorbed, with an oral bioavailability of only 2.5%. Peak concentrations are seen at 1 to 3 hours. Aliskiren has a half-life of 24 to 40 hours, and protein binding of 47% to 51%. It is partly metabolized (about 19%) in the liver by CYP 3A4 to *O*-demethylated and carboxylic acid derivatives. The remainder of the drug is excreted unchanged in the feces.



• **Fig. 26.9** Possible mechanisms of action of natriuretic peptides (NP). Atrial and brain natriuretic peptides interact with NP-A and NP-B receptors to reduce blood pressure by vasodilation and enhanced salt and water excretion. *GFR,* glomerular filtration rate.

Remikiren has a similar low bioavailability (< 6%), a half-life of 1.5 hours, and clearance similar to hepatic blood flow. The effect lasts about 24 hours. It is recommended that the dose of both drugs be reduced in patients with renal impairment.[74,75]

Ivabradine is a specific sinus node inhibitor that slows heart rate without having negative inotropic effects by inhibition of I_f ("funny channel") currents. The effects of ivabradine on heart rate also lead to an increased diastolic time and, hence, increased coronary flow. It is an alternative to a β blocker or heart rate-limiting calcium channel blocker and also has antianginal action when given with a β blocker. It has some antihypertensive effect through its action on heart rate. Use of ivabradine can be accompanied by the development of significant side effects: visual symptoms (including blurring of vision), headache, dizziness, and bradycardia.[76]

Natriuretic Peptides

Natriuretic peptides (atrial and brain natriuretic peptides [ANP and BNP, respectively]) act via transmembrane NP-receptors (NP-A, NP-B). Agonists binding to NP-A receptors cause vasodilation with increased glomerular filtration rate and enhanced Na^+ and water excretion, while NP-B receptor stimulation inhibits renin production. These peptides reduce blood pressure through vasodilation of both the arterial and venous systems (Fig. 26.9). A number of new therapeutic approaches are being developed related to these peptides. These include neural endopeptidase (NEP) inhibitors (e.g., candoxatril), vasopeptidase inhibitors (e.g., omapatrilat, which inhibits both ACE and NEP), exogenous ANP and BNP (e.g., nesiritide; recombinant BNP), and exogenous ANP as a coronary vasodilator.

Endothelin and Endothelin Blockade

Endothelins are vasoconstrictors found in endothelial cells that were first discovered in 1985 and identified in 1988.[77] There are four distinct endothelin peptides (1, 2, 3, and 4). ET-1 and ET-3 are the endothelins present in vascular endothelial cells; ET-2 and ET-4 are found in the kidneys and intestines, and ET-3 is also found in the intestines, brain, lungs, and adrenal glands.

ET-1 is synthesized as a 212 residue precursor (prepro-ET) that undergoes cleavage by an atypical endopeptidase of the metalloprotease type to big ET-1 and, subsequently, ET-1. This latter cleavage occurs both intracellularly and on the surface of endothelial and smooth muscle cells. The stimuli to endothelin synthesis include the release of any of a series of noxious vasoconstrictor mediators—including activated platelets, endotoxins, thrombin, various cytokines, cell and tumor growth factors, angiotensin II, antidiuretic

hormone, and epinephrine, as well as other stimuli such as hypoxia and insulin.

Inhibitors to synthesis include NO, natriuretic peptides, prostaglandins PGE_2 and PGI_2, and heparin. It is probable that ET-1 is stored as a preformed molecule in the endothelial cells, while the release mechanism is poorly understood. It is a 21 amino acid peptide with vasoconstrictor and mitogenic properties, being a growth factor for both vascular smooth muscle and fibroblasts. The release of ET-1 appears to be stimulated by hypoxemia and inhibited by NO. There are two distinct endothelin receptors: ET-A and ET-B. Both are G protein–coupled, with ET-1 preferentially activating ET-A. This receptor is, in turn, coupled to second messengers (including phospholipase C, protein kinase C, and IP_3). The mRNA for endothelin ET-A receptors is expressed in many human tissues, including vascular smooth muscle, heart, lungs, and kidney. Stimulation of ET-A receptors brings about vasoconstriction and cell proliferation, while ET-B stimulation causes release of NO and prostacyclin.[78] Patients with pulmonary hypertension can have enhanced pulmonary production and increased circulating levels of ET-1.[79,80]

There are two broad classes of blockers—selective to one or other receptor, and nonselective. All are undergoing evaluation in patients with pulmonary hypertension. They have beneficial effects in the management of the condition by reducing vascular resistance and altering vascular remodeling.[78]

Bosentan can be given as either a continuous infusion or as an oral preparation. The orally active preparation of this nonselective endothelin blocker has a half-life of about 7 hours. It is metabolized by CYP and is an inducer of CYP 4AA and 2C9.[81]

Sitaxentan is an endothelin receptor blocker with a specificity of A : B receptors of 6500:1 (this compares with a ratio of 20:1 for bosentan; a blocker is said to be selective if the ratio is greater than 100:1). Sitaxentan is also orally active and rapidly absorbed, with a T_{max} of 1 to 4 hours. Its elimination half-life is about 10 hours, and it is metabolized by CYP 2C9 and 3A4. The compound has also been shown to be a competitive inhibitor of CYP 2C9, 2C19, and 3A4/5.

Ambrisentan is another nonselective blocker with an A : B specificity of 77:1. It has a high oral bioavailability and a long half-life, making it a once-a-day drug.

Darusentan is an endothelin A receptor antagonist that reduces both systolic and diastolic pressures. It might be a useful therapy in patients with refractory hypertension.

Key Points

- Pharmacologic control of blood pressure can occur through central or peripheral actions, primarily effects on the sympathetic autonomic nervous system or on the tone of the peripheral vasculature.
- Interactions with four classes of adrenergic receptors—α_1, α_2, β_1, and β_2—can modulate blood pressure. Antagonists at the α_1 receptor counteract the hypertensive effects of α_1 agonists and reduce the vascular hypertrophy seen in hypertension. Antagonists at β_1 and β_2 receptors reduce heart rate and modulate sympathetic effects.
- β-adrenoceptor blockers include two classes—the amino-oxypropanols (propranolol, metoprolol, esmolol, carvedilol) and the hydroxyaminoethyls (sotalol and labetalol). Pharmacologically, there are three classes: partial agonists (bucindolol and xamoterol), inverse agonists (metoprolol, bisoprolol, nebivolol, sotalol) that stabilize the receptor in an inactive state, and neutral (competitive) antagonists (carvedilol, propranolol) that bind to the receptor without selectivity for active or inactive state. Further functional classification distinguishes antagonists as β_1 selective or nonselective, as having ISA, or as having membrane-stabilizing actions.
- Antagonists at β_1 receptors reduce myocardial remodeling while preserving β_2-mediated cardiac protection. Selective β_1 blockers also have negative inotropic and chronotropic effects.
- For the treatment of hypertension, β-adrenoceptor blockers with inverse agonist activity, or those with associated α_1 adrenoceptor blocking activity (labetalol, carvedilol), might be preferred.
- Most peripheral vasodilators act through regulation of intracellular Ca^{2+} concentration in vascular smooth muscle. Vasodilators increase intracellular cAMP or cGMP and bring about vasodilation by phosphorylation of phospholamban and promotion of increased uptake of Ca^{2+} into the sarcoplasmic reticulum.
- Calcium blockers block Ca^{2+} entry through L-type voltage-gated Ca^{2+} channels, leading to vasodilation. The three structural classes of blockers—phenylalkylamines (verapamil), benzothiazepines (diltiazem), and dihydropyridines (nifedipine)—have two main actions, vasodilation and negative inotropy.
- Nitrovasodilators either cause spontaneous release of NO or undergo active reduction prior to NO release. NO activates guanylyl cyclase to produce cGMP that activates protein kinase G and activates myosin light chain phosphatase, which dephosphorylates light chains to produce muscle relaxation.
- Inhibition of the renin–angiotensin system can occur through direct inhibition of ACE, angiotensin II receptor antagonism, or direct renin inhibition.
- Endothelins activate ET-A receptors to cause vasoconstriction and smooth muscle proliferation; endothelin antagonists mainly block the ET-A receptor to cause vasodilation.
- Potassium channel openers act by decreasing membrane potential through the efflux of K^+, thus reducing the activity of voltage-gated Ca^{2+} channels.
- Magnesium is a calcium channel blocker that also acts as an antihypertensive agent by stimulating production of prostaglandin E_1 and NO and by altering the vascular smooth muscle response to vasoactive agents.
- The eicosanoids (prostaglandins E_1 and E_2; and prostaglandin I_2, known as prostacyclin) bind specific prostanoid receptors, leading to increased intracellular cAMP, activation of protein kinase A, and inhibition of smooth muscle contraction.
- Treatment options for pulmonary hypertension include calcium channel blockers, direct-acting nitrovasodilators (e.g., nitroglycerin rather than nitroprusside), inhaled NO, endothelin blockers, prostanoids (prostacyclin), and phosphodiesterase 5 inhibitors (sildenafil and cogeners).
- Revamped guidelines for the management of hypertensive patients are among the most important emerging developments in the field. The new guidelines call for a lower therapeutic blood pressure target (< 130/80 mm Hg) that will necessitate two-agent therapy in many patients.

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Kirsten R, Nelson K, Kirsten D, et al. Clinical pharmacokinetics of vasodilators. Part I. *Clin Pharmacokin*. 1998;34:457–482. Kirsten R, Nelson K, Kirsten D, et al. Clinical pharmacokinetics of vasodilators. Part II. *Clin Pharmacokin*. 1998;35:9–36. Two review papers defining the mechanism of action and pharmacokinetic properties of vasodilator drugs used in the treatment of hypertension (Ref. 10, Ref. 40).Kroen C. Does elevated blood pressure at the time of surgery increase perioperative cardiac risk? Proceedings of the 2nd Annual Cleveland Clinic Perioperative Medicine Summit. *Cleve Clin J Med*. 2006;33:s5–s6. Elevated blood pressure by itself has not been shown to increase the incidences of perioperative cardiac events. However, target organ damage caused by chronic hypertension can confer increased cardiac risk. A useful review of some of those issues relating to the assessment and treatment of the patient with hypertension (Ref. 65).

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Antiarrhythmic Drugs

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CHAPTER OUTLINE

Historical Perspective

Basic Pharmacology
- Singh-Vaughan Williams Classification of Antiarrhythmic Drugs
- Sodium Channels and Class I Antiarrhythmic Drugs
- β Receptors and Class II Antiarrhythmics
- Potassium Channels and Class III Antiarrhythmic Drugs
- Calcium Channels and Class IV Antiarrhythmics

Clinical Pharmacology
- Categories of Arrhythmogenic Mechanisms
  - *Automaticity*
  - *Triggered*
  - *Conduction*

Clinical Application
- Class I—Sodium Channel Blockers
  - *Class Ia Na_v Channel Blockers*
  - *Class Ib Na_v Channel Blockers*
  - *Class Ic Na_v Channel Blockers*
- Class II—β Blockers
- Class III—Potassium Channel Blockers
- Class IV—Calcium Channel Blockers

Emerging Developments
- Molecular Genetics of Arrhythmias
  - *Long QT Syndrome*
  - *Short QT Syndrome*
  - *Brugada Syndrome*
  - *Other Inherited Arrhythmia Syndromes*
- hERG Drug Interactions
- Gene Therapy Guided by Molecular Genetics of Inherited Arrhythmias

Historical Perspective

The heart, and more specifically the heartbeat, has throughout history served as an indicator of well-being and disease, both to the physician and to the patient. Through one's own heartbeat, one can feel the physiologic manifestations of joy, thrills, fear, and passion; the rigors of a sprint or long-distance run; the instantaneous effects of medications, recreational drugs, or toxins; the adrenaline of a rollercoaster ride or a penalty shootout in a World Cup final. Although the complexities of the heart continue to humble the scientists and physicians who study it, the heart is unique in that, despite the complexity of its physiology and the richness of both visceral and romantic imagery associated with it, its function can be distilled down to that of a simple pump, the function and dysfunction of which we now understand a great deal about (see Chapter 24). The history of development of pharmacologic agents to correct abnormalities in heart rhythm is, however, emblematic of drug development as a whole: major successes combined with paradoxes, damaging side effects, and the often frustrating intransigence of what would seem the most intuitive targets for antiarrhythmics—ion channels.[1,2]

In ancient Greek, Egyptian, and Chinese cultures, the pulse was recognized as a means to assess health, and for millennia it was the only measure of cardiac physiology and pathophysiology. In second-century Rome, Galen's work *De Pulsibus* became the first great treatise on the pulse as a window into human health and established Galen as the father of his discipline.[3] It was not for another 1500 years that the great physician, scientist, and naturalist William Harvey, of Folkestone in England, published his landmark (and then controversial) work *An Anatomical Exercise Concerning the Motion of the Heart and Blood in Animals*. This introduced the theory that blood circulates throughout the body, a hypothesis tested rigorously by Harvey with experiments on animals and the cadavers of executed criminals.[4] In the late 19th and early 20th centuries, Waller and Einthoven founded the field of electrocardiography, facilitating quantitative differential diagnoses of cardiac arrhythmias. This paved the way for modern cardiology and advances such as Wolff, Parkinson, and White's neurocardiac theory, the discovery of atrial fibrillation (AF), and the increasingly sophisticated molecular genotype-phenotype correlations from which we benefit today.[5,6]

These latter advances also owe much to the work of molecular geneticists in the 1990s whose Herculean efforts (before routine high-throughput sequencing) helped identify the mutant ion channel genes underlying inherited arrhythmias such as long QT syndrome, working hand in hand with cellular electrophysiologists and physicians to exemplify the bedside-to-bench model of modern molecular medicine. Having said this, β blockers, the first antiarrhythmics of the modern era, were developed in the later 1950s to early 1960s not with ion channels in mind, but were a by-product of Sir James W. Black's desire to create improved therapies for angina and essentially "to stop the effects of adrenaline on the heart" following the death of his father after a myocardial infarction. The resulting class II antiarrhythmic drug, propranolol, ushered in a new era of drug development and proved effective in therapy of disorders including angina, arrhythmia, and hypertension.[7]

Abstract

Disturbances in cardiac rhythm, also termed cardiac arrhythmias, can arise from structural heart disease, adverse drug interactions, or inherited gene variants in ion channels or the proteins that regulate them. Cardiac arrhythmias range from relatively common, chronic arrhythmias such as atrial fibrillation, to the rarer but more acutely dangerous ventricular arrhythmias that can culminate in ventricular fibrillation, which is rapidly lethal unless defibrillation is administered. Because ion channels and their regulators conduct electrical currents in the heart that determine cardiac rhythm, most anti-arrhythmic drugs act, directly or indirectly, on cardiac ion channels. As different types of cells in specific regions of the heart each carry their own signature array of ion channels, anti-arrhythmic drugs can be chosen to target the specific regions in which the arrhythmia originates or is most critically manifested. In this chapter, after a brief historical perspective, we review anti-arrhythmic drugs, first discussing them in the context of the widely used Singh-Vaughan Williams classification system. Next, after a description of the major arrhythmogenic mechanisms, we discuss in detail clinical application of the various classes of anti-arrhythmics. In the final section, we cover inherited cardiac channelopathies and how they have guided our understanding of cardiac physiology, pathophysiology and its treatment, before discussing pharmacogenetics of adverse drug interactions and ideas about future gene therapy approaches. The chapter is intended to be a guide to the major classes of anti-arrhythmic drugs, their usage and mechanisms of action, and, where appropriate, mechanistic insights into the ion channels that they target.

Despite the vast array of imaging, molecular, and electrocardiographic diagnostic tools available to cardiologists and other physicians, measurement of the pulse will likely be central to routine examination of the cardiac and holistic health of individuals for the foreseeable future. Timely, rhythmic beating of the heart is essential for health. When the heart develops sustained nonrhythmic beating, generally termed *arrhythmia,* the consequences can range from mild (e.g., syncope) to lethal (sudden cardiac death). Cardiac arrhythmias are treated by surgical ablation, electronic pacemaker, cardioversion, pharmacologic agents, or a combination of these, depending on the location and nature of the causal factor. For example, in the case of ventricular fibrillation—a life-threatening, chaotic tachycardia—electrical defibrillation is required immediately to prevent sudden cardiac death. In contrast, in many cases of AF there is an underlying structural defect in the atria that can be successfully treated using radiofrequency catheter ablation—for example, to prevent the aberrantly conducting area from being an arrhythmogenic focus.

This chapter focuses on antiarrhythmic medications as frequently encountered in the perioperative and critical care settings. These are a broad class of drugs, incorporating numerous structural classes and modes of action, that are used based on the suspected or known molecular etiology of the arrhythmia to be treated. Recent advances in the understanding of the molecular basis for generation of electrical currents in the heart, and also the genetic basis of many cardiac arrhythmias, have contributed to the development and use of antiarrhythmic drugs. Furthermore, these advances have demonstrated the basis for the proarrhythmic action of some drugs—paradoxically, even some drugs that are classified and used as antiarrhythmics.

To fully understand the mechanism of action of antiarrhythmic drugs, one must understand both the underlying cause of the arrhythmia, and the molecular target of the antiarrhythmic; these may or may not be the same entity. Accordingly, this chapter includes not only a description of the basic and clinical pharmacology of the major classes of cardiac arrhythmias, but also a discussion of the mechanistic underpinnings of these arrhythmias.

Basic Pharmacology

Singh-Vaughan Williams Classification of Antiarrhythmic Drugs

Antiarrhythmic drugs include a wide range of structural and functional classes. Although not perfect, a highly useful framework for their classification is that proposed by Singh and Vaughan Williams, usually referred to as the *Singh-Vaughan Williams (SVW) classification*. The SVW classification categorizes antiarrhythmic drugs into four classes (Table 27.1). Class I denotes sodium (Na^+) channel blocking activity, with resultant delay in phase 0 depolarization and/or altered action potential duration. Class II agents counteract the effects of endogenous catecholamines (in particular epinephrine and norepinephrine) by antagonism of β adrenergic receptors, and hence are known as β blockers or β antagonists. Class III antiarrhythmics prolong the action potential and refractory period, acting primarily by potassium (K^+) channel blockade. Class IV agents reduce heart rate, primarily by L-type calcium (Ca^{2+}) channel blockade, which slows conduction through the sinoatrial (SA) and atrioventricular (AV) nodes.[8,9] (For a more detailed discussion of cardiac electrophysiology and myocyte depolarization, see Chapter 23).

The primary reason that the SVW classification is to some extent imperfect is that many, if not most, antiarrhythmic drugs exhibit physiologically significant actions in more than one of the four classes. Typically the classification is based on the action that was first described for each drug, which is generally but not necessarily the most therapeutically significant mechanism of action for all types of arrhythmia for which the drug is prescribed. This discrepancy can occur because of nonspecificity of the drug, or because major metabolites of the drug exhibit different activity than that of the drug itself. Furthermore, some important antiarrhythmic drugs, including digoxin and adenosine, do not fit primarily into any of the four classes. However, the SVW classification is still the most useful framework for describing antiarrhythmic drugs, especially if one considers the net effect of each drug rather than all its specific molecular targets. The clinical pharmacology of the major antiarrhythmic drugs is summarized in Table 27.2.

TABLE 27.1 Singh-Vaughan Williams Classification of Antiarrhythmic Agents

Class	Mechanism of Action	Drugs
Ia	Na^+ channel blockade, prolonged repolarization	Procainamide, quinidine, disopyramide
Ib	Na^+ channel blockade, shortened repolarization	Lidocaine, mexiletine, phenytoin, tocainide
Ic	Na^+ channel blockade, repolarization unchanged	Encainide, flecainide, propafenone
II	β-adrenoceptor antagonist	Esmolol, metoprolol, propranolol
III	Marked prolongation of repolarization	Amiodarone, bretylium, ibutilide, sotalol
IV	Calcium channel blockade	Diltiazem, verapamil

Sodium Channels and Class I Antiarrhythmic Drugs

Voltage-gated Na^+ (Na_v) channels open in response to cell membrane depolarization to permit influx of Na^+, further depolarizing the cell. The predominant Na_v channel in human cardiac electrophysiology is $Na_v1.5$, which is encoded by the *SCN5A* gene. In most cardiac myocytes, $Na_v1.5$ activation mediates the upstroke in phase 0 of the action potential, in which the membrane potential is depolarized from around −70 mV to +20 mV as the result of Na^+ influx (Fig. 27.1A). $Na_v1.5$, like other mammalian Na_v channels, inactivates rapidly, which together with the transient outward K^+ current, I_{to}, shapes the notch in phase 1 at the beginning of the human cardiac myocyte action potential.[10]

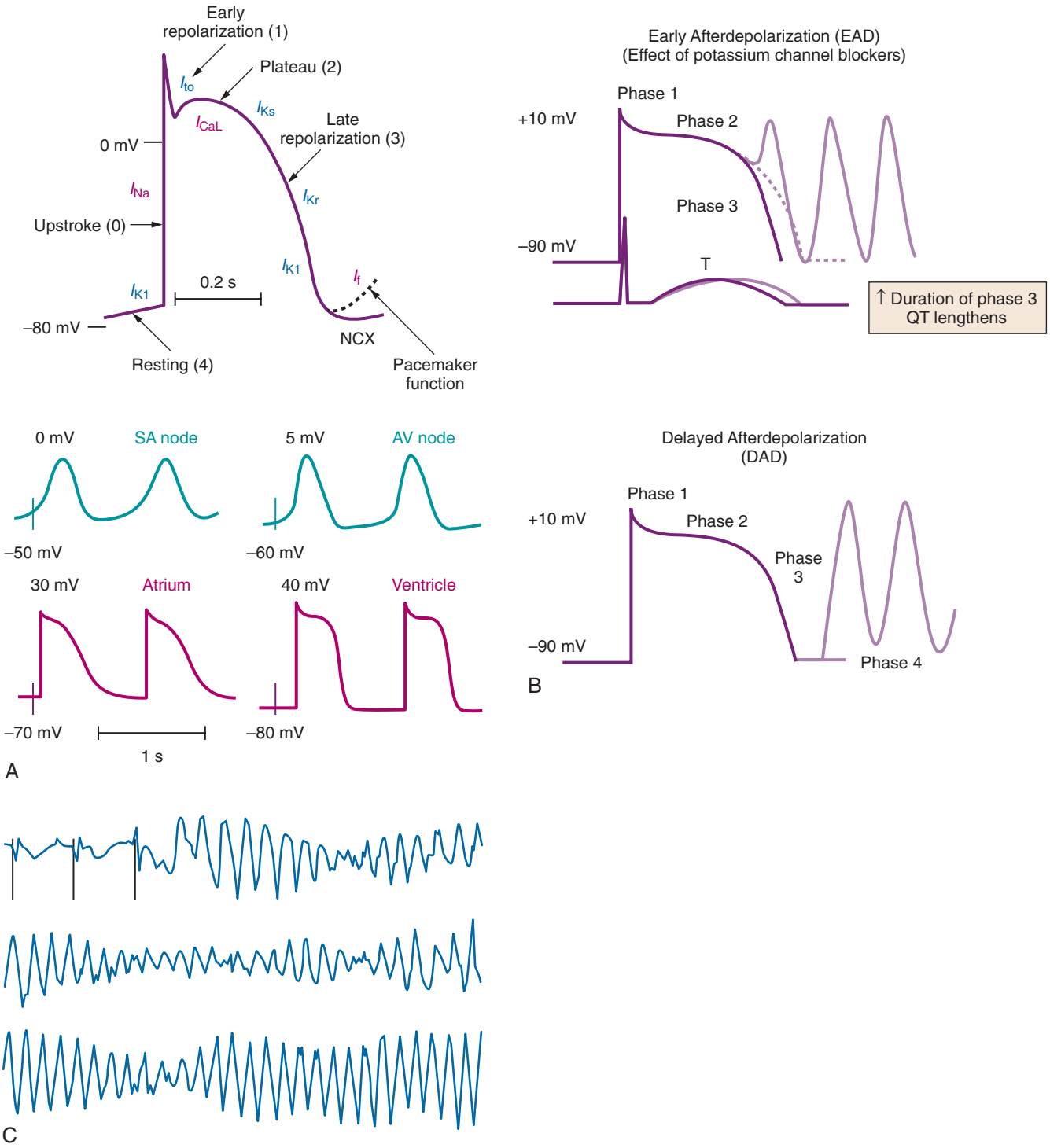
Class I antiarrhythmics exhibit Na_v channel blocking activity. These drugs are often referred to as "membrane stabilizing agents" because by blocking cardiac Na_v channels, which mediate myocyte depolarization, they reduce cellular excitability. Na_v channels are composed of a 24-transmembrane-segment pore-forming α subunit that consists of four homologous domains (DI-DIV) and also bears four voltage-sensing domains and one or more inactivation gates (Fig. 27.2A). The $Na_v1.5$ α subunits form cardiac ion channel complexes with single-transmembrane segment β subunits, encoded by the *SCNxB* genes, which modify $Na_v1.5$ function and pharmacology.[11]

Class I antiarrhythmic drugs are thought to bind in the inner pore vestibule of Na_v channels, with drugs from different structural

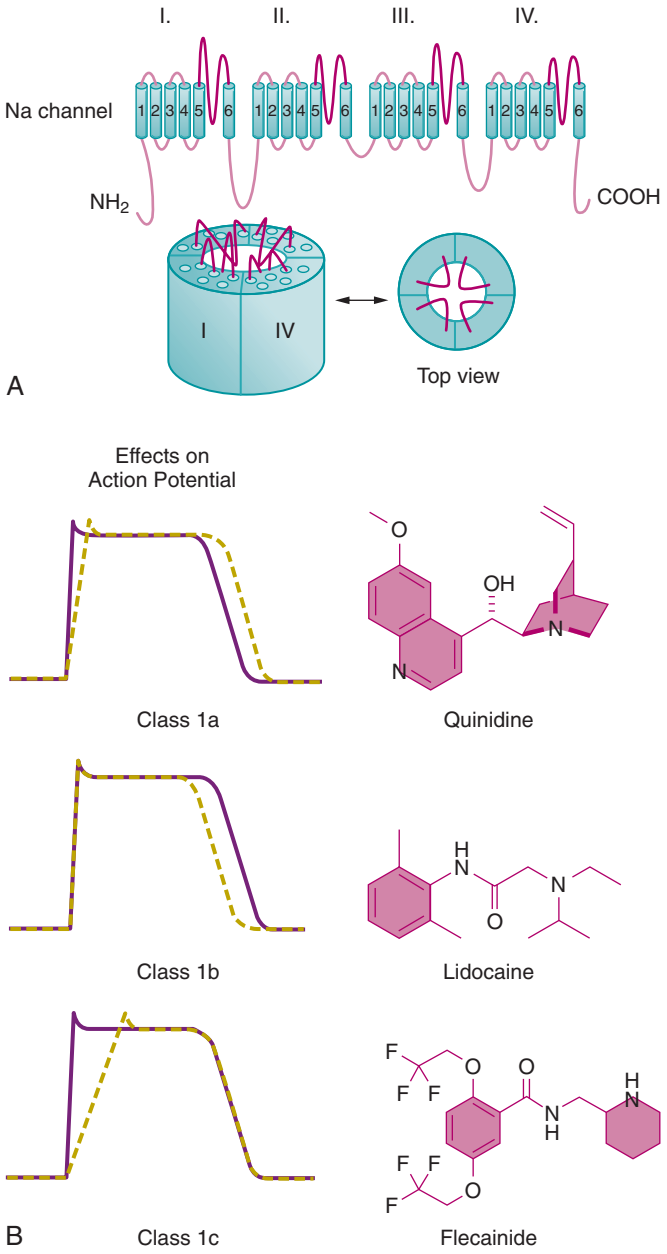
TABLE 27.2 Antiarrhythmic Drugs

Class	Mechanism	Specific Drugs	Clinical Uses	Adverse Effects
Ia	Na^+ channel block (intermediate kinetics); K^+ channel block; repolarization prolonged	Quinidine Procainamide Disopyramide	Ventricular arrhythmias Prevention of paroxysmal recurrent atrial fibrillation Conversion of atrial flutter and fibrillation (quinidine, procainamide) Maintenance of sinus rhythm after conversion of atrial flutter and fibrillation Wolff-Parkinson-White syndrome (procainamide)	QTP/torsades de pointes, nausea, diarrhea, hepatotoxicity, myelosuppression Lethal ventricular arrhythmias, QTP/torsades de pointes, hypotension Lupus-like syndrome, blood dyscrasias Proarrhythmic, torsades de pointes, negative inotropy Parasympatholytic
Ib	Na^+ channel block (fast kinetics); repolarization shortened	Lidocaine Tocainide Mexiletine	Ventricular tachycardia/fibrillation (lidocaine) Atrial fibrillation	Seizure, tremor, confusion/delirium Ataxia, tremor
Ic	Na^+ channel block (slow kinetics); no effect on repolarization	Flecainide Propafenone	Prevention of paroxysmal atrial fibrillation Recurrent tachyarrhythmias of abnormal conduction system Contraindicated immediately after myocardial infarction	Proarrhythmic, heart failure Proarrhythmic, nausea
II	β blockade Propranolol also shows class I effect	Nonselective Propranolol Nadolol β_1 selective Esmolol Metoprolol Atenolol Bisoprolol Nonselective β/α blockade Carvedilol Labetalol	Reduce myocardial infarction mortality Prevention of recurrence of tachyarrhythmias Rate control	Bradycardia, hypotension, fatigue, depression
III	K^+ channel block Sotalol is also a β blocker Amiodarone and dronedarone have class I, II, and III activity	Sotalol Ibutilide Dofetilide Amiodarone Dronedarone Bretylium (no longer available in U.S.)	Wolff-Parkinson-White syndrome Ventricular tachycardia/fibrillation (sotalol bretylium, amiodarone) Conversion of atrial flutter and fibrillation (ibutilide, sotalol, dofetilide, amiodarone) Maintenance of sinus rhythm after conversion of atrial flutter and fibrillation (sotalol, dofetilide, amiodarone, dronedarone)	Proarrhythmic, QTP/torsades de pointes, bradycardia, heart failure Proarrhythmic, QTP/torsades de pointes Proarrhythmic, QTP/torsades de pointes Hypotension, bradycardia Pulmonary, neurologic, hepatic, dermatologic, ophthalmic, thyroid Increased mortality with heart failure Nausea, vomiting, diarrhea Proarrhythmic, hypotension
IV	Ca^{2+} channel block	Dihydropyridine (selective vasodilators) Nifedipine, nicardipine, amlodipine, isradipine Benzothiapine (less vasodilation; sinoatrial and atrioventricular node block) Diltiazem Phenylalkylamine (sinoatrial and atrioventricular node block) Verapamil	Hypertension Prevention of recurrent paroxysmal supraventricular tachycardia Reduce ventricular rate in atrial fibrillation Prevention of recurrent paroxysmal supraventricular tachycardia Reduce ventricular rate in atrial fibrillation	 Bradycardia, hypotension, ankle swelling Bradycardia, hypotension, constipation
Other	Adenosine receptor activation Sodium pump inhibition Ca^{2+} channel block and other effects	Adenosine Digoxin Magnesium	Supraventricular arrhythmias Heart failure, atrial fibrillation Torsades de pointes	 Bradycardia, nausea, vomiting, visual disturbances Hypotension, weakness

QTP, QT interval prolongation.



• **Fig. 27.1** Cardiac action potentials and the electrocardiogram. A, *Upper,* a generic cardiac action potential illustrating the phases and major currents involved. *NCX,* sodium/calcium exchanger. *Lower,* comparison of nodal (*SA,* sinoatrial; *AV,* atrioventricular), atrial, and ventricular action potentials. B, *Upper,* ventricular action potential superimposed on an electrocardiogram (ECG) showing the QT interval–prolonging effects of potassium channel block and resultant early afterdepolarizations. *Lower,* delayed afterdepolarizations. C, ECG showing torsades de pointes. (Trace from Braunwald E, Zipes DP, Libby P, eds. *Heart Disease*. 6th ed. Philadelphia: WB Saunders; 2001:868.)



• **Fig. 27.2** Sodium channels and the class I antiarrhythmics. A, Topology and subunit organization of the voltage-gated Na^+ (Na_v) channel α subunit. The 24-transmembrane segments form four homologous domains *(I-IV)* that fold to create the ion pore. B, *Left,* effects of class Ia, Ib, and Ic antiarrhythmics *(dotted lines)* on cardiac myocyte action potentials *(purple lines)*. *Right,* exemplar class Ia *(Quinidine)*, Ib *(Lidocaine)*, and Ic *(Flecainide)* antiarrhythmics.

classes, including lidocaine, flecainide, and quinidine, and the anticonvulsant phenytoin, binding to an overlapping but nonidentical site influenced experimentally by mutations in the S6 transmembrane segment of domain IV.[12] Drugs in class I are subcategorized as Ia, Ib, or Ic depending on their effects on Na^+ channel conduction and resultant effects on action potentials in cardiac myocytes expressing the predominant cardiac form of Na_v channel, $Na_v1.5$ (Fig. 27.2B).

$Na_v1.5$ is relatively insensitive to the canonical and lethal Na_v channel antagonist tetrodotoxin (TTX), a nerve toxin present, among other animal sources, in the nerves, skin, and gonads of the Japanese puffer fish, *Fugu rubripes*. *F. rubripes* is saddled with the dual distinction of having the shortest known genome of any vertebrate organism and being a delicacy in Japan that must be prepared by certified chefs to decrease the chances of ingestion of lethal doses of TTX by adventurous diners. Compared with its effects on $Na_v1.5$, TTX acts with up to 10^3-fold higher potency on the predominantly neuronal Na_v channel subtypes $Na_v1.1$-1.3 *(SCN1A-3A)* and the skeletal muscle–expressed channel $Na_v1.4$ *(SCN4A)*.[13] TTX, nicknamed "zombie powder" because its paralysis- and coma-inducing effects have led to its use in voodoo ceremonies (it does not cross the blood-brain barrier; those ingesting sublethal doses are potentially conscious while paralyzed), is therefore not a useful antiarrhythmic (owing to its inefficacy and lethality at low doses). However, TTX prolongs the local anesthetic effect of bupivacaine when the two are coadministered.[14] A recent high-resolution x-ray crystallographic structure of an Na_v channel from *Arcobacter butzleri* has provided a first look at this class of proteins essential to function of nerve and muscle, and will likely enhance future class I antiarrhythmic development (see Chapter 20).[15]

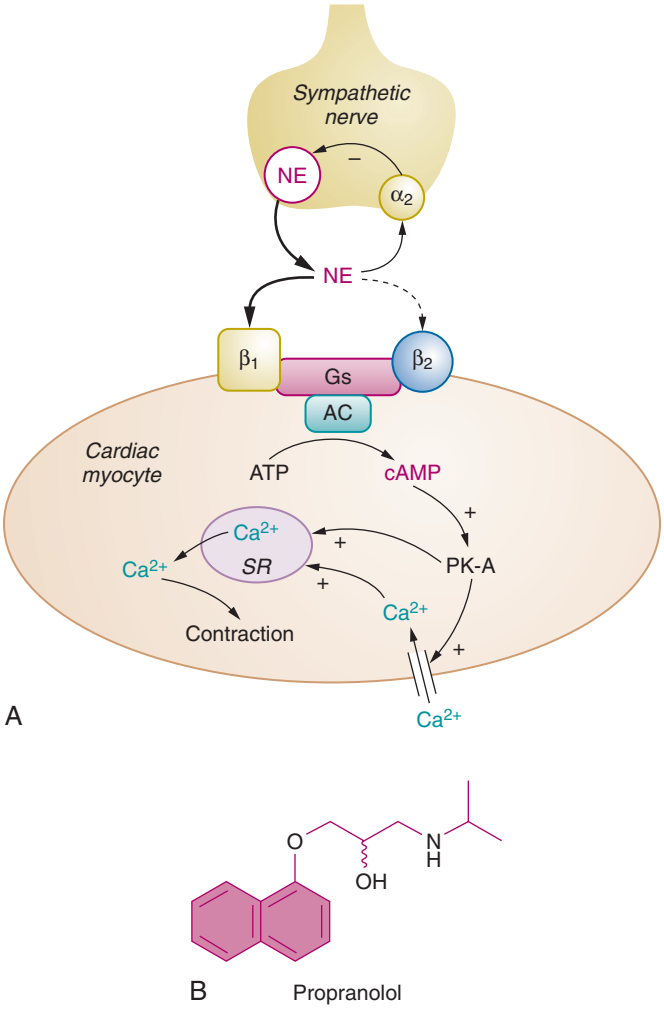
β Receptors and Class II Antiarrhythmics

Class II antiarrhythmic drugs, also known as β blockers, antagonize the β-adrenergic receptor (β receptor). This β blockade prevents activation of adenylyl cyclase and the consequent increase in intracellular cyclic adenosine monophosphate (cAMP), and thus also activation of its principal downstream target cAMP-dependent protein kinase (PKA), and the promotion of maximal myocardial performance that normally results from the enhancement of sympathetic nervous tone (Fig. 27.3; see Chapters 13 and 14).

β Blockers are selective, in that they do not block other receptors, and specific, in that they do not antagonize cardiac stimulation and vasodilatation elicited by agents other than β agonists. All β blockers share the basic structure of a β sympathomimetic side chain, which confers affinity for the receptor, along with an aromatic substituent, which determines potency; most are derivatives of the class-defining agent propranolol (see Fig. 27.3B). β Blockers are effective as antiarrhythmic agents because, by blocking the action of the sympathetic nervous system on the heart, they depress SA and AV node function, decrease conduction and automaticity, and prolong atrial refractory periods. β Blockers also reduce blood pressure, probably arising from a combination of reduced cardiac output, renal renin release, and perhaps even effects within the central nervous system (see Chapter 26).[16,17] Inasmuch as an exaggerated increase in sympathetic tone typifies the deleterious reaction to congestive heart failure, β blockers, particularly the cardioselective ones, are used successfully also in the treatment of this ailment.[18] Propranolol is marketed as a *D,L*-racemic mixture (see Chapter 1 for a discussion of the pharmacologic implications of chirality), the reason being that the *L*-form is the β blocker while the *D*-form is a "membrane stabilizer," which adds antiarrhythmic effect to the β-blocking properties of the *L*-enantiomer.

Potassium Channels and Class III Antiarrhythmic Drugs

Class III antiarrhythmic drugs are defined by their ability to block K^+ channels. This activity increases action potential duration in cardiac myocytes and prolongs the refractory period—that is, it extends the period during which the heart is refractory to premature electrical stimuli. Cardiac K^+ channels exhibit a much wider variety



• **Fig. 27.3** β-Adrenergic signaling and the class II antiarrhythmics. A, Schematic showing β-adrenergic signaling and its effects on cardiac function. *AC,* Adenylyl cyclase; *Gs,* G-stimulatory protein; *NE,* norepinephrine; *PK-A,* cAMP-dependent protein kinase; *SR,* sarcoplasmic reticulum. B, Structure of the canonical β blocker, propranolol.

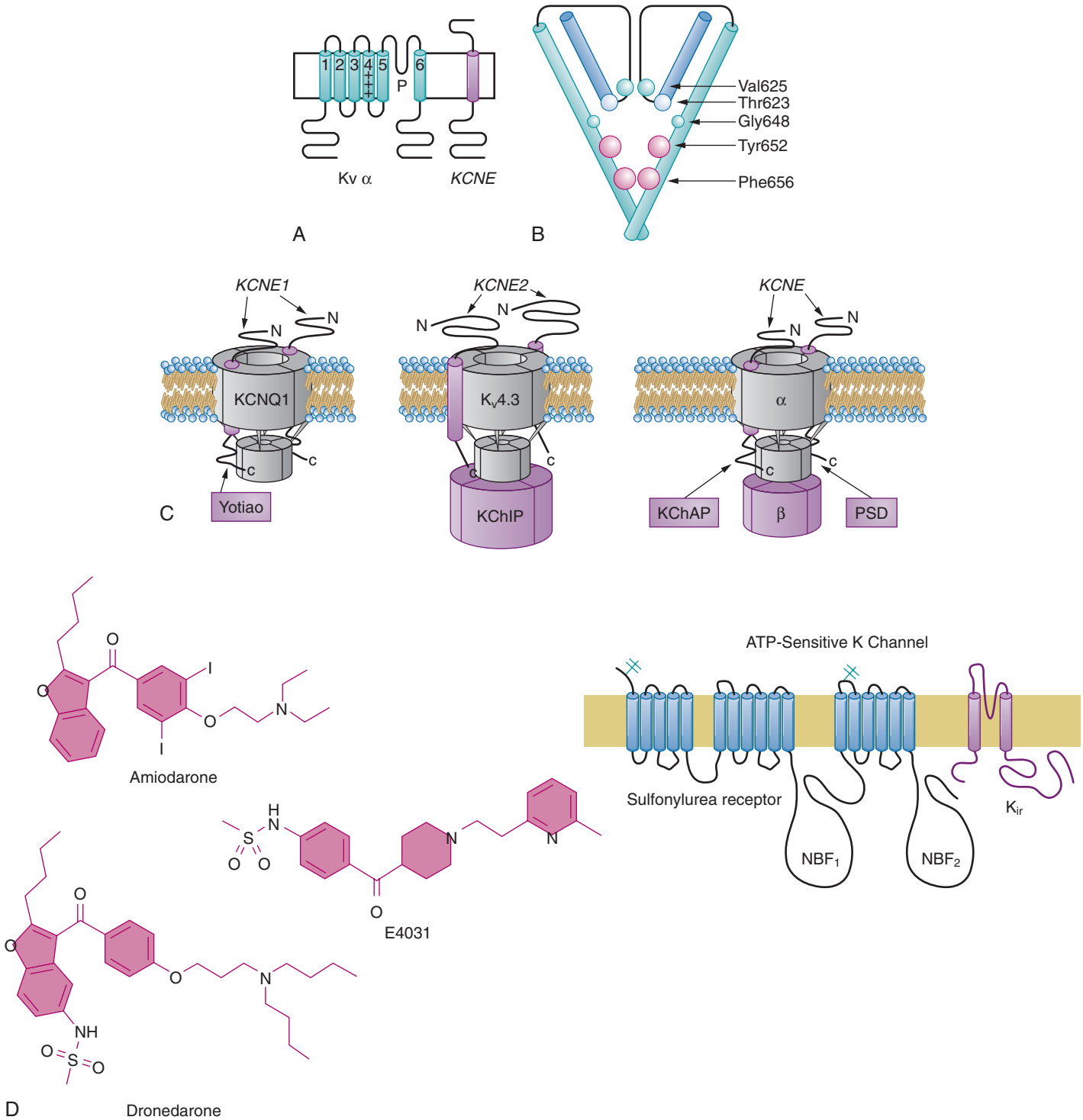
than other cardiac ion channels. The two most physiologically and therapeutically important families of K^+ channels in the heart, based on current understanding, are the voltage-gated K^+ (K_v) channels and inward rectifier potassium (K_{ir}) channels.[19,20] Channels in both these families are predominantly involved in the repolarization phases of the cardiac myocyte action potential, because both K_v and K_{ir} channels pass inward K^+ currents only when the cell membrane potential is negative to the K^+ equilibrium potential, which is around −80 mV under physiologic conditions.

K_v channels are each composed of several subunit types. Similar to Na_v channels, the pore-forming α subunits of K_v channels are arranged in a 24-transmembrane-segment array forming an aqueous central pore with external voltage-sensing modules (Fig. 27.4A). However, in K_v channels, this is composed of a tetramer of noncovalently linked α subunits (each subunit having six transmembrane segments) rather than one contiguous α subunit with four homologous six-segment domains as in Na_v and Ca_v channels. In K_v channel α subunits, the fourth transmembrane segment (S4) bears the basic residues that confer voltage sensitivity, while S6 lines the pore (Fig. 27.4A). High-resolution x-ray crystallographic structures of bacterial and eukaryotic K_v channels have revolutionized the study of these ubiquitous and essential proteins, including current understanding of drug binding sites.[21,22]

The most important K_v α subunits in human ventricular repolarization are the *ether-à-go-go* related gene product (hERG; also named *KCNH2*) and *KCNQ1*. Tetramers of each of these coassemble with multiple single-transmembrane-domain ancillary or β subunits from the *KCNE* gene family. *KCNQ1-KCNE1* complexes primarily generate the slowly activating I_{Ks} current; hERG-*KCNE2* complexes generate I_{Kr}; and each of the five KCNE proteins probably regulates these and other α subunits in the heart too.[23–26] I_{Kr} and I_{Ks} are crucial to phase 3 repolarization (see Fig. 27.1A); therefore blocking these currents delays ventricular repolarization, which can be proarrhythmic or antiarrhythmic depending on the disease state and other genetic and environmental factors.[27] hERG is particularly sensitive to drug block by a wide range of drugs, owing to its bearing an unusual array of hydrophobic residues, not conserved among other K_v channels, in an internal pore cavity also predicted to be wider than in other K_v channels (Fig. 27.4B).[28]

Inhibitors of K_v channels tend to bind in one of three distinct sites: the outer vestibule, the inner vestibule (drugs in these classes would be considered pore blockers), or on the voltage sensor, which is rarer among small molecules but is seen with some toxins from venomous animals, such as hanatoxin and SGTx from tarantula spiders.[29] The canonical inhibitors of hERG and *KCNQ1* are E-4031 and chromanol 293B, respectively, both of which bind in the inner vestibule and show relatively high specificity for their targets. Additionally, both drugs are sensitive to the presence of *KCNE* subunits in complex with the α subunits.[30] E-4031 will not be used in the future for antiarrhythmic therapy because pure hERG antagonists such as this cause dangerous repolarization delays. I_{Ks} inhibitors are still being considered because it might be therapeutically useful to counteract the upregulation of I_{Ks} during periods of high sympathetic activity associated with arrhythmia triggering. Other important K_v channel targets of class III antiarrhythmic drugs include the K_v4 α subunits that generate human ventricular I_{to} (particularly active during phase 1 of the ventricular action potential), and $K_v1.5$, which generates the ultrarapidly activating K^+ current, I_{Kur}, important in atrial myocyte repolarization. K_v4 and $K_v1.5$ α subunits are also regulated by the *KCNE* subunits.[31,32] In addition, all the K_v channels discussed herein are regulated by a host of cytoplasmic β subunits and other regulatory proteins (Fig. 27.4C), each of which can affect channel pharmacology either directly or indirectly, because changes in gating alter drug binding kinetics.[30,33]

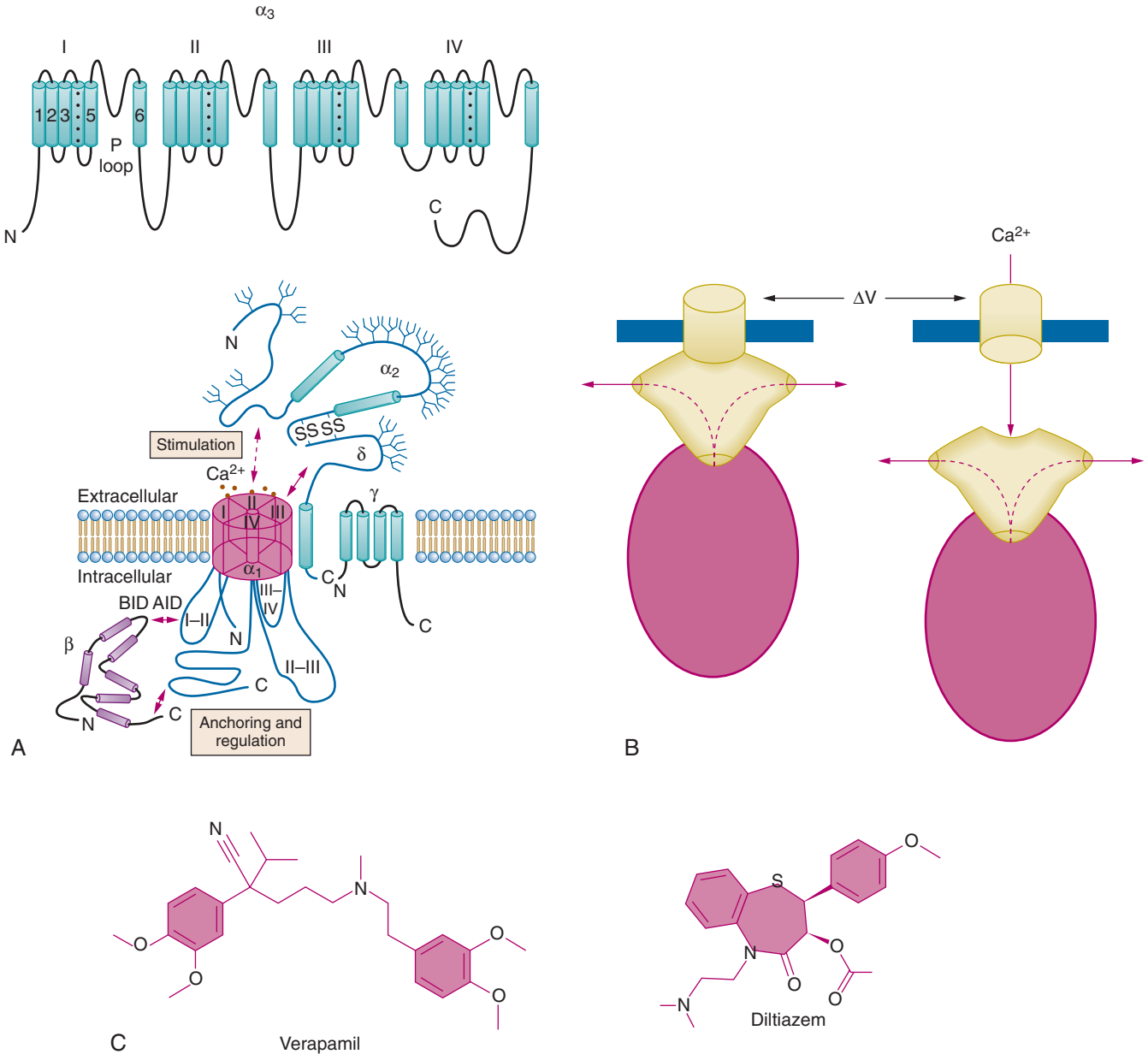
K_{ir} channels do not possess a voltage sensor but exhibit inward rectification because they are inhibited at more positive membrane potentials by intracellular constituents, including magnesium (Mg^{2+}) and polyamines such as spermine. These channels are composed of a tetramer of α subunits, each with only two transmembrane segments, around a central, aqueous, K^+-selective pore (Fig. 27.4D). The ventricular inward rectifier current I_{K1} is generated by $K_{ir}2$ family α subunits and contributes to stabilizing the cardiac potential, passing current at either end but less so when the myocyte is strongly depolarized (see Fig. 27.1A). The K_{ATP} channel, which also probably contributes to cardiac excitability, is an octamer of four $K_{ir}6$ α subunits and four membrane-spanning sulfonylurea receptor subunits that render it sensitive to adenosine triphosphate (ATP).[19] A host of class III drugs, including amiodarone and dofetilide, inhibit K_{ir} channels by direct pore block within the inner vestibule.[34,35]



• **Fig. 27.4** Potassium channels and the class III antiarrhythmics. A, Topology of a K_v α subunit and a *KCNE* β subunit. B, Left, drug binding site within the ether-à-go-go related gene product (hERG) K_v α subunit. Residues in *red* are crucial for binding of a variety of drugs, such as cisapride and terfenadine, and undergo π-bonding with the aromatic rings of methanesulfonanilides. *Green* and *blue* residues are less impactful on cisapride and terfenadine binding but important for methanesulfonanilide binding.[104] *Right,* structures of some class III antiarrhythmic drugs. C, Cartoons of some heteromeric K_v channels containing α subunits, and both transmembrane and cytoplasmic β subunits. D, Topology of a K_{ir} α subunit and an SUR subunit. *ATP,* Adenosine triphosphate; *K,* potassium; *KChAP,* kt channel associated protein; *KChIP,* K_v channel–interacting protein; K_{ir}, inward rectifier potassium; *NBF,* nucleotide-binding fold; *SUR,* sulfonylurea receptor.

Calcium Channels and Class IV Antiarrhythmics

Class IV agents slow AV nodal conduction, primarily by L-type Ca^{2+} channel (LTCC) antagonism. LTCCs mediate the upstroke of nodal cell action potentials, unlike true atrial and ventricular myocyte action potentials in which the upstroke is mediated primarily by the faster activating and inactivating Na_v channel, $Na_v1.5$. Hence, nodal action potentials exhibit a much slower upstroke than that of typical atrial and ventricular myocytes (see Chapter 23). The transmembrane topology of voltage-gated Ca^{2+} channel (Ca_v) α subunits mirrors that of the Na_v channel α subunits: 24 transmembrane segments around an aqueous pore. LTCCs also incorporate a requisite array of ancillary subunits: the cytoplasmic β subunit, transmembrane δ and γ subunits, and extracellular α_2 subunit (Fig. 27.5A). In cardiac muscle, the LTCC $Ca_v1.2$ α subunit is located in the T-tubules and is activated by cellular depolarization, via its voltage-sensing apparatus, which moves upon membrane depolarization and opens the discrete but connected pore. Ca^{2+} influx through $Ca_v1.2$, down the Ca^{2+} concentration gradient, helps depolarize the cell and increase cytosolic [Ca^{2+}] directly, but it also works indirectly by activating the sarcoplasmic reticulum–located ryanodine receptor (RyR2 in cardiac muscle) through Ca^{2+}-activated Ca^{2+} release. In skeletal muscle, the mechanism is somewhat different: $Ca_v1.1$ is mechanically linked to RyR1



• **Fig. 27.5** Calcium channels and the class IV antiarrhythmics. A, *Upper,* topology of a voltage-gated Ca^{2+} channel α subunit (Ca_v). Note similar structure to Na_v shown in Fig. 27.2. *Lower,* heteromeric voltage-gated Ca^{2+} channel complex with $\alpha_2\delta$ accessory subunits. B, Juxtaposition of voltage-gated Ca^{2+} channel at the cell surface membrane *(blue)* and the sarcoplasmic reticulum–located ryanodine receptor in skeletal muscle *(left)* and cardiac muscle *(right)*. C, Structures of verapamil and diltiazem, key class IV antiarrhythmic drugs. *BID,* B-interacting domain; *AID,* α-interacting domain; *Ca^{2+},* calcium ion; *SS,* disulfide bond.

and acts as the latter's voltage sensor. Thus in skeletal muscle, RyR1 is activated primarily by membrane depolarization, with the $Ca_v1.1$ S4 domains acting as the RyR1 voltage sensors (see Fig. 27.5B).[36,37]

Most clinically relevant Ca_v channel blockers are in one of three chemical classes: the dihydropyridines, which are not generally indicated for arrhythmias; the phenylalkylamines, exemplified by verapamil; and the benzothiazepines, exemplified by diltiazem.[38] Diltiazem and verapamil (see Fig. 27.5C) are thought to bind overlapping but distinct sites within the S6 segments of repeats III and IV, and the Ca^{2+} selectivity filter of the α_1 subunit of the cardiac LTCC $Ca_v1.2$.[39–41]

Clinical Pharmacology

Categories of Arrhythmogenic Mechanisms

The mechanistic bases for most, if not all, arrhythmias can be placed in one of three categories. These are discussed with the most common modes of treatment.[42–47]

Automaticity

Arrhythmias in this category arise from changes to the normal process of automaticity essential for cardiac rhythm (see Fig. 27.1). They can be further separated into two subcategories:

Normal automaticity arrhythmias are those that elicit speeding or slowing of the heartbeat, initially at least maintaining regular beating, although this is lost at some point—for example, at extremely high heart rates, owing to an intrinsic inability of ion channels to function rapidly enough in concert. Arrhythmias in this category include sinus tachycardia and ventricular tachycardia (both being an increased heart rate). *The most common pharmacologic treatment of sinus tachycardia and ventricular tachycardia is with β blockers (class II antiarrhythmics).*

Abnormal automaticity arrhythmias are those in which regular activity is lost immediately and involve spontaneous impulse formation in partially depolarized cells (membrane potentials in the range of −40 to −60 mV). Examples of arrhythmias that can fall into this category include ventricular tachycardias and ectopic atrial tachycardias in the subacute phase (within 48 hours) following myocardial infarction, exercise-induced idiopathic ventricular tachycardias, and catecholamine-sensitive idiopathic ventricular tachycardias. *The most common pharmacologic treatment of idiopathic rhythms and ectopic atrial tachycardias is with Ca^{2+} channel blockers (class IV antiarrhythmics).*

Sinus rhythm is regulated by pacemaker channels (i.e., hyperpolarization-activated, cyclic nucleotide-gated monovalent cation-nonselective channels known as *HCN*), and to a greater or lesser extent, Ca^{2+} oscillations. Hence, human HCN4 mutation is associated with sinus-mediated pathologic slowing of the heart rate (sinus bradycardia).

Triggered

Triggered arrhythmias are those in which a mistimed beat occurs before the previous beat is complete (see Fig. 27.1B). The ion channels involved in orchestrating each cardiac myocyte action potential must work in concert to generate rhythmic contraction of the heart. Because the various classes of ion channels each have distinct gating kinetics and refractory periods, if one type of ion channel dysfunctions, it can act asynchronously with the others, potentially causing triggered arrhythmias. Triggered arrhythmias can be separated into two main classes:

Early after-depolarizations (EADs) occur when myocardial repolarization is delayed sufficiently that the next action potential in a given cardiac myocyte begins before that myocyte is fully repolarized. A common clinical consequence is the arrhythmia referred to as *torsades de pointes* (TdP). TdP is so named because it appears on the electrocardiogram (ECG) as a twisted ribbon owing to the variance in magnitude of the voltages associated with each heartbeat (see Fig. 27.1C). TdP most often occurs because of pharmacologic inhibition of specific ventricular myocyte K^+ channels, which results in a delay in ventricular myocyte repolarization and consequent prolongation of the QT interval on the ECG. A number of drugs inhibit these channels and can lead to TdP, including several drugs commonly used in anesthesia; some of the major QT interval prolonging drugs are summarized in Table 27.3. The QT interval represents the time from the onset of ventricular depolarization to the end of ventricular repolarization; prolongation of this interval can indicate long QT syndrome, of which there are now many well-defined subtypes with distinct molecular etiologies. When sufficiently long delays in repolarization occur, Na_v channels can recover from their refractory period and open before repolarization is complete, leading to an EAD in phase 2, 3, or 4 of the ventricular or atrial action potential (see Fig. 27.1B). *The most common pharmacologic treatment of TdP is with magnesium sulfate, β blockers (class II antiarrhythmics), and/or Ca^{2+} channel blockers (class IV antiarrhythmics).*

Delayed after-depolarizations (DADs) classically occur in digitalis toxicity. Digitalis toxicity can occur through a variety of mechanisms, but all serve to raise intracellular Ca^{2+} concentration, generating a net depolarizing current that, together with the tendency of digitalis to increase vagal tone, leads to DADs (among other possible classes of arrhythmias). Unlike most EADs, DADs begin after repolarization but before the next appropriately timed depolarization—that is, in phase 4 of the cardiac action potential (see Fig. 27.1B). *The most common pharmacologic treatment of DADs arising from digitalis toxicity is with Ca^{2+} channel blockers (class IV antiarrhythmics).*

Conduction

Commonly arising from structural damage to the heart, but also from certain drug-ion channel interactions, localized slowed conduction within regions of the heart can cause reentrant arrhythmias that can be categorized into two main types:

Reentrant circuits arise when one area of the heart contains a region of slowed ion conduction. When such regions occur, primarily resulting from the refractory period of Na_v channels arising from their rapid and extensive inactivation and its recovery, reentrant circuits are formed because normal conduction cannot proceed unidirectionally but can proceed in a circle (Fig. 27.6A). They can be microreentrant (involving a localized region within [e.g., one chamber of the heart]) or macroreentrant, involving more than one chamber (Fig. 27.6B). Such circuits are incompatible with normal cardiac rhythm because they disturb the (essentially) unidirectional wave of depolarization/repolarization required for normal contraction to occur. These types of circuits cause atrial flutter and ventricular and supraventricular tachycardias. *Monomorphic ventricular tachycardia is treated with class Ia Na_v channel blockers or K^+ channel blockers (class III antiarrhythmics). AV node reentrant tachycardias (supraventricular tachycardia or SVT), which arise from reentry in the region of the AV junction, are treated with Ca^{2+} channel blockers (class IV antiarrhythmics) or adenosine.*

Fibrillation occurs when many microreentrant circuits span an entire chamber of the heart. This is a different situation from a

TABLE 27.3 Drugs Known to Prolong QT Interval

Generic Name	Class	Comments
Amiodarone	Antiarrhythmic	Females > males, torsades de pointes risk low
Arsenic trioxide	Anticancer	
Astemizole	Antihistamine	No longer available in U.S.
Bepridil	Antianginal	Females > males
Chloroquine	Antimalarial	
Chlorpromazine	Antipsychotic; antiemetic	
Cisapride	Gastrointestinal stimulant	No longer available in U.S.; available in Mexico
Citalopram	Antidepressant	
Clarithromycin	Antibiotic	
Disopyramide	Antiarrhythmic	Females > males
Dofetilide	Antiarrhythmic	
Domperidone	Antiemetic	Not available in U.S.
Droperidol	Sedative; antiemetic	
Erythromycin	Antibiotic; gastrointestinal stimulant	Females > males
Flecainide	Antiarrhythmic	
Halofantrine	Antimalarial	Females > males
Haloperidol	Antipsychotic	When given intravenously or at higher-than-recommended doses
Ibutilide	Antiarrhythmic	Females > males
Levomethadyl	Opioid agonist	Not available in U.S.
Mesoridazine	Antipsychotic	
Methadone	Opioid agonist	Females > males
Moxifloxacin	Antibiotic	
Ondansetron	Antiemetic	
Pentamidine	Anti-infective	Females > males
Pimozide	Antipsychotic	Females > males
Probucol	Antilipemic	No longer available in U.S.
Procainamide	Antiarrhythmic	
Quinidine	Antiarrhythmic	Females > males
Sevoflurane	Volatile anesthetic	
Sotalol	Antiarrhythmic	Females > males
Sparfloxacin	Antibiotic	
Terfenadine	Antihistamine	No longer available in U.S.
Thioridazine	Antipsychotic	
Vandetanib	Anticancer	

See www.azcert.org for more information.

single macroreentrant circuit and is typically classified (according to the chambers in which it is occurring) as AF or ventricular fibrillation. The substrate for AF is probably most commonly structural heart disease, and while it is typically not acutely dangerous, it requires treatment. This is partly because it suggests an underlying defect and partly because a significant risk in AF is the formation of atrial thrombi that can result in launching of systemic emboli when sinus rhythm is reestablished. Approximately 2 to 3 million people in the United States have AF; the majority are in the aging population, and this number is expected to rise as the population ages. Another common cause of AF is major surgery such as open heart surgery or lung resection, with the underlying mechanism not being entirely clear. Hyperthyroidism can also cause AF; return to euthyroidism abrogates the AF in the majority of cases. *AF is most commonly treated with Na_v channel blockers (class Ia antiarrhythmics) or K^+ channel blockers (class III antiarrhythmics).*

Ventricular fibrillation, in contrast, is acutely life-threatening because the heart in ventricular fibrillation cannot pump blood effectively. An estimated 300,000 people in the United States die annually of sudden cardiac death, with ventricular fibrillation among the most common lethal arrhythmias. Ventricular fibrillation must be rapidly treated (within minutes) using direct current shock. Cardiopulmonary resuscitation (CPR) can be used to keep the brain alive until defibrillation is possible, but CPR cannot restore normal cardiac rhythm. *Amiodarone is the first-line antiarrhythmic drug clinically demonstrated to increase return of spontaneous circulation in refractory ventricular fibrillation and pulseless ventricular tachycardia unresponsive to CPR, defibrillation, and vasopressor therapy. If amiodarone is unavailable, lidocaine can be considered as a second-line drug with less evidence of efficacy compared with amiodarone. Magnesium sulfate is used for TdP associated with a long QT interval.*

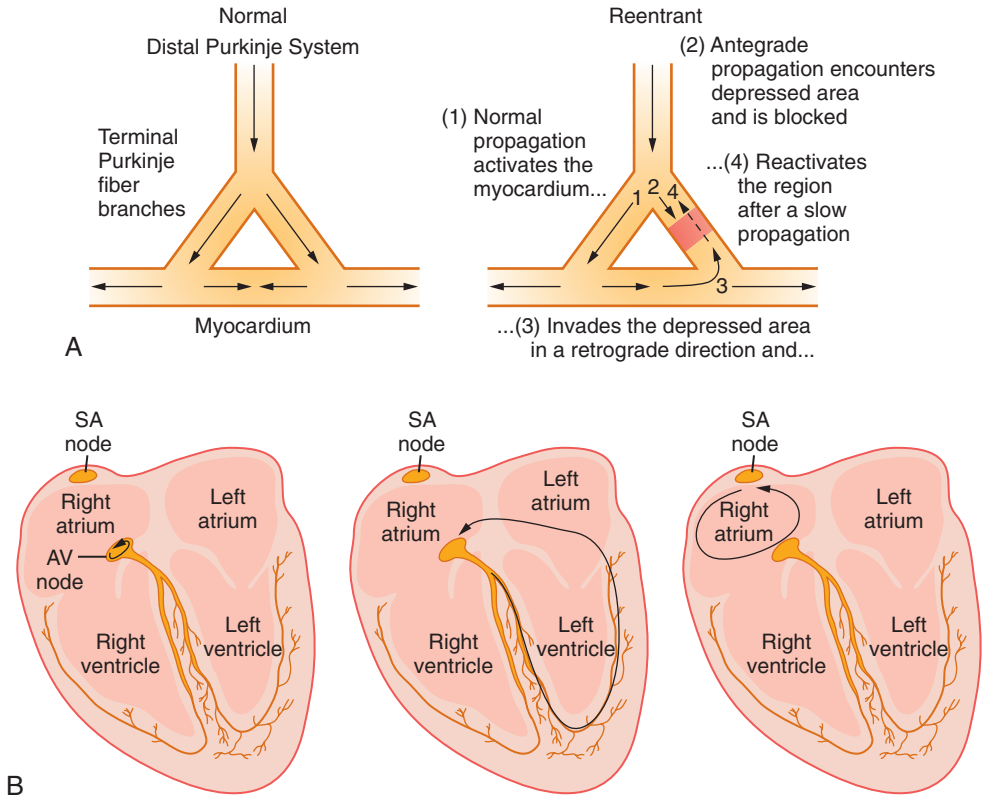
Clinical Application

Class I—Sodium Channel Blockers

Class Ia Na_v Channel Blockers

The class Ia antiarrhythmics block ion conduction through $Na_v1.5$, the principal cardiac Na^+ channel; this delays and reduces the magnitude of peak depolarization in cardiomyocytes and thus prolongs the action potential. Refractoriness is also increased in that Na_v channels require a greater hyperpolarization and longer time to recover from inactivation in the presence of class Ia agents. These effects can be therapeutic if the heart is beating too rapidly or in an uncoordinated fashion. Therefore class Ia antiarrhythmics can be indicated for symptomatic premature ventricular beats and ventricular and supraventricular tachyarrhythmias. They can also be used to prevent the acutely life-threatening condition ventricular fibrillation.

Quinidine exemplifies the advantages and potential drawbacks of class Ia antiarrhythmic drugs, and of the SVW classification itself. Aside from blocking $Na_v1.5$ channels in the activated state, which slows phase 0 depolarization (see Fig. 27.2B), quinidine also blocks certain voltage-gated K^+ channels, which in turn delays phase 3 repolarization and can in itself be proarrhythmic, prolonging the QT interval on the ECG (Fig. 27.1C). It also widens the QRS complex through its effects on $Na_v1.5$. Quinidine can also decrease the slope of phase 4 depolarization in Purkinje fibers, thereby reducing automaticity. Because quinidine has anti–muscarinic-based



• **Fig. 27.6** Reentrant circuits. A, Anatomy of a reentrant circuit. Depending on the relative speed of conduction and duration of refractory periods in two alternate longitudinal pathways, anterograde propagation can be blocked in one pathway, whereas retrograde propagation progresses, creating a reentrant circuit. B, Examples of microreentrant and macroreentrant circuits in the heart. *Left,* a microreentrant circuit in the atrioventricular (AV) node; *center,* a macroreentrant circuit spanning the AV node and left atrium and ventricle; *right,* a microreentrant circuit in the right atrium. *SA,* Sinoatrial.

vagolytic properties that work against its direct action on the SA and AV nodes, it can actually increase conduction through these nodes. This presents problems because it can cause 1 : 1 conduction of AF, thereby also increasing ventricular rate. Thus, if used for AF, quinidine (and the related class Ia agent, procainamide) must be accompanied by an AV node blocking agent to prevent this (e.g., class II or IV antiarrhythmics).

Quinidine is also a notable antimalarial: it kills the schizont parasite of *Plasmodium falciparum* and gametocyte parasite stages of *Plasmodium* spp. Quinidine is associated with a number of contraindications and precautions aside from the AV conduction issues noted earlier: It can increase digoxin levels by decreasing renal and extrarenal clearance and can aggravate myasthenia gravis.[48]

Procainamide (available only in an intravenous formulation in the United States) is another important class Ia antiarrhythmic that can be used to treat AF in Wolff-Parkinson-White syndrome (WPWS). Other class Ia agents include ajmaline, lorajmaline, prajmaline, disopyramide, and sparteine.

Class Ib Na_v Channel Blockers

The class Ib antiarrhythmics have relatively little effect on conduction velocities and low proarrhythmic potential. They exhibit rapid Na_v channel binding kinetics and their main actions are to decrease the duration of the ventricular myocyte action potential and the refractory period (see Fig. 27.2B). Class Ib drugs have little effect on atrial myocyte action potentials, and therefore on atrial tissue, since they are, at baseline, relatively short compared with ventricular action potentials. Thus these drugs are primarily used to treat ventricular arrhythmias.[49]

Lidocaine (see Fig. 27.2B) is the archetypal class Ib antiarrhythmic. Like all class Ib drugs, its rapid binding and unbinding rates (endowing it with use dependency or frequency dependency) greatly diminish its effects at low heart rates and exaggerate its effects at high heart rates. Lidocaine selectively targets the open and inactivated states of $Na_v1.5$, with low affinity for the deactivated (closed or resting) state. For this reason, lidocaine and other class Ib drugs can be efficacious in the therapy of rapid heart rate conditions, including ventricular tachycardia and ventricular fibrillation prevention, and in cases of symptomatic premature ventricular beats. Other notable class Ib drugs include mexiletine (which is metabolized to lidocaine), phenytoin, and tocainide.[47]

Class Ic Na_v Channel Blockers

Class Ic antiarrhythmics exhibit relatively slow Na_v channel binding kinetics, and can be used to treat both atrial and ventricular arrhythmias. Drugs in this class are indicated for treatment of nonsustained ventricular tachycardias, but they are contraindicated when there is underlying heart disease such as myocardial infarction or left ventricular hypertrophy.[50] Class Ic agents typically slow Na_v channel conduction, delaying the peak depolarization and somewhat prolonging the QT interval (Fig. 27.2B).

Flecainide (see Fig. 27.2B), an important class Ic antiarrhythmic, displays little end-organ toxicity but can exhibit significant proarrhythmic effects. Interestingly, flecainide is now thought to also inhibit Ca^{2+} release from the cardiac sarcoplasmic reticulum Ca^{2+} release channel, ryanodine receptor 2 (RyR2), endowing it with therapeutic activity in individuals with catecholaminergic polymorphic ventricular tachycardia (CPVT).[51] The more well-recognized, class Ic action of flecainide confers its effectiveness in prevention of paroxysmal AF and flutter, paroxysmal supraventricular tachycardias, and sustained ventricular tachycardias.[52]

Class II—β Blockers

β-Adrenoceptor antagonists, also known as β blockers, are pharmacologic agents that competitively antagonize the β effects of catecholamines on the heart, blood vessels, bronchi, and so on (see Chapters 13 and 14). Propranolol was introduced in 1965 as the first therapeutically useful β blocker and more than 20 analogs are available today. They are used not only as antiarrhythmics, but also as antianginals and antihypertensives, in that they limit cardiac oxygen consumption and lower plasma renin activity. Depending on their relative β-receptor affinities, β blockers are classified as nonselective (or "blanket" β blockers) when they block both β_1- and β_2-receptor subtypes such as propranolol, or cardioselective (i.e., β_1-selective), such as metoprolol, atenolol, and nebivolol. Third-generation β blockers endowed with vasodilating properties are also available, such as pindolol and carvedilol, which are therapeutically used in congestive heart failure.

Duration of action varies among the various analogs; esmolol has the shortest duration ($t_{1/2}$ ~9 minutes) and nadolol is the longest-acting drug ($t_{1/2}$ ~24 hours), allowing once-daily dosing. Lipid/water solubility of the various β blockers influences the route of elimination: the more lipid-soluble are eliminated primarily by the liver (e.g., propranolol and metoprolol), and the more water-soluble are eliminated primarily by the kidney (e.g., atenolol and nadolol). Thus hepatic cirrhosis and renal failure can prolong the action of lipid- and water-soluble β blockers, respectively.

Adverse effects of β blockers are due mainly to β_2-blocking effects. Among these, bronchospasm in patients with bronchial asthma or chronic obstructive pulmonary disease can cause severe dyspnea. Peripheral vasoconstriction can also occur with blockade of vascular β_2 receptors, as shown by a relatively rare worsening of symptoms of peripheral vascular disease (e.g., intermittent claudication, Raynaud phenomenon). On the other hand, excessive β_1 blockade can cause bradycardia, hypotension, and AV node conduction block.

β-Adrenoceptor stimulation enhances $I_{Ca\text{-}L}$ and $I_{Ca\text{-}T}$ currents and slows Ca^{2+} channel inactivation. It also increases sinus rate by increasing the I_f pacemaker current and increases Ca^{2+} storage in the SR, leading to DAD (see Fig. 27.1B). By inhibiting all of these effects, β blockers exert an antiarrhythmic action that is particularly effective whenever sympathetic activity is increased, such as in stressful conditions, acute myocardial infarction, and CPR following cardiac arrest. Bradycardia and slowing of AV nodal conduction (prolongation of the PR interval) are typically observed. Therefore β blockers are valuable in terminating reentrant arrhythmias that include the AV node, and in controlling ventricular rate in AF or flutter. β Blockers can also be used to treat postoperative AF, which commonly occurs following cardiac or thoracic surgery. Postoperative AF incidence is twofold to fivefold higher in patients whose β blockers are discontinued postoperatively. Sotalol is a methanesulfonanilide β blocker that also exhibits class III antiarrhythmic properties because it blocks potassium channels including hERG. Sotalol reduces incidence of postoperative AF, although its use is limited because it increases risk of TdP and bradycardia.

Overall, β blockers are effective in treating or preventing arrhythmias that share as a common denominator increased sympathetic activity. These include paroxysmal atrial tachycardia resulting from exercise or emotion, exercise-induced ventricular arrhythmias, arrhythmias associated with pheochromocytoma, arrhythmias associated with myocardial infarction, and all the arrhythmias accompanied by angina or hypertension.[17,53]

Class III—Potassium Channel Blockers

K_v channels are the primary target for class III antiarrhythmics. By blocking K_v channels, class III agents prolong the action potential and therefore increase refractoriness (see Fig. 27.4B). These drugs can thus be highly efficacious in the treatment of a variety of tachyarrhythmias, both ventricular and atrial. One of the great paradoxes of arrhythmia therapy is that action potential prolongation can be either therapeutic or life-threatening depending on the nature of the genetic, electrical, and/or structural defect in the patient. Although K_v channel blockade can help control dangerous tachycardia, it can also precipitate TdP because of its QT-prolonging effects; this in turn can lead to lethal ventricular fibrillation.

The problem with many class III agents is that they inhibit the hERG K_v channel (which generates I_{Kr} as explained earlier) in a reverse use-dependent manner that does not increase block with heart rate, but rather does the opposite. This impairs the crucial I_{Kr} repolarization current, delaying phase 3 repolarization, most aggressively in bradycardia and less so in tachycardia, which can lead to a dangerously proarrhythmic tendency.

Two significant advances in the field of class III antiarrhythmic development are overcoming these problems. The first advance is exemplified by amiodarone (see Fig. 27.4B), a drug that actually has actions in all four SVW classes, but the major therapeutic effect of which is thought to result from its class III effects.[54] The big advantage of amiodarone over earlier agents (although it was first described in 1961, it was only approved for use in the United States in 1985) is that it inhibits both I_{Kr} and I_{Ks}. I_{Ks} is generated by a heteromer of the *KCNQ1* K_v α subunit and most commonly the KCNE1 β subunit, and is the primary slow-activating component of the delayed rectifier K^+ current acting in phase 3 repolarization. I_{Ks} rises to prominence, in terms of its role in repolarization, at higher heart rates because *KCNQ1-KCNE1* channels accumulate in the activated state, and conversely at these rates I_{Kr} is less effective at ventricular repolarization—hence the reverse use dependence of "pure" I_{Kr} blockers. I_{Ks} probably acts as a safety factor, or repolarization reserve, to compensate for the relative impotency of I_{Kr} at high heart rates. Amiodarone, by blocking both I_{Kr} and I_{Ks}, exhibits a safer and more efficacious action on phase 3 repolarization. A related drug, dronedarone, lacks the iodine that is associated with some side effects of amiodarone, including skin photosensitivity and ocular abnormalities, and the former is therefore safer (although less efficacious) and still has the dual action of I_{Kr} and I_{Ks} antagonism, as does azimilide.[55–57] Azimilide, however, and tedisamil (which inhibits I_{Kr}, I_{to} and the ATP-sensitive inwardly rectifier K^+ current I_{KATP}) have proven marginally efficacious and also torsadogenic, leading to doubts about their ultimate usefulness in AF therapy.[58,59] Their key problem is that they do not present a big enough therapeutic window to reverse atrial tachyarrhythmias without causing an unsafe

delay in ventricular repolarization—that is, they lack atrial specificity.

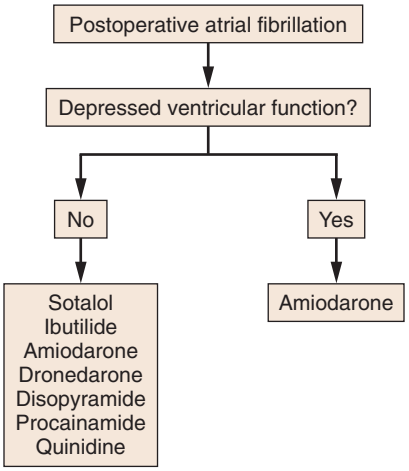
Most individuals with AF exhibit chronic, sustained atrial arrhythmia, with clinical manifestations ranging from palpitations to heart failure. The majority of chronic AF cases are linked to underlying disorders, including structural heart disease, chronic alcohol use, hyperthyroidism, and pulmonary embolism. In addition, cardiothoracic surgery predisposes to postoperative AF, with an estimated incidence of ~30% following cardiac surgery, for example.[60] Prophylactic amiodarone has been shown to decrease the incidence of postoperative AF, although it did not decrease postoperative mortality.[61,62]

Perhaps as many as a third of AF patients have "lone" AF, in which underlying heart or extracardiac disease is either occult or absent. Of these patients, some harbor ion channel mutations thought to be the substrate for AF. The KCNQ1 K_v channel gene is again involved. A key step in AF is thought to be shortening of the atrial effective refractory period; therefore it is intuitive that, as with short QT syndrome, gain-of-function mutations in *KCNQ1* are linked to AF, in that they have the capacity to hasten repolarization. In addition, mutations in several members of the *KCNE* gene family of β subunits are associated with AF by increasing currents through the respective *KCNQ1-KCNE* channel complex.[63–65] Inherited mutations in *KCNA5,* which encodes the atrially expressed K_v1.5 potassium channel α subunit, also associate with AF. Nonchannel genes associated with AF include renin-angiotensin system genes, probably in combination with environmental agents that elevate blood pressure.[66,67]

Therapeutic approaches to AF involve not just lengthening of the atrial effective refractory period (pharmacologically or by electrical cardioversion), but also surgery to prevent recurrence and anticoagulation for stroke prevention. With respect to pharmacologic intervention to control the heart in AF, control of rhythm appears to offer no significant advantage in terms of mortality or stroke risk compared to controlling the rate—that is, returning the heart rate to somewhere between 60 and 100 beats/min. However, rhythm control is desirable in newly diagnosed AF, and in other cases is dictated by patient-specific factors, and remains the strategy of choice. For pharmacologic rate control, β blockers and Ca^{2+} channel blockers are most often used, whereas for pharmacologic rhythm control, Na^+ channel blockers or K^+ channel blockers are used. The pharmacologic control of postoperative AF is summarized in Fig. 27.7.

This introduces the second potentially promising direction in class III antiarrhythmic development. The dependency of the human heart for hERG-mediated ventricular repolarization is problematic in an increasingly medicated population owing to the predilection of hERG for nonspecific drug block. In addition, hERG protein folding (part of the process that ensures that hERG channels reach the cell surface and pass K^+ ions) is highly sensitive to both drugs and inherited single–amino acid substitutions. This incredibly unfortunate combination of circumstances is due in part to the fact that, for the majority of human evolution, drugs have not been an environmental factor and thus have not had an impact on natural selection.[68]

However, nature has provided a fortuitous solution to the hERG targeting conundrum. Some potassium channels are enriched in human atria compared with ventricles, thus providing possible therapeutic targets for selective lengthening of atrial effective refractory periods. One example of this is that the ultrarapidly activating K_v current, I_{Kur}, is generated by the K_v1.5 (gene name *KCNA5*) K_v channel α subunit in human atrium, but K_v1.5 is not



• **Fig. 27.7** Rhythm control for postoperative atrial fibrillation. Given the side effect profile of amiodarone, it is generally reserved for use when other drugs are ineffective, contraindicated, or not well tolerated. Dronedarone is contraindicated in patients with acutely decompensated heart failure. Sotalol may be used with caution in selected patients with mild to moderate reduction in left ventricular ejection fraction. (Modified from Martinez EA, Bass EB, Zimetbaum P, et al. Control of rhythm: American College of Chest Physicians Guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. *Chest*. 2005;128[Suppl 2]:48S–55S.)

significantly functionally expressed in human ventricles. In theory, pharmacologic inhibition of K_v1.5 could lengthen the atrial refractory period enough to be of therapeutic benefit in human AF. Crucially, because it does not contribute to ventricular repolarization, specific K_v1.5 inhibition does not delay ventricular repolarization and therefore is not torsadogenic.

There are some caveats vis-à-vis K_v1.5 blockers. While Kv1.5 is in a different α subunit subfamily, it has been difficult to develop selective K_v1.5 antagonists that do not also inhibit hERG at therapeutic concentrations. This in itself might be tolerated because the concomitant Na_v block by drugs in this class can counteract hERG inhibition. More importantly, I_{Kur} blockers have not yet proven a clinical success. MK-0448, the first I_{Kur}-selective blocker tested in clinical trials, did not alter atrial (or ventricular) refractoriness, possibly because I_{Kur} is not as influential in the human atrium as it is in model animals such as dogs.[69] In addition, I_{Kur} appears to be reduced due to remodeling in persistent AF, potentially further diminishing its usefulness as a target for AF therapy.[70] This still leaves a therapeutic window for future I_{Kur} blockers in paroxysmal AF, where remodeling has not yet occurred. Other atrially expressed K^+ channels with potential as therapeutic targets in AF include KCNJ3 and KCNJ5, which generate $I_{K,ACh}$, small conductance Ca^{2+}-activated K^+ channels, and K_{2P} channels (two-pore, background K^+ channels).[71]

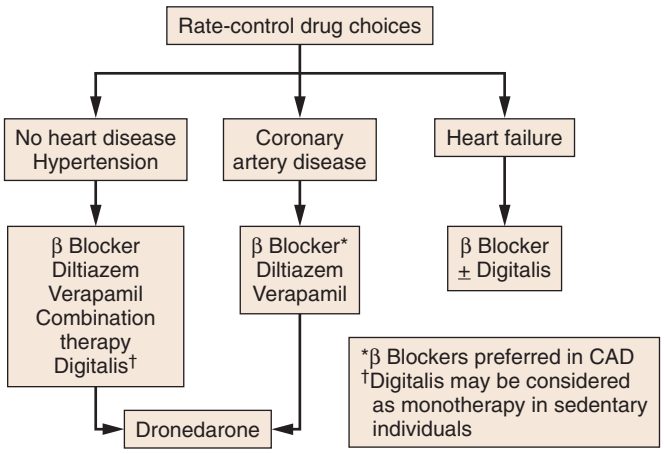
Class IV—Calcium Channel Blockers

The class IV antiarrhythmics block voltage-gated Ca^{2+} channels; the primary target with respect to arrhythmias is the cardiac L-type Ca^{2+} channel, Ca_v1.2. Whereas in atrial and ventricular myocytes the primary role of Ca^{2+} is signaling in muscular excitation-contraction coupling, in nodal cells its primary role is electrical conduction of a depolarizing signal. By lowering ventricular myocyte intracellular [Ca^{2+}], some class IV antiarrhythmics decrease the

force of contraction of the heart, an effect referred to as *negative inotropy*. By slowing conduction through nodal cells, some class IV drugs reduce the heart rate, an effect referred to as *negative chronotropy* (Chapter 23).

The dihydropyridines (e.g., nifedipine) are used to treat increased systemic vascular resistance but are not generally indicated for arrhythmias. The phenylalkylamines, exemplified by verapamil, are relatively myocardial-specific and cause negative inotropy with minimal vasodilation or reflex tachycardia. Verapamil is indicated for angina, with two probable main modes of action: dilatation of the main coronary arteries and arterioles, inhibiting coronary vasospasm, and reduction of oxygen utilization via unloading of the heart achieved by relaxing the peripheral arterioles. As an antiarrhythmic, verapamil is highly effective at slowing ventricular contraction rate in patients with atrial flutter or AF because it slows AV node conduction in a rate-dependent manner. This rate dependence also accounts for the fact that verapamil generally is much less effective at reducing already normal AV conduction rates—a desirable property—although it can occasionally induce AV node block in the absence of preexisting conduction defects. Verapamil is effective in reducing the frequency of episodes of paroxysmal supraventricular tachycardia, but it can also induce ventricular fibrillation in patients with atrial flutter or fibrillation and a coexisting AV accessory pathway.[72–74]

The benzothiazepines, exemplified by diltiazem, exhibit myocardial specificity intermediate between the dihydropyridines and phenylalkylamines. Diltiazem causes excitation-contraction uncoupling, relaxation of coronary vascular smooth muscle, and dilatation of coronary arteries, but has relatively modest negative inotropic effects. Diltiazem is typically prescribed for angina and hypertension and is quite effective in lowering blood pressure in hypertensive individuals, with little effect on normotensives. It is also reportedly as effective as verapamil in the treatment of supraventricular tachycardias, and is also indicated for atrial flutter and AF. Its negative dromotropic effect (slowing of conduction through the AV node) reduces oxygen consumption by increasing the time required for each heartbeat.[75,76] The rational selection of drugs for controlling heart rate is summarized in Fig. 27.8.



• **Fig. 27.8** Selection of rate-control drug therapy is based on the presence or absence of underlying heart disease and other comorbidities. Combination therapy might be required. *CAD,* Coronary artery disease. (Modified from Gillis AM, Verma A, Talajic M, et al. Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: rate and rhythm management. *Can J Cardiol.* 2011;27:47–59.)

Emerging Developments

Molecular Genetics of Arrhythmias

A combination of molecular genetics, recombinant DNA technology, and physiologic techniques is revealing the secrets of many cardiac arrhythmias; intuitively, the majority of the genes linked thus far to abnormal cardiac rhythm are those that express ion channel proteins.[27] Many of these same ion channels are targets for clinically important antiarrhythmic and proarrhythmic drugs. An understanding of the precise molecular basis for an individual's arrhythmia can remove some of the uncertainty about how best to treat the arrhythmia, and facilitates genetic or other forms of testing of family members, permitting early diagnosis and preventive measures to avoid potentially lethal cardiac events.

Long QT Syndrome

A delay in ventricular myocyte repolarization can prolong the QT interval on the ECG and lead to TdP and even ventricular fibrillation. The most common inherited causes of this phenomenon are loss-of-function mutations in ventricular, voltage-gated K_v channels, which are primarily responsible for ventricular myocyte repolarization by virtue of K^+ efflux to restore a negative membrane potential (see Fig. 27.1A). Around 45% of individuals diagnosed with inherited long QT syndrome (LQTS) whose DNA has been sequenced have loss-of-function mutations in the *KCNQ1* gene. *KCNQ1* encodes the K_v channel pore-forming (α) subunit of the same name. *KCNQ1* mutations underlie long QT syndrome type 1 (LQT1), which is further divided into the autosomal dominant Romano-Ward syndrome and the recessive cardioauditory Jervell and Lange-Nielsen syndrome (JLNS). Individuals with loss-of-function mutations in both *KCNQ1* alleles (i.e., JLNS) exhibit both LQTS and profound sensorineural deafness. *KCNQ1*, in protein complexes with *KCNE1*, a single-transmembrane segment ancillary (β) subunit, generates the slowly activating ventricular repolarization current, I_{Ks}.[77]

I_{Ks} is important for phase 3 repolarization in the ventricular action potential, particularly when the dominant ventricular repolarization K^+ current, I_{Kr} (see later text) is compromised, or during sustained exercise or other prolonged sympathetic activation. The *KCNQ1-KCNE1* potassium channel is also expressed in the inner ear, where it is responsible for K^+ secretion into the endolymph (hence the deafness in JLNS). Individuals with *KCNE1* mutations (1%–2% of sequenced LQTS cases) are classified as having LQT5; they exhibit Romano-Ward syndrome or JLNS with similar symptoms as LQT1 patients, indicating the *KCNE1* β subunit is important for I_{Ks}.

I_{Kr} is generated by hERG, the voltage-gated K^+ channel α subunit encoded by the *KCNH2* gene, probably in complexes with the *KCNE2* β subunit and perhaps others. *KCNH2* loss-of-function mutations (LQT2) account for ~40% of known LQTS cases; *KCNE2* mutations (LQT6) account for ~1%.

The third most commonly linked LQTS gene is *SCN5A,* which encodes the $Na_v1.5$ cardiac voltage-gated Na^+ channel that underlies the upstroke in phase 0 of the cardiac myocyte action potential (see Figs. 27.1A and 27.2). $Na_v1.5$, like all voltage-gated Na^+ channels, inactivates rapidly, which together with the transient outward K^+ current, I_{to}, causes the notch at the beginning of the human ventricular myocyte action potential. Gain-of-function mutations in *SCN5A,* particularly those that increase Na^+ influx during phases 2 and 3 when the majority of $Na_v1.5$ channels are normally inactivated, delay repolarization because they produce

persistent depolarizing force (Na^+ influx). *SCN5A* mutations account for 5% to 10% of LQTS cases and are categorized as LQT3. $Na_v1.5$ is an important antiarrhythmic target, with many drugs known to alter its inactivation kinetics.[78,79]

The remaining molecularly defined inherited LQTS cases are relatively rarer and are spread among other genes encoding K^+ channel subunits, Ca^{2+} channel subunits, and channel-associated proteins.

Short QT Syndrome

Shortening of the QT interval, indicating premature ventricular repolarization, can also be pathogenic, further illustrating the importance of timely electrical activity in the heart. The majority of sequenced short QT syndrome (SQTS) cases are, intuitively, associated with *KCNQ1* or *KCNH2* gain-of-function mutations. SQT1 is associated with *KCNH2* mutation; SQT2 with *KCNQ1;* and the inward rectifier K^+ channel gene *KCNJ2* with SQT3. SQTS is characterized by a corrected QT interval (QTc) of less than 300 msec, and manifests as palpitations, syncope, and sudden cardiac death; patients with a QTc of up to 330 msec are also diagnosed with SQTS if they have had an arrhythmic event such as ventricular fibrillation, syncope, or resuscitated sudden cardiac death. Also associated with an increased risk of both atrial and ventricular fibrillation, SQTS has been found to respond to hydroquinidine, whereas class IC and III antiarrhythmics were unable to prolong the QT interval in this context. However, the current therapy of choice is an implantable cardioverter-defibrillator.[80–82]

Brugada Syndrome

In contrast to the long and short QT syndromes, the majority of sequenced Brugada syndrome cases (perhaps representing 30% of all cases) have been linked to loss-of-function mutations in the *SCN5A* voltage-gated Na^+ channel gene that encodes $Na_v1.5$. Brugada syndrome is an autosomal dominant, idiopathic form of ventricular fibrillation that manifests on the ECG as persistent ST-segment elevation in the right precordial leads, together with complete or incomplete right bundle branch block. Patients with Brugada syndrome are strongly predisposed to life-threatening ventricular fibrillation even with a structurally normal heart, and Brugada syndrome was recently found to be clinically and genetically the same disorder as sudden unexplained nocturnal death syndrome described in Southeast Asia, where Brugada syndrome is endemic and is often mistaken for a supernatural curse by poorly educated people.

In patients with Brugada syndrome, the transient outward K^+ current that forms a notch at the start of the ventricular action potential is inadequately balanced by the voltage-gated Na^+ current owing to loss of function in $Na_v1.5$, which is considered a trigger for ventricular tachycardia and fibrillation. Accordingly, gain-of-function mutations in the *KCNE3* and *KCNE5* β subunits, which can regulate the K^+ channel underlying I_{to} ($K_v4.3$), have also been associated with Brugada syndrome.[83] An implantable cardioverter-defibrillator is again the treatment of choice for patients with Brugada syndrome, but quinidine can be used to inhibit I_{to}, and isoproterenol and cilostazol can bolster the voltage-gated Ca^{2+} current to the same end—that is, reduction of the action potential notch that provides a substrate for potentially catastrophic ventricular microreentry circuits.[84,85]

Other Inherited Arrhythmia Syndromes

Other inherited arrhythmia syndromes include cardiac conduction disease, WPWS, CPVT, and various sinus node disorders.[77,86]

Lev-Lenègre syndrome, a progressive cardiac conduction disease, has been linked to *SCN5A* loss-of-function gene variants, and is characterized by slowed conduction, pathologic slowing of cardiac rhythm and conduction system fibrosis. A pacemaker or implantable cardioverter-defibrillator is the most common therapeutic strategy, although pharmacologic intervention can also be indicated.

WPWS, in its rare familial form, is linked to mutations in the *PRKAG2* gene, which encodes the γ2 regulatory subunit of AMP-activated protein kinase, but in the sporadic form of the disease this gene is rarely implicated. Other genetic associations include mitochondrial DNA mutations and, in association with hypertrophic cardiomyopathy, *TNNI3* and *MYBPC3* gene variants.[87,88] WPWS manifests as supraventricular arrhythmias associated with palpitations, and preexcitation and syncope. WPWS is caused by an abnormal accessory electrical circuit that is present at birth (known as "the bundle of Kent"), and surgical ablation of this pathway is almost always successful in eliminating the cause and symptoms of WPWS. However, the marginally less effective but much less invasive measure of radiofrequency catheter ablation is now typically used in WPWS.[89,90]

CPVT is observed clinically as exercise- or emotional stress–induced syncope and sudden cardiac death, and on the body surface ECG as bidirectional or polymorphic ventricular tachycardia. Two genes involved in excitation-contraction coupling have been linked to CPVT: *RyR2* (which encodes the cardiac ryanodine receptor, a sarcoplasmic reticulum Ca^{2+} release channel) and *CASQ2* (encoding calsequestrin, which stores releasable Ca^{2+} within the sarcoplasmic reticulum). Increased RyR2 activity or decreased calsequestrin expression generates spontaneous Ca^{2+} transients and DADs. CPVT is treated with β blockers, implantable cardioverter-defibrillator, and/or other antiarrhythmic medications.

Sinus rhythm is dictated by hyperpolarization-activated, cyclic-nucleotide–gated monovalent cation channels known as HCN or pacemaker channels (and to a greater or lesser extent, Ca^{2+} oscillations, a matter of current debate). Hence, HCN4 mutation is associated with sinus-mediated pathologic slowing of the heart rate (sinus bradycardia). *SCN5A* sodium channel gene mutations have been linked to sick sinus syndrome, and atrial standstill—which is also associated with a loss-of-function sequence variant in the gene encoding connexin 43, a transmembrane protein that forms gap junctions important to intercellular coupling.

hERG Drug Interactions

I_{Kr} is the dominant phase 3 repolarization current (see Fig. 27.1A), and by an evolutionary quirk, the hERG α subunit has a propensity for inhibition by a wide range of otherwise potentially clinically useful drugs (see Fig. 27.4). This unfortunate situation has led drug regulatory agencies including the U.S. Food and Drug Administration to mandate that all potential new medications, and current medications linked to increased sudden death or QT prolongation, are subjected to time-consuming and expensive testing for potential hERG antagonism and QT prolongation in experimental preparations including canine Purkinje fibers, which are part of the specialized conduction system of the heart that rapidly conducts signals from the AV node to the ventricles. Indeed, hERG safety concerns have spawned an industry in their own right, with companies being formed the major directive of which is to facilitate hERG safety testing via product development or outsourcing of cellular electrophysiology.[91] QT prolongation and TdP thought to result from block of cardiac hERG channels has resulted in withdrawal of drugs for a variety of indications. Between 1997

and 2001, 10 prescription drugs were withdrawn from the U.S. market, 4 because of links to increased incidence of TdP: the antihistamines Seldane (terfenadine) and Hismanal (astemizole), the heartburn medication Propulsid (cisapride monohydrate), and the antibiotic grepafloxacin.

Interestingly, some medications (e.g., Trisenox [arsenic trioxide], a last-resort treatment for acute promyelocytic leukemia), and the majority of LQTS-linked *KCNH2* mutations, are now known to reduce I_{Kr} because of hERG misfolding and/or mistrafficking, rather than impaired conduction or gating of channels at the plasma membrane as was first thought. It remains to be seen whether this holds for other cardiac ion channels, but it is clinically relevant because it will influence the therapeutic strategies used to repair I_{Kr} in these cases: Small molecules have been identified that fix LQTS-associated mutant hERG channels, probably by creating nucleation points to aid channel folding.[92–95] Future antiarrhythmics could even be targeted toward enhancing "normal" hERG trafficking to overcome other repolarization deficiencies.

Gene Therapy Guided by Molecular Genetics of Inherited Arrhythmias

An interesting experimental approach to treatment of arrhythmias is to introduce genes that regulate cardiac rhythm based on their ability to regulate specific ion channels. Three examples stand out in the literature; it should be noted that gene therapy is currently only in experimental and trial phases owing to an array of side effects, not specific to the introduced gene but rather to the delivery method, often a virus.

In the first example, researchers have exploited the ability of the *KCNE3* K^+ channel β subunit to accelerate ventricular repolarization by increasing current through the *KCNQ1* K_v α subunit. In the heart, *KCNQ1-KCNE1* normally generates the slowly activating I_{Ks} repolarizing current. However, in the colon, *KCNQ1* complexes with *KCNE3*, a subunit that locks the *KCNQ1* voltage sensor (and thus pore) open, producing a constitutively active yet K^+-selective channel that regulates cAMP-stimulated chloride secretion in vivo.[96,97] When *KCNE3* was introduced into the guinea pig ventricular cavity by injection of adenovirus containing the *KCNE3* gene, the result was a shortening of the action potential and a reduction in QT interval, stemming from the resultant increase in *KCNQ1* current (which would have been especially marked at negative voltages, where *KCNQ1-KCNE1* is typically closed).[98]

Second, introduction of HCN channel genes into quiescent ventricular myocytes shows promise for converting them into pacemaker cells. HCN expression endows them with automaticity, the ability to fire spontaneously, because HCN channels open in response to hyperpolarization and initiate depolarization.[99,100]

Third, a natural polymorphism (Q9E) in the *KCNE2* ancillary subunit that regulates the hERG K_v α subunit, increases the sensitivity of hERG-*KCNE2* channels to block by the macrolide antibiotic clarithromycin. The polymorphism was discovered in an African American woman with ventricular fibrillation precipitated by clarithromycin, and was later found to be present in 3% of African Americans but absent in Caucasian Americans. This finding was exciting because it uncovered a pharmacogenomic mechanism for increased susceptibility to adverse effects for a significant fraction of a specific ethnic group. However, it was also used ingeniously to engineer experimentally chamber specificity to erythromycin susceptibility with therapeutic goals in mind. Thus viral introduction of Q9E-*KCNE2* into the porcine atrium rendered hERG channels within the atrium severalfold more susceptible to block by clarithromycin than their ventricular, wild-type hERG-*KCNE2* counterparts. Clarithromycin was found to selectively prolong the atrial refractory period in these pigs without significantly affecting ventricular action potentials, exploiting the increased sensitivity of the mutant *KCNE2*–containing atrial channels.[25,101–103]

Future work will build on all these discoveries to create bench-to-bedside medicine that uses each patient's own molecular lesion to tailor highly patient- and target-specific, bespoke gene- and stem cell–related therapies.

Key Points

- Antiarrhythmic drugs are organized into the Singh-Vaughan Williams classification, which is a useful framework for categorizing by primary mode of action.
- Most antiarrhythmics can be classified into more than one of the four categories. Amiodarone, one of the most efficacious, falls into all four classes.
- Class I antiarrhythmics block voltage-gated Na^+ channels and are subcategorized into Ia, Ib, and Ic depending on their binding kinetics, which dictate their effects on cardiac myocyte action potentials. They are used for ventricular arrhythmias, but are currently less commonly used because of potential proarrhythmic effects.
- Class II antiarrhythmics block β-adrenergic signaling and slow heart rate. Sinus tachycardia and ventricular tachycardia are treated with β blockers.
- Class III antiarrhythmics block K^+ channels, prolonging the cardiac myocyte action potential and refractory period. They are used for conversion and prevention of atrial fibrillation/flutter, and in the case of amiodarone in the treatment of ventricular tachycardia/fibrillation.
- Class IV antiarrhythmics block Ca^{2+} channels, slowing nodal conduction and reducing intracellular [Ca^{2+}], without eliminating sympathetic regulation. Ca^{2+} channel blockers are used for treatment of idiopathic rhythms, ectopic atrial tachycardias, and atrioventricular nodal reentrant supraventricular tachycardias.
- Atrial fibrillation is most commonly treated with Na^+ channel blockers (class 1a) or K^+ channel blockers (class III).
- A number of drugs from a variety of drug classes often used in anesthesia, as well as certain channel mutations, can predispose to torsades de pointes by blocking specific K^+ channels and prolonging the QT interval. This is usually treated with intravenous magnesium.

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Cardiopulmonary Resuscitation

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CHAPTER OUTLINE

Historical Perspective
- Oxygen Delivery, Consumption, and the Margin of Error
- Compensated Hypovolemia and Supply-Dependent Oxygen Consumption
- Early Goal-Directed Therapy

Cardiopulmonary Resuscitation
- Compression and Decompression
- Ventilation and Blood Flow During CPR
- CPR and Intracranial Pressure
- Optimizing Chest Compression/Decompression
- Automated Chest Compression Devices
- Targeted Temperature Management After Resuscitation

Emerging Developments
- Extracorporeal Life Support for Refractory Cardiac Arrest

The objective of cardiopulmonary resuscitation CPR) in the critically ill patient is optimization of both oxygen delivery (Do_2) and aerobic metabolism. Shock is defined as dysoxia, or an abnormality in tissue oxygenation. The variables altering the clinical state of shock include Do_2, tissue uptake of oxygen ($\dot{V}O_2$), and the tissue metabolic rate of oxygen (MRO_2). The various shock states are defined by causes of decreased Do_2. Resuscitation maneuvers improve Do_2, optimize tissue uptake of oxygen, and preserve metabolic rate of oxygen. This chapter reviews the cardinal tenets of oxygenation, the physiology of CPR, and the scientific basis of practices of resuscitating the critically ill patient.

Historical Perspective

Peter Safar is credited with the first published account of expired gas ventilation via mouth-to-mouth or mouth-to-airway techniques using a novel device of two fused oral airways in 1957.[1] Closed chest compression in humans was famously first described in the medical literature by Kouwenhoven and colleagues in 1960.[2] However, origins of CPR are evident in 18th-century descriptions the management of drowning victims, as well as prior Biblical descriptions of Elisha who "went up and lay on the child and put his mouth on his mouth…and the flesh of the child became warm."[3,4] In the 1960s the combination of chest compressions and mouth-to-mouth ventilation was popularized as "cardiopulmonary resuscitation" or CPR. It was at this time that the American Heart Association (AHA) was formed and took up the task of teaching physicians, and later the general public, to perform CPR. An ad hoc committee wrote the first guidelines for CPR established by the National Academy of Sciences of the National Research Council in 1966.[5] Over the past 50 years, a breadth of research and several revisions to the CPR guidelines were made; however, survival rates for both out-of-hospital and in-hospital survival for in-hospital cardiac arrest and CPR are 15% and 22%, respectively.[6] Neurologic deficits occur in 30% to 50% of patients after out-of-hospital cardiac arrest.[7]

Oxygen Delivery, Consumption, and the Margin of Error

Normal homeostatic mechanisms ensure greater Do_2 than the total tissue uptake of oxygen ($Do_2 > \dot{V}O_2$; see Chapter 24).[8] This "margin of error" maintains aerobic metabolism during extreme situations, when Do_2 is diminished, or when tissue oxygen uptake increases. Do_2 is the process by which oxygen is transported from the pulmonary system to the systemic capillary beds (expressed as milliliters per minute per meter squared), and is expressed as the product of the cardiac index (CI) and arterial blood oxygen content (CaO_2): $Do_2 = CI * CaO_2$. The cardiac index is the cardiac output (Q) normalized for body surface area (BSA): CI = Q/BSA. Normal values of cardiac output and cardiac index in an average size adult are 4.0 to 8.0 L/min and 2.5 to 4.0 L/min per meter squared, respectively. The content of CaO_2 depends on the volume of oxygen bound to hemoglobin (Hbg) and of free oxygen dissolved in blood ($CaO_2 = 1.39 * Hgb * SaO_2 + 0.003 * PaO_2$), where PaO_2 is the partial pressure of alveolar oxygen. SaO_2 represents the oxygen saturation, PaO_2 the arterial oxygen tension (in millimeters of mercury), and 0.003 the plasma solubility coefficient of oxygen (Table 28.1). The vast majority of oxygen is bound to hemoglobin such that even at very high oxygen tensions the additional dissolved oxygen contributes little to overall CaO_2.

The oxygen uptake from systemic capillaries ($\dot{V}O_2$) represents oxygen consumption, as oxygen is not stored in tissue. The Fick principle derives oxygen consumption from the difference in oxygen content between arterial and venous blood, $\dot{V}O_2 = Q * (CaO_2 - CvO_2)$. Normal oxygen consumption in a resting adult is 110 to 160 mL/min per meter squared; $\dot{V}O_2$ less than 100 mL/min meter squared indicates impaired tissue oxygenation. The oxygen extraction ratio (O_2ER) is the ratio of oxygen consumption to Do_2 ($O_2ER = \dot{V}O_2/DO_2$), and reflects tissue avidity for oxygen. Normal, global O_2ER is 0.2 to 0.3, so only 20% to 30% of delivered oxygen is used.[9] The O_2ER varies for different tissues, with renal O_2ER less than 0.15 and cardiac O_2ER greater than 0.6.

Mixed venous oxygen saturation reflects the state of global oxygen utilization. Oxygen that is not extracted returns to the

Abstract

Resuscitation maneuvers improve oxygen delivery, optimize tissue uptake of oxygen, and preserve the metabolic rate of oxygen. This chapter reviews the cardinal tenets of oxygenation, the evidence-based practices of resuscitating the critically ill patient, and the physiology of cardiopulmonary resuscitation (CPR). Our understanding of CPR physiology continues to grow, but morbidity and mortality after cardiac arrest remain poor. Optimizing circulation during CPR and avoiding common errors encountered are initial steps toward improving outcomes. Advances and experience with new technology, including automated devices and extracorporeal life support, are actively being pursued.

Keywords

critical oxygen delivery
early goal-directed therapy
cardiac pump theory
thoracic pump theory
extracorporeal cardiopulmonary resuscitation

TABLE 28.1 Key Equations Relevant to Oxygen Delivery and Metabolism

Cardiac index (CI)	$CI = Q/BSA$
Arterial oxygen content (Ca_{O_2})	$Ca_{O_2} = 1.39 * Hgb * Sa_{O_2} + 0.003 * Pa_{O_2}$
Oxygen delivery (D_{O_2})	$D_{O_2} = CI * Ca_{O_2}$
Oxygen consumption ($\dot{V}_{O_2}$; Fick principle)	$\dot{V}_{O_2} = Q^*(Ca_{O_2} - Cv_{O_2})$
Mixed venous oxygenation (Scv_{O_2}; Fick principle)	$Scv_{O_2} = Sa_{O_2} - [\dot{V}_{O_2}/(Hgb * 1.36 * Q)]$
Oxygen extraction ratio (O_2ER)	$O_2ER = \dot{V}_{O_2}/D_{O_2}$

BSA, Body surface area; *Cv_{O_2}* oxygen content of venous blood; *Hgb*, hemoglobin; *Pa_{O_2}* arterial oxygen tension; *Q*, cardiac output; *Sa_{O_2};* oxygen saturation.

mixed venous circulation. Assuming an SaO_2 of 100%, normal mixed venous saturation ($ScvO_2$) of 70% implies 30% extraction of the oxygen delivered. Rearrangement of the Fick equation yields $ScvO_2 = SaO_2 - \dot{V}O_2/(Hgb * 1.36 * Q)$. Normal $ScvO_2$ sampled from the pulmonary artery is 65% to 75%, implying an oxygen extraction of ~25% to 35%. $ScvO_2$ is inversely proportional to oxygen consumption and directly proportional to arterial saturation, hemoglobin concentration, and cardiac output. Therefore maneuvers to improve $ScvO_2$ aim to increase arterial oxygen content and delivery.

Compensated Hypovolemia and Supply-Dependent Oxygen Consumption

In shock, D_{O_2} is reduced and in response vital organ beds become more oxygen avid. The O_2ER increases to maintain aerobic metabolism. Extraction can rise from 20% to 30% to a maximal extraction of 80%. A diminished margin of error (normal $DO_2 > \dot{V}O_2$) of D_{O_2} is compensated by a greater O_2ER. "Compensated hypovolemia" describes the response to decreased D_{O_2} in which increased O_2ER allows maintenance of $\dot{V}O_2$. When DO_2 diminishes to a critical point, maximal extraction has been reached, aerobic metabolism is no longer supported, $\dot{V}O_2$ is wholly dependent of D_{O_2} and cellular energy production is limited by the supply of oxygen. This threshold of DO_2 marks tissue dysoxia and the shock state (Fig. 28.1).

The critically ill patient often survives below the critical DO_2 and organ perfusion is entirely supply dependent. This can be due to blood flow redistribution or direct tissue injury, which prevents changes in the O_2ER. A static O_2ER hinders a patient's ability to maintain aerobic metabolism in the face of decreased delivery. This supply dependence underscores the importance of D_{O_2} during shock and demonstrates the physiologic basis of goal-directed therapy.

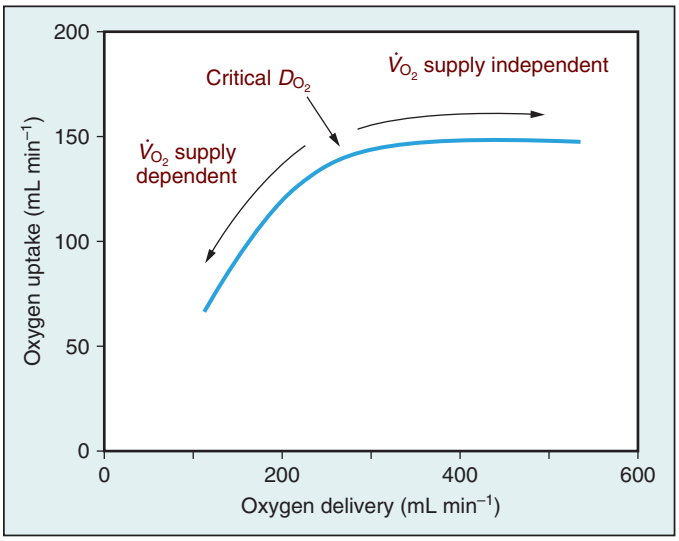
Early Goal-Directed Therapy

Evidence supports maximizing D_{O_2} in high-risk surgical patients to replenish tissue oxygen and prevent organ dysfunction.[10] Resuscitation to supranormal DO_2 after severe trauma improves survival and decreases ventilator days, mean organ failures per patient, and total intensive care unit days.[11] Similar management

TABLE 28.2 Advanced Cardiovascular Life Support (ACLS) Drug Chart[26]

Drug	Indication	IV/IO Dosage
Adenosine	Tachycardia	6 mg, may administer second dose of 12 mg
Amiodarone	Tachycardia	150 mg over 10 min
Amiodarone	VT/VF	300 mg, repeat 150 mg
Atropine	Bradycardia	0.5 mg, repeat 3–5 min up to 3 mg
Diltiazem	Tachycardia	15–20 mg over 2 mins, then 20– 25 mg after 15 mins
Dopamine infusion	Bradycardia	2–10 µg/kg/min
Epinephrine	VT/VF/asystole/ PEA	1 mg, repeat 3–5 min
Epinephrine infusion	Bradycardia	2–10 µg/kg/min
Lidocaine	VT/VF	1–1.5 mg/kg, then 0.5–0.75 mg/kg every 5 min
Magnesium sulfate	Torsade de pointes	2 g
Metoprolol	Tachycardia	5 mg, repeat 2–5 min up to 20 mg
Procainamide infusion	Tachycardia	20–50 mg/min
Sotalol	Tachycardia	100 mg (1.5 mg/kg) over 5 min
Verapamil	Tachycardia	2.5–5 mg, then 5–10 mg every 15–30 min

IO, Intraosseous; *IV*, intravenous; *PEA;* pulseless electrical activity; *VF;* ventricular fibrillation, *VT;* ventricular tachycardia,



• **Fig. 28.1** The biphasic relationship between oxygen delivery (D_{O_2}) and oxygen consumption ($\dot{V}O_2$).[9]

of septic shock reduces overall hospital mortality; CI and DO_2 are augmented by volume expansion, blood transfusion, mechanical ventilation with a high fraction of inspired oxygen (FIO_2), and inotropic drugs.[12] In this 1990 cohort, these measures reduced septic shock mortality from 70% to 80% to 59%. The dynamic nature of septic shock is described as an ebb and flow, shifting from hyperdynamic physiology to an end-stage hypodynamic state. The mortality benefit from these early studies is attributed to the perpetuation of a hyperdynamic state.

The basis of goal-directed therapy is the benefit of maximizing parameters of Do_2. The natural history of septic shock involves an imbalance of Do_2 and oxygen demand, leading eventually to global dysoxia and death. This progression hinges on the critical "golden hour" during which the pathophysiology transitions to multiorgan failure. In a seminal 2000 trial, Rivers and colleagues recommended expeditious, protocolized intervention during this golden hour.[13] Interventions aim to augment Do_2 in the first 6 hours after onset of septic shock by increasing central venous pressure with intravascular volume expansion (central venous pressure goal 8–12 mm Hg), increasing mean arterial pressure (MAP) with vasoactive agents (mean arterial pressure goal 65–90 mm Hg), and maximizing $ScvO_2$ with red cell transfusion and inotropic support ($ScvO_2$ > 70%). The Surviving Sepsis Campaign, an international consortium tasked to recommend best practices for sepsis management, endorsed early goal-directed therapy as first-line treatment. This "6-hour bundle" was disseminated internationally as the standard of care for sepsis management[14] by the Surviving Sepsis Campaign as well as the U.S. National Quality Forum and Centers for Medicare and Medicaid Services.[15] This streamlined approach to sepsis management consists of risk stratification to identify the transition from systemic inflammatory response syndrome to severe disease, source control and antibiotic therapy, and hemodynamic optimization (Fig. 28.2).

Cardiopulmonary Resuscitation

The AHA regularly revises the guidelines for Basic Life Support and Advanced Cardiovascular Life Support based on the latest evidence supporting CPR survival. According to the most recent AHA recommendations, closed chest compression should be conducted at a rate of 100 to 120 compressions per minute while allowing full recoil of the chest between compressions, compression depth of 2 to 2.5 inches, minimal interruptions between compressions achieving adequate ventilation with 2 breaths for every 30 compressions, and an emphasis on compressions before ventilation. A thorough understanding of the basic physiology in CPR and the ramifications of high-quality CPR is essential for improving overall survival.

Compression and Decompression

Closed chest cardiac resuscitation entails the physical compression and decompression of the chest in a cyclic fashion to promote organ perfusion. Although the exact mechanism is controversial, there are two leading concepts of the mechanism by which CPR generates perfusion—the cardiac pump concept and the thoracic pump mechanisms (Fig. 28.3).[16,17]

The cardiac pump mechanism describes squeezing the heart between the sternum and spine with concurrent increase in intrathoracic pressure. With each compression, a pressure gradient is created between the right atrium and left ventricle, which propels blood forward. The closure of the atrioventricular valves prevents reflux of blood.[18] The concomitant rise in pressure in the right atrium and aorta forces blood forward in the circulation. The thoracic pump mechanism proposes that the heart, with an open mitral valve, acts as an open conduit during compression. With each cycle, a pressure gradient is formed between intrathoracic and extrathoracic arteries, and this drives blood out of the heart; the valves in the venous system prevent reflux of blood.[19]

Paradis and colleagues supported this thoracic pump concept with direct measurement of pressure changes in the venous and arterial systems during CPR. The jugular venous bulb to right atrium pressure (JVB-RA) gradient, and the aortic arch to right atrium pressure (Ao-RA) gradient represented cerebral perfusion and coronary artery perfusion pressures during CPR. During chest compressions, the JVB-RA gradient was positive during chest wall relaxation. The Ao-RA gradient was positive during chest compression. They concluded that forward flow was preserved to the brain and heart, and blood did not flow retrograde owing to the presence of one-way valves.[19]

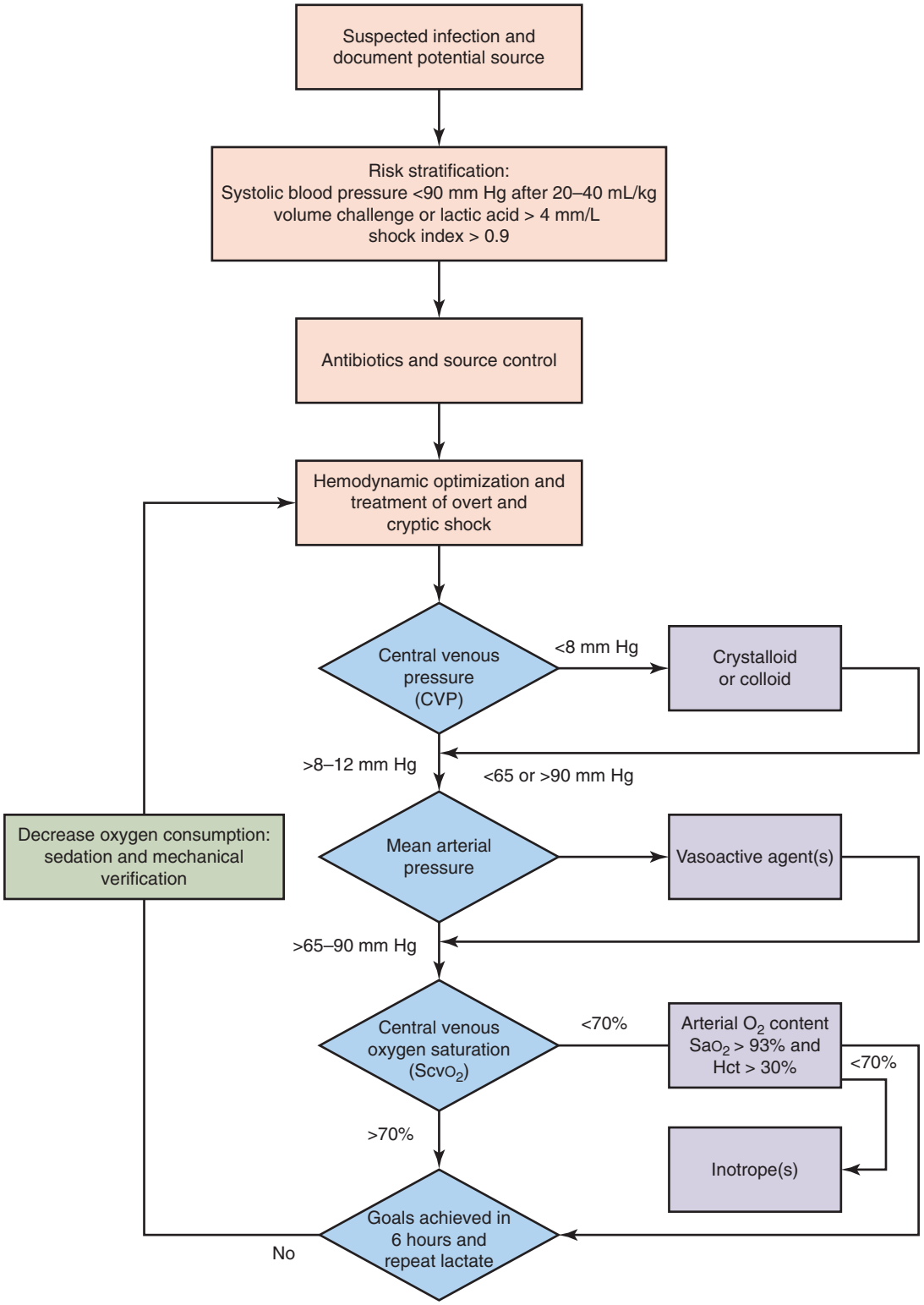
Transesophageal echocardiography during cardiac arrest helps to elucidate whether the cardiac pump or thoracic pump concept is the physiologic basis for blood flow during CPR.[18,20] It is generally accepted that if the mitral valve is closed during cardiac compression, the cardiac pump mechanism predominates, and if the mitral valve is open the thoracic pump mechanism is predominant. Transesophageal echocardiography during CPR has shown the mitral valve to be closed during CPR, which supports the cardiac pump mechanism. Early initiation of CPR led to a blood flow pattern consistent with the cardiac pump mechanism, and patients were more likely to have a return of spontaneous circulation.[20] With later onset of CPR or more prolonged CPR, circulation tended to reflect a thoracic pump mechanism, and patients had a lower incidence of return of spontaneous circulation.[20,21]

Although compression propels blood forward, decompression decreases intrathoracic and intracardiac pressures and promotes passive venous return to the heart. In closed chest CPR, allowing full chest recoil between compressions is crucial for creating this gradient.

Ventilation and Blood Flow During CPR

West and colleagues described three zones of lung perfusion (Fig. 28.4; see Chapter 29).[22] In zone 1 alveolar pressure is greater than arteriolar and venous capillary pressure ($P_{alveolar} > P_{arteriolar} > P_{venous}$), and dead space ventilation is present. In zone 2, arteriolar pressure is greater than alveolar pressure and venous capillary pressure ($P_{arteriolar} > P_{alveolar} > P_{venous}$),[22] and dead space ventilation persists. Gas exchange occurs primarily in zone 3, where arteriolar pressure is greater than both venous capillary pressure and alveolar pressure ($P_{arteriolar} > P_{venous} > P_{alveolar}$).

During CPR, positive-pressure ventilation allows pulmonary gas exchange. *Hypoxic pulmonary vasoconstriction* occurs when PaO_2 < 50 mm Hg, potentially impeding blood flow during CPR.[23] Oxygenation is a critical part of CPR to prevent this compensatory vasoconstriction to optimize blood flow across the pulmonary bed and maintain CaO_2. A balance between the ventilation rate and tidal volume is also necessary to maximize both ventilation and perfusion. Positive-pressure ventilation is deleterious because increased intrathoracic pressure impedes venous return and compresses the pulmonary vasculature. This vascular compression recruits a larger portion of the lung into West zone 1, with substantial expansion of dead space. The balance between compression and ventilation is crucial; hypoventilation results in hypercarbia,

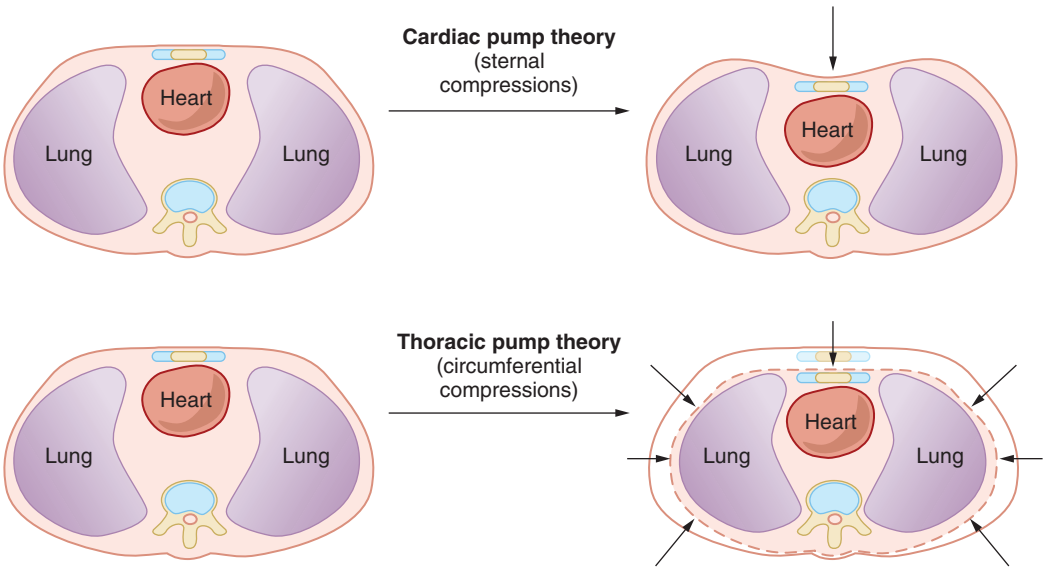


• **Fig. 28.2** The 6-hour bundle for treating sepsis.[15] *Hct,* Hematocrit; *Sao_2,* oxygen saturation; *$Scvo_2$,* mixed venous saturation.

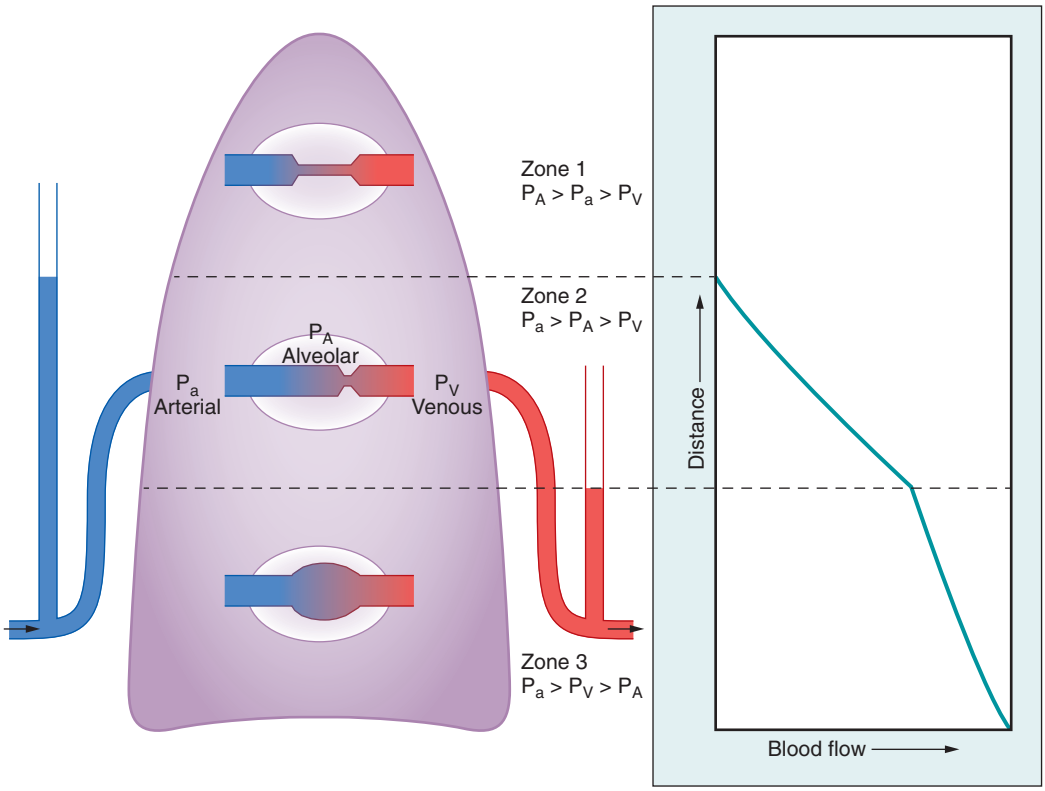
and hyperventilation impedes cardiac output. The AHA now recommends a compression:ventilation ratio of 30:2, which is reduced compared with earlier guidelines, in the presence of an advanced airway. A target tidal volume of 8 mL/kg is recommended to prevent ventilation-perfusion mismatch.

CPR and Intracranial Pressure

Neurologic injury after cardiac arrest is devastating; therefore maintenance of adequate cerebral perfusion during CPR is paramount. Increased intrathoracic pressure from both positive-pressure ventilation and chest compression restricts cranial venous drainage,



• **Fig. 28.3** Cardiac pump and thoracic pump mechanisms of cardiopulmonary resuscitation.



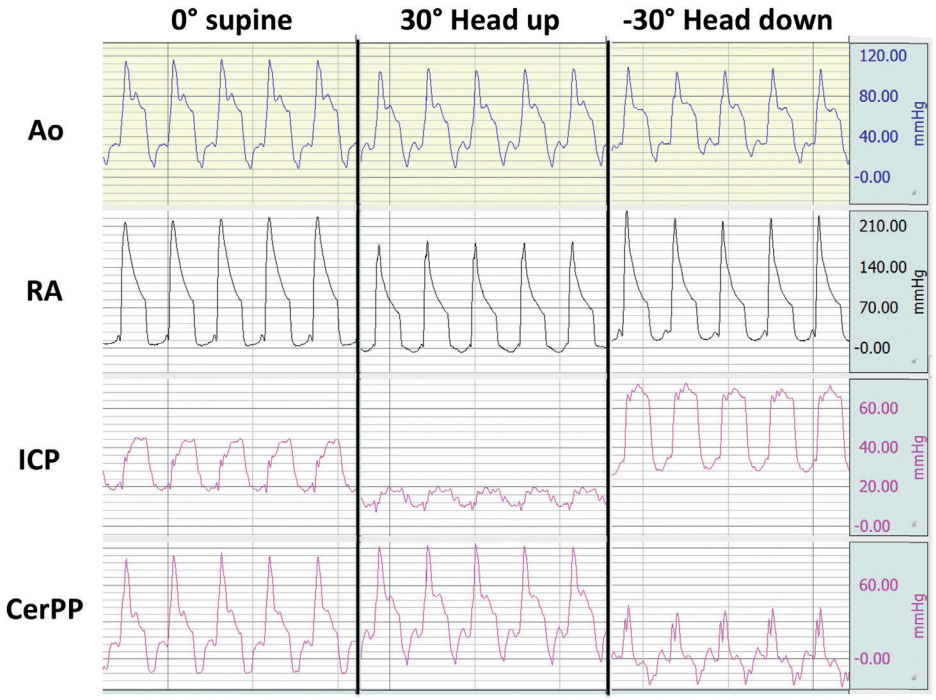
• **Fig. 28.4** The West zones of lung ventilation and perfusion.[22] P_a, Arterial pressure; P_A, alveolar pressure; P_v, venous pressure.

decreases cerebral perfusion, and elevates intracranial pressure (ICP). The paravertebral venous, epidural plexus, and spinal fluid systems all fail to drain adequately, resulting in increased ICP.[16,24]

Cerebral perfusion during CPR has been studied in a porcine model comparing three positions: supine, 30-degree Trendelenburg, and 30-degree reverse Trendelenburg (Fig. 28.5). In reverse Trendelenburg position, cerebral perfusion pressure was highest and ICP was lowest. In the Trendelenburg position, ICP was highest and central perfusion pressure was lowest. This study also demonstrated the importance of allowing full recoil of the chest during the decompression phase of CPR to augment passive cerebral venous drainage and subsequently decrease ICP.[25]

Optimizing Chest Compression/Decompression

Providing high-quality CPR is pivotal to survival after cardiac arrest. The 2015 AHA guidelines recommend chest compressions at a rate of 100 to 120 compressions per minute, with a depth of 5 to 6 cm (2 to 2.5 inches), allowing full chest recoil between compressions, a 30:2 compression-to-breath ratio with an advanced



• **Fig. 28.5** Aortic pressures, right atrial pressures, intracranial pressures, and cerebral perfusion pressures at supine, 30-degree Trendelenburg, and 30-degree reverse Trendelenburg positions.[25] Note: With sustained cardiopulmonary resuscitation, the arterial blood pressure generated will have varying effects on cerebral perfusion pressure depending on patient positioning. *Ao,* Aortic pressure; *ICP,* intracranial pressure; *RA,* right atrial pressure; *CerCPP,* cerebral perfusion pressure.

airway, and limiting interruptions of chest compression to less than 10 seconds.[26] High-quality CPR and adherence to the AHA guidelines maximize coronary perfusion and increase effectiveness of defibrillation.[27]

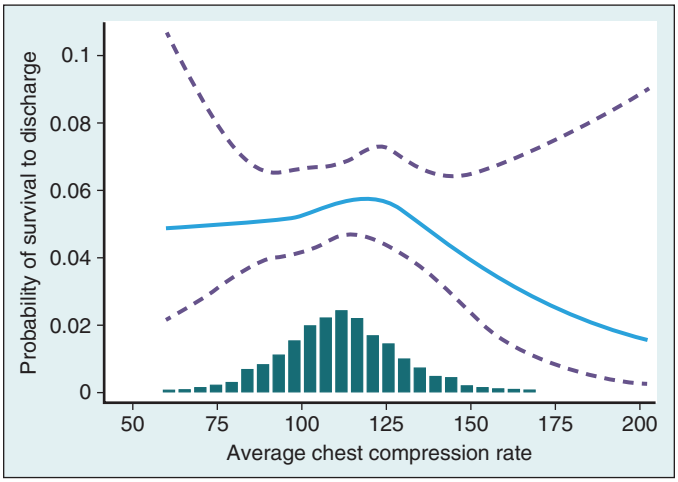
A compression rate of 100 to 120 compressions minute is ideal; lower rates provide insufficient cardiac output and forward flow, and higher rates are inadequate for diastolic filling. With compression rates outside the recommended range, morbidity and mortality increase.[16] In the North American Randomized Multicenter Resuscitation Outcomes Consortium PRIMED trial in 2015, half of the study subjects had compression rates outside the recommended range, which was associated with higher mortality.[28] This study supports compression rates of 100 to 120 compressions per minute, which are associated with the greatest survival to hospital discharge (Fig. 28.6).[28] Chest compression rate and depth are inversely related: rates above 120 compressions per minute lead to shallow compression depth (<5 cm) and are associated with lower survival (Fig. 28.7).[29]

Deeper compression depths of 5 to 6 cm are associated with increased survival following cardiac arrest.[30] However, excessive depth impedes cerebral venous drainage, elevates ICP and decreases cerebral perfusion pressure. Incomplete decompression of the chest does not allow full recoil; cerebral perfusion is deleteriously affected, systemic venous return is impaired, and overall forward flow is decreased (see Fig. 28.7).[16,31] Excessive positive pressure ventilation increases intrathoracic pressure and results in similar hemodynamic problems (Fig. 28.8).[16,32]

Automated Chest Compression Devices

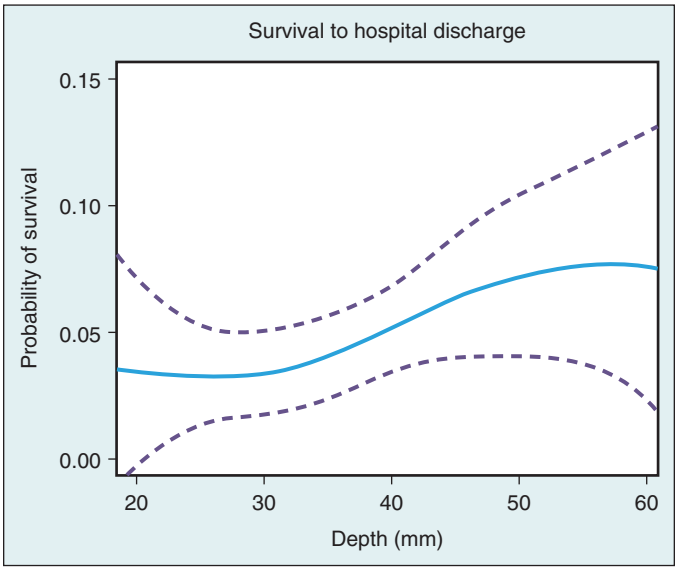
Automated chest compression (ACC) devices are commercially available. Advantages of ACC devices include consistency of compression depth, optimal compression rate, and lack of fatigability of the CPR provider. Compared with high-quality chest compressions (maintaining adequate force and depth), ACC devices generate higher right atrial pressures and higher cerebral perfusion pressure.[33] However, routine use of such devices remains controversial. Meta-analysis of studies comparing ACC with traditional CPR does not demonstrate survival benefit to admission for out-of-hospital cardiac arrest.[34]

Uses of ACC devices during percutaneous coronary intervention illustrate particular situations of potential benefit. For cardiac arrest due to acute myocardial infarction, successful resuscitation is unlikely



• **Fig. 28.6** Rate of chest compression and probability of survival to hospital discharge.[28] Solid line represents the average rate of chest compression and the associated probability of survival. The dashed lines represent the 95% confidence intervals based on the study results.

without reperfusion of the occluded coronary artery. In addition to providing perfusion, pulsatile flow is necessary to visualize the coronary arteries and perform angioplasty or stenting. Continuing CPR during cardiac catheterization has many limitations including radiation exposure for the individual providing compressions as well as physical impedance by imaging equipment. ACC devices have been reported as a viable means to maintain CPR during percutaneous coronary intervention.[35] ACC devices might pose a risk to patients due to interruption of compressions when placing the device, and injury to other organs or the heart, especially with prolonged use.[36–39] But injury to the chest wall or liver during CPR is not unique to automated devices.[40]

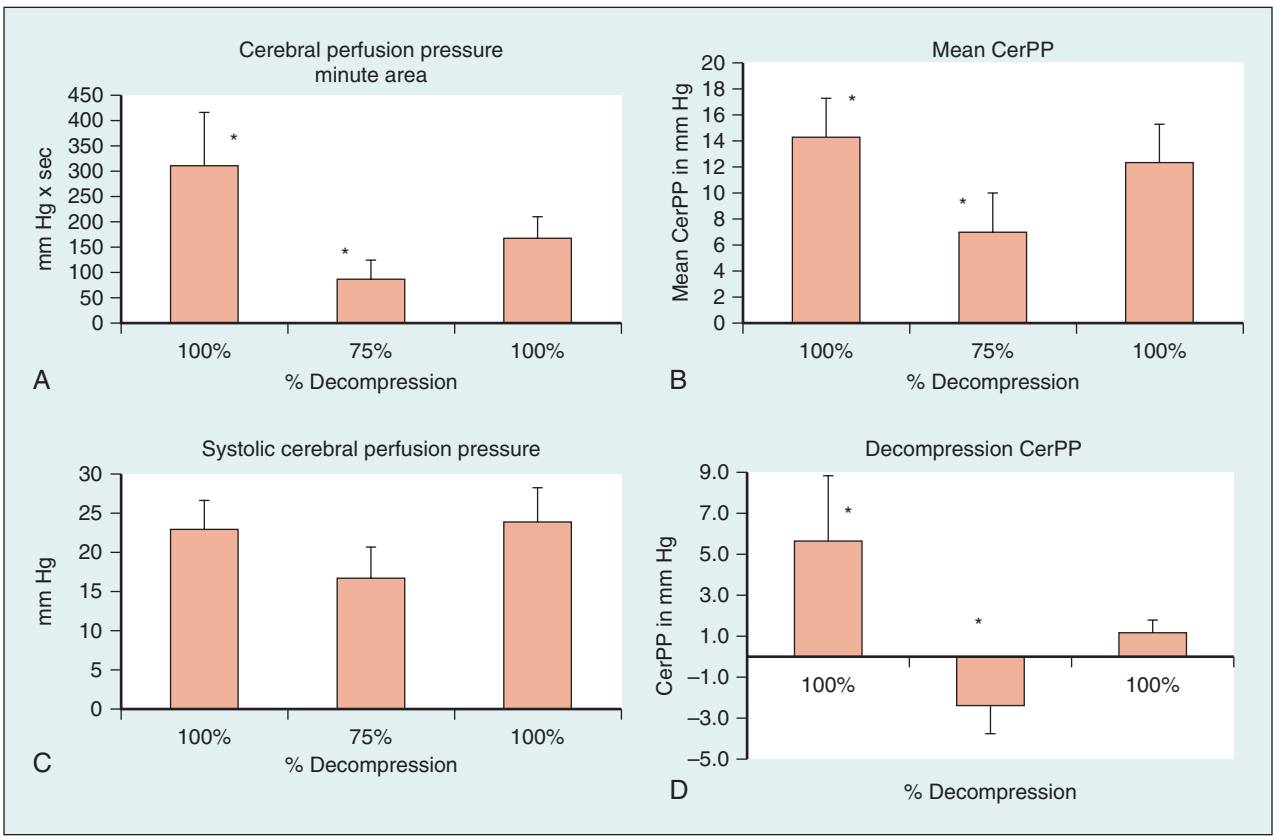


• **Fig. 28.7** Depth of chest compression and probability of survival to hospital discharge.[29] Solid line represents the average depth of chest compression and the associated probability of survival. The dashed lines represent the 95% confidence intervals based on the study results.

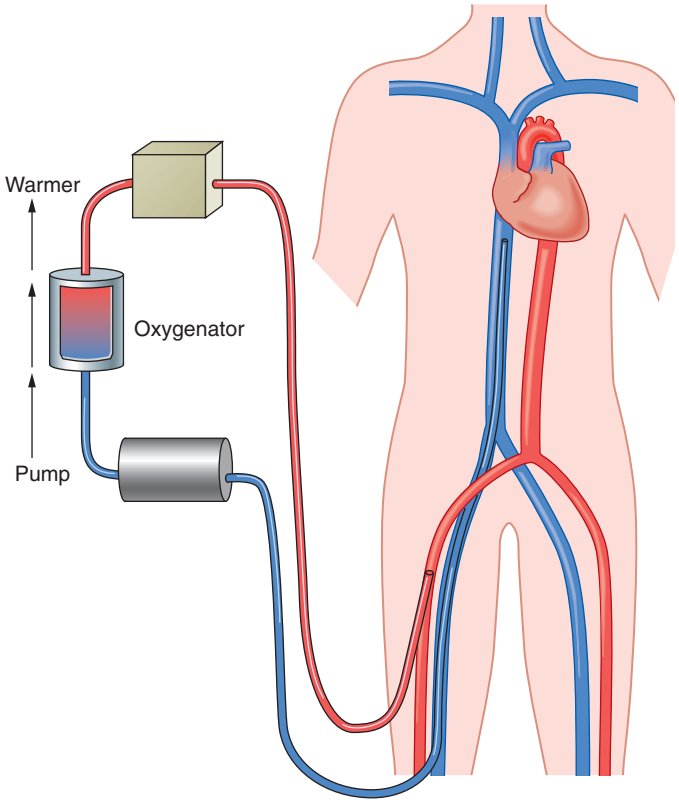
Targeted Temperature Management After Resuscitation

Unless there is an immediate return of neurologic function, targeted temperature management is recommended after return of spontaneous circulation (ROSC) after cardiac arrest.[26] With more than 5 minutes of cessation of blood flow or a low blood flow state, reperfusion injury can occur mediated by generation of free radicals and other metabolic toxins.[41] Neurologic deficits are common among survivors of cardiac arrest. Multiple studies have shown that mild hypothermia after cardiac arrest with ROSC is associated with improved neurologic outcomes.[24] Although the mechanisms by which hypothermia induces neuroprotection are uncertain, postulated mechanisms include reduction in cerebral oxygen consumption, reduced inflammatory mediators associated with cerebral edema, reduced free radical injury, and reduced cerebral acidosis. Release of free fatty acids and neurotransmitters (e.g., glutamate) is also reduced, which can reduce excitotoxic cell death.[41–45]

The Hypothermia after Cardiac Arrest Study Group performed a multicenter randomized controlled trial of the effects of mild



• **Fig. 28.8** Cerebral perfusion pressure *(CerPP)* with differing percentages of decompression.[31]



• **Fig. 28.9** Venoarterial extracorporeal oxygenation cannulation (VA ECMO).[53] In VA ECMO, venous blood is taken out of the body from the venous cannula and oxygenated via the oxygenator and warmed before returning the blood into the arterial cannula and ultimately into the patient's circulation.

therapeutic hypothermia (32°C–34°C) on neurologic outcome after ROSC in patients with out-of-hospital ventricular fibrillation or ventricular tachycardia cardiac arrest. Subjects treated with therapeutic hypothermia had a more favorable neurologic recovery compared with the control group, with reduced mortality and greater preservation of cerebral function at 6-month follow-up.[41] A subsequent multicenter randomized controlled trial in 2013 compared the morbidity and mortality of patients who received therapeutic hypothermia at 33°C versus 36°C after out-of- hospital cardiac arrest. The study did not demonstrate a significant difference in all-cause mortality or neurologic recovery between the two groups.[46]

It is generally accepted that temperature control after cardiac arrest improves neurologic outcome. However, it is unclear whether therapeutic cooling or prevention of hyperthermia provides the true benefit. In addition, therapeutic hypothermia is not without complications, which include decreased cardiac output, electrolyte abnormalities, increased infection risk, cardiac arrhythmias, and need for sedation.

More recent studies of the efficacy of targeted temperature management question current guideline recommendations. For example, targeted temperature management was associated with lower survival to hospital discharge among patients in cardiac arrest with both shockable and nonshockable rhythms.[47] The targeted temperature management group also had lower 1-year survival and lower rates of favorable neurologic outcome. In another trial of targeted temperature management for in-hospital cardiac arrest in children,[48] the targeted temperature management and normothermic groups did not differ in neurologic function or 1-year survival after in-hospital cardiac arrest. It is possible that patient characteristics and quality and type of CPR are more important factors in the overall outcome of patients with cardiac arrest than targeted temperature management.[49]

Emerging Developments

Extracorporeal Life Support for Refractory Cardiac Arrest

Survival after cardiac arrest remains very low: about 10% for out-of-hospital arrest and about 20% for in-hospital arrest.[50] Even with optimal CPR, perfusion is severely compromised and neurologic injury is not uncommon. With the resurgence in popularity for extracorporeal membrane oxygenation (ECMO) owing to the H1N1 influenza outbreak in 2009, many programs started to use temporary mechanical circulatory support for cardiogenic shock.[51] Many centers subsequently introduced venoarterial extracorporeal membrane oxygenation for cardiogenic shock and ultimately for refractory CPR, also known as extracorporeal cardiopulmonary resuscitation (ECPR). Based on observational studies, use of ECPR can increase survival to discharge to as high as 48%.[52] ECPR should be used within the first 30 minutes of CPR, with consideration up to 60 minutes after arrest, and should be reserved for patients with a reversible cause of cardiac arrest.[50] ECPR is usually performed via femoral artery and femoral vein cannulation owing to ease of access during CPR (Fig. 28.9).

Key Points

- Knowledge and application of CPR physiology continues to grow, but morbidity and mortality after cardiac arrest remain high: less than 20% survival for out-of-hospital cardiac arrest and less than 40% for in-hospital cardiac arrest.
- When oxygen delivery diminishes to a critical level and maximal extraction has been reached, aerobic metabolism and oxygen consumption are wholly dependent on oxygen delivery.
- The hemodynamic goals in the first 6 hours after onset of septic shock include improvement of central venous pressure with intravascular volume expansion, increase in mean arterial pressure with vasoactive agents, and maximization of mixed venous saturation with blood transfusion and/or inotropic support.
- Maintaining chest compression rates at 100 to 120 compressions per minute with a 30 : 2 compression-to-breath ratio, and allowing full chest recoil between compressions maximizes both forward flow and time for diastolic filling of the heart.
- Optimizing circulation during CPR is essential to improving outcomes. Possible mechanisms of CPR include cardiac and thoracic pumps mechanisms.
- Extracorporeal membrane oxygenation is emerging as treatment for refractory cardiac arrest with reversible underlying disease.

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29

Pulmonary Physiology

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CHAPTER OUTLINE

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Humoral Control
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Molecular Physiology
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Emerging Developments
Carbon Dioxide Oscillations and Control of Ventilation
Asthma Phenotypes and Targeted Therapies
Remodeling of Airways

This chapter describes the physiology of the respiratory system by detailing the control systems and mechanisms of air movement into and out of the lungs that allow oxygen and carbon dioxide to exchange with blood. Emphasis is placed on those systems where the molecular physiology is understood as these systems constitute targets for the actions of drugs on the respiratory system, both beneficial and harmful.

Pulmonary Ventilation

Ventilation is the process by which air is drawn into and out of the lungs and delivered to the alveoli for gas exchange. It can be divided into an active inspiratory phase and most often a passive expiratory phase. Contraction of the inspiratory muscles increases the volume of the chest cavity, thus reducing intrathoracic pressure and causing air to move down its pressure gradient from the mouth. To achieve this, the respiratory muscles must overcome the inherent elasticity of the respiratory system as well as resistance to gas flow in the airways. This resistance consists of elastic resistance of lung tissue and chest wall, resistance from surface forces at the alveolar gas/liquid interface, frictional resistance to gas flow through the airways, resistance to deformation of thoracic tissues, and finally a negligible component of inertia associated with movement of gas and tissue.

Expiration is usually a passive process during which the respiratory muscles relax, allowing the elastic tissues of the chest wall to return to their resting position. The point at which the tendency for the lung to contract equals the tendency of the chest wall to expand is the resting position of the respiratory system, the functional residual capacity (FRC).

Muscles of Ventilation

During inspiration, subatmospheric pressure occurs throughout the airway. Collapse of large airways is prevented by their cartilaginous structure and of small airways by the elasticity of surrounding lung tissue, but in the pharynx collapse can easily occur. In conscious individuals, upper airway collapse is prevented by a combination of both tonic muscle activity and phasic inspiratory contraction of the pharyngeal dilator muscles. This muscle activity is controlled via reflex stimulation of mechanoreceptors in the larynx and pharynx that respond to subatmospheric pressure by rapidly (<50 msec) activating the pharyngeal dilators. Similar responses in the laryngeal muscles result in abduction of the vocal cords during inspiration and adduction in expiration. Adduction of the cords in early expiration is believed to act to slow expiratory flow rate and thus help prevent alveolar collapse.

The diaphragm is the principal muscle for inspiration and is responsible for around three-quarters of the tidal volume during resting inspiration in the supine posture. Intercostal muscles also contribute to inspiration, particularly when in an upright position and when there is increased ventilation (e.g., with exercise or with

Abstract

This chapter describes the control systems and mechanisms of air movement into and out of the lungs to allow oxygen and carbon dioxide to exchange with blood. Emphasis is placed on those systems where the molecular physiology constitutes targets for the actions of drugs on the respiratory system. Coordinated contraction of airway, intercostal, and diaphragm muscles is required to cause inspiration of gas into the lungs. Expiration is normally passive but when ventilation increases (e.g., in response to exercise), expiration becomes active with contraction of the internal intercostal and abdominal muscles. Most bronchial smooth muscle is found in the 12th to 16th generations of the airway, and four mechanisms control muscle tone in these airways: neural, humoral, direct physical and chemical, and local cellular pathways. Neural control is the most important in normal lung, but airway smooth muscle contains numerous adrenoreceptors that respond to circulating catecholamines. In healthy lungs ventilation and perfusion are well matched and approximately equal, but in diseased lungs or during general anesthesia there are discrepancies between the two that can adversely affect gas exchange, impairing both oxygenation and carbon dioxide elimination. Regional hypoxic pulmonary ventilation is a reflex that acts to divert pulmonary blood flow away from hypoxic areas of lung and is an important mechanism for optimizing ventilation-perfusion relationships. The respiratory pattern is generated within the medulla, which coordinates the voluntary and involuntary demands of respiratory activity via multiple neuronal connections. Reflex control of breathing occurs in response to both carbon dioxide and oxygen.

Keywords:

respiration
inhalation
exhalation
airway resistance
bronchioles
asthma
airway remodeling

dyspnea from lung pathology). The external intercostal and parasternal portions of the internal intercostal muscles are normally active during inspiration, but changes in posture and other activities involving movement of the trunk affect which muscles are active in each phase of respiration. Other muscles such as the scalenes and sternocleidomastoids can also contribute to inspiration.

When supine, the weight of the abdominal contents assists in passive expiration by pushing the diaphragm cephalad. When upright or while hyperventilating, however, the internal intercostals and abdominal wall muscles contract to assist expiration. Many of the respiratory muscles have additional functions, including maintenance of posture, coughing, sneezing, and speech. Each of these functions must be integrated with the muscles' primary role in breathing.

The Airway

Gas flow within the airways is predominantly turbulent in the pharynx, larynx, and large airways, becoming more laminar in smaller airways as gas velocity decreases. For laminar flow, the flow rate is related to the fourth power of the radius (r^4) of a straight tube as described by the Poiseuille equation. Lung volume has a large effect on airway diameter, so the relationship between lung volume and airway resistance is hyperbolic. Airway resistance is low at FRC, and increasing lung volume further has little effect. In contrast, a small reduction in lung volume results in a large increase in resistance. The main sites of resistance within the airway are the nose and major bronchi. Speed of airflow rapidly decreases as air passes from large to small airways, with the aggregate cross-sectional area increasing to very large values after the eighth generation of airway (small bronchi, 1–2 mm in diameter).[1]

In addition to conducting gas to and from alveoli the pharynx, larynx and large airways "condition" inspired gas by warming and humidifying each breath to fully saturated with water vapor at body temperature before the gas reaches the smaller airways. The airway lining is also responsible for defending the lungs from the myriad inhaled particles that would damage the alveoli or gain access to the body if they reached the gas exchanging regions of the lung. All of these functions are achieved by the airway epithelium producing airway lining fluid, which provides the water required for humidification and contains large amounts of a sticky glycoprotein called mucin, which is responsible for capturing inhaled particles and removing them from the lung. Excessive secretion of mucin or abnormal airway lining fluid function is a feature of many respiratory diseases, including smoking, chronic obstructive pulmonary disease, and cystic fibrosis, leading to often irreversible narrowing of larger airways.

Most airway diseases also involve reduction in the diameter of small airways as the result of bronchospasm and mucosal edema. This reduction in diameter in turn causes increased airway resistance and decreased gas flow. A large proportion of current pharmacotherapy for airway disease targets airway smooth muscle and inflammation in an attempt to increase airway diameter and gas flow.

Cellular Physiology

Most bronchial smooth muscle is found in the 12th to 16th generations of airway, which are bronchioles typically with a diameter of less than 1 mm. They have no cartilaginous support and their walls contain a high proportion of smooth muscle relative to luminal diameter.

Four mechanisms are involved in controlling muscle tone in small airways: neural pathways, humoral (via blood) control, direct physical and chemical effects, and local cellular mechanisms. Neural control is the most important in normal lung, with direct stimulation and humoral control contributing under some circumstances. Cellular mechanisms, particularly mast cells, have little influence under normal conditions but are important in airway disease.

Neural Control

The parasympathetic nervous system is the most important determinant of bronchomotor tone and when activated can completely obliterate the lumen of small airways. Both afferent and efferent nerve fibers travel via the vagus nerve (X) with efferent ganglia in the bronchial walls. Afferent nerves arise from receptors under the tight junctions of the bronchial epithelium and respond either to noxious stimuli acting directly on the receptors or to cytokines released by cellular mechanisms such as mast cell degranulation. Efferent nerves release acetylcholine, which acts at M_3 muscarinic receptors to cause contraction of airway smooth muscle, while also stimulating M_2 prejunctional muscarinic receptors to exert negative feedback on acetylcholine release. Stimulation of any part of the reflex arc results in bronchoconstriction. Some degree of resting tone is normally present and therefore permits a small degree of bronchodilation when vagal tone is reduced in a similar fashion to vagal control of heart rate.[2]

In contrast to the parasympathetic system, the sympathetic system is poorly represented in the lung and not yet proven to be of major importance in humans. Indeed, it appears unlikely that there is any direct sympathetic innervation of airway smooth muscle.

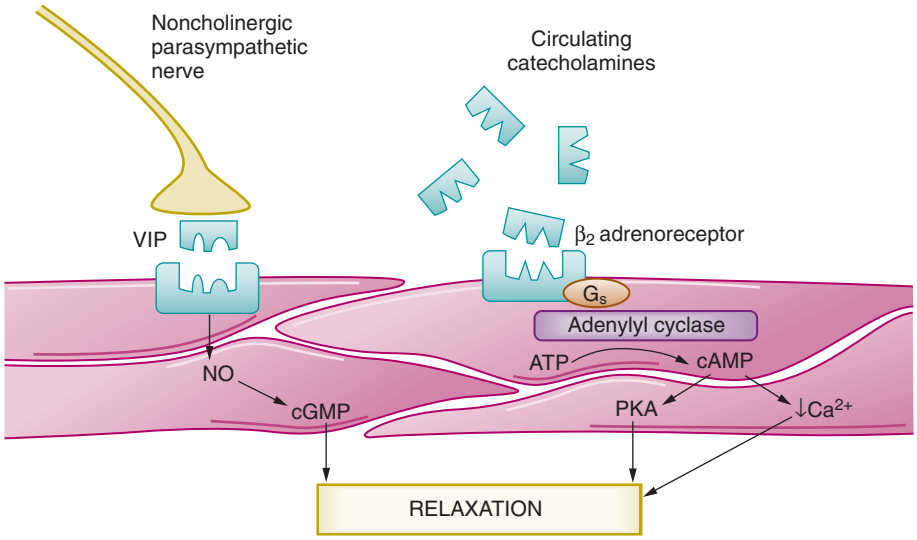
The airways are provided with a third autonomic control system, the nerves of which are neither adrenergic nor cholinergic, and are referred to as noncholinergic parasympathetic nerves (Fig. 29.1).[2] This is the only potential bronchodilator nervous pathway in humans, though the exact role of these nerves remains uncertain. The efferent fibers run in the vagus nerve and pass to the smooth muscle of the airways where they cause slow (minutes) and prolonged relaxation of bronchi. The major neurotransmitter is vasoactive intestinal peptide, which produces airway smooth muscle relaxation by promoting production of nitric oxide (NO). How NO relaxes airway smooth muscle is not as fully understood as its effect on vascular smooth muscle, but resting airway tone does seem to involve NO mediated bronchodilation.

Humoral Control

Despite the minimal significance of sympathetic innervation, airway smooth muscle has plentiful β_2-adrenergic receptors that are highly sensitive to circulating epinephrine and act via complex second-messenger systems (see Fig. 29.1 and described later).[3] Basal levels of epinephrine probably do not contribute to airway muscle tone, but this mechanism is brought into play during exercise or during the sympathetic "stress response." There are α-adrenergic receptors that cause bronchoconstriction, but these are not thought to be of physiologic significance.

Physical and Chemical Effects

Direct stimulation of the respiratory epithelium activates the parasympathetic reflex described previously, thereby causing bronchoconstriction. This is a protective reflex that evolved to prevent inhaled particles gaining access to the lower respiratory tract by effectively reducing airway size and air flow to distal lung units. This type of protection is necessary because the thin alveolar capillary membrane (to facilitate gas transfer) is a vulnerable interface



• **Fig. 29.1** Schematic diagram of the two major bronchodilator systems present in the human airway. On the left is the neural bronchodilator pathway, involving fibers of the vagus nerve that release vasoactive intestinal peptide *(VIP),* which in turn increases nitric oxide *(NO)* production to stimulate the formation of cyclic guanosine monophosphate *(cGMP)* and bring about relaxation of airway smooth muscle cells. On the right is the G-protein (G_s)-coupled β_2 adrenoreceptor, which responds to circulating epinephrine to cause relaxation of the airway via production of cyclic adenosine monophosphate *(cAMP)* and activation of protein kinase A *(PKA). ATP,* Adenosine triphosphate; *Ca^{2+},* calcium ion.

TABLE 29.1 Mediators Involved in Control of Bronchial Smooth Muscle Activity in Inflamed Airways

Source	Bronchoconstriction Mediator	Receptor	Bronchodilation Mediator	Receptor
Mast cells, other proinflammatory cells	Histamine	H_1	Prostaglandin E_2	EP
	Prostaglandin D_2	TP	Prostacyclin (PGI_2)	EP
	Prostaglandin $F_{2\alpha}$	TP		
	Leukotrienes C_4, D_4, E_4	$CysLT_1$		
	PAF	PAF		
	Bradykinin	B_2		
C-fibers	Substance P	NK_2		
	Neurokinin A	NK_2		
	CGRP	CGRP		
Endothelial, epithelial cells	Endothelin	ET_B		

B, Bradykinin; *CGRP,* calcitonin gene-related peptide; *EP,* prostaglandin E–specific prostanoid receptor; *ET,* endothelin; *H,* histamine; *LT,* leukotriene; *PAF,* platelet-activating factor; *PG,* prostaglandin; *NK,* neurokinin; *TP,* thromboxane-specific prostanoid receptor.

From Barnes PJ. Pharmacology of airway smooth muscle. *Am J Respir Crit Care Med.* 1998;158:S123–S132; and Thirstrup S. Control of airway smooth muscle tone. I—electrophysiology and contractile mediators. *Respir Med.* 2000;94:328–336.

between the internal milieu and the outside world. Physical factors known to produce bronchoconstriction include mechanical stimulation of the upper airway (e.g., by laryngoscopy) and the presence of a foreign body in the airway. Inhalation of particulate matter, an aerosol of water, or just cold air can also cause bronchoconstriction, particularly in patients with asthma. Many chemical stimuli also result in bronchoconstriction, including liquids with low pH such as gastric acid, and irritant gases such as sulfur dioxide, ammonia, ozone, and nitrogen dioxide.

Local Cellular Mechanisms

Inflammatory cells found in the lung include mast cells, eosinophils, neutrophils, macrophages, and lymphocytes. These inflammatory cells are stimulated by a variety of pathogens, but some can also be activated by the direct physical factors described earlier. Once activated, cytokine production causes amplification of the response, and a variety of mediators are released that can cause bronchoconstriction (Table 29.1). These mediators are produced in normal individuals, but patients with airway disease are usually "hyperresponsive" and so develop bronchospasm more easily.

Molecular Physiology

There are two opposing systems that control bronchial smooth muscle tone: signaling pathways resulting in increased intracellular cyclic adenosine monophosphate (cAMP), reduced intracellular

calcium ions (Ca^{2+}), and bronchodilation, and pathways resulting in increased inositol triphosphate (IP_3), increased Ca^{2+}, and bronchoconstriction.

Bronchodilator Pathway

These pathways are summarized in Fig. 29.1. The molecular basis for the function of β_2-adrenoreceptors is now clearly elucidated.[4] This G-protein–coupled receptor contains 413 amino acids and has 7 transmembrane helices. The agonist binding site is deep within the hydrophobic core of the protein, which sits within the lipid bilayer of the cell membrane. This affects the interaction of drugs at the binding site. Lipophilic drugs form a depot in the lipid bilayer from which they can repeatedly interact with the binding site of the receptor, producing a longer duration of action than hydrophilic drugs. Receptors exist in either activated or inactivated form, the former state occurring when the third intracellular loop is bound to the α-subunit of the G_s-protein. Agonists of the β_2 receptor probably do not induce a significant conformational change in the protein structure but rather stabilize the activated conformation, allowing this to predominate.

β_2-Adrenoreceptor stimulation results in activation of G_s, a guanosine triphosphate (GTP)-binding regulatory protein, which in turn activates adenylyl cyclase. This enzyme catalyzes the conversion of adenosine triphosphate (ATP) to cAMP. cAMP inhibits the release of Ca^{2+} from intracellular stores in addition to activating protein kinase A, which in turn phosphorylates proteins regulating the interaction of actin and myosin. As a result of these actions, smooth muscle cells relax, leading to bronchodilation (see Fig. 29.1).

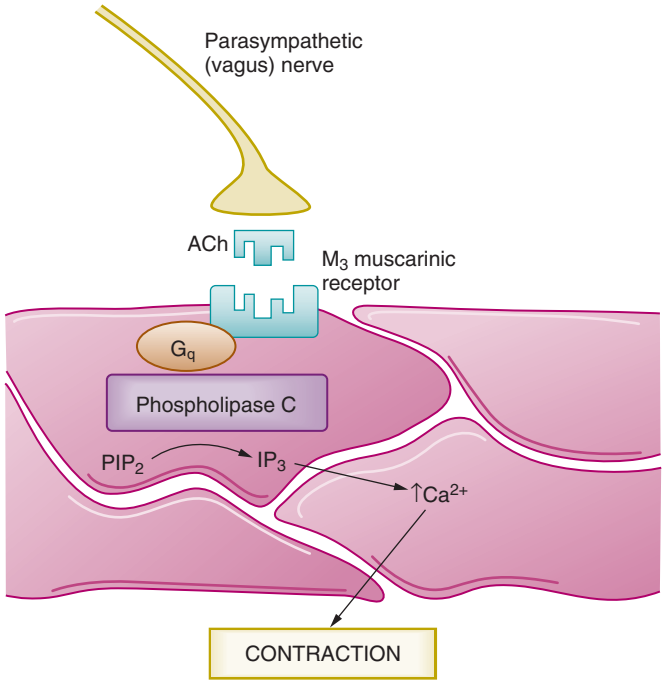
Intracellular cAMP is rapidly hydrolyzed by phosphodiesterase (PDE). Seven subtypes of PDE have been identified with subtypes 3, 4, and 7 predominating in the lungs. Several phosphodiesterase inhibitors are available (e.g., theophylline), which function by prolonging smooth muscle relaxation resulting from β_2-receptor stimulation. However, older PDE inhibitors are nonspecific and as a result, their use in the treatment of bronchoconstriction is limited by side effects.[5] Newer, more specific, inhibitors (e.g., of PDE subtype 7) may also have an antiinflammatory effect in lung disease.[6]

Two β_2-receptor genes are present in humans, with 18 polymorphisms described, giving rise to a large number of possible phenotypic variants. Some clinical differences are observed between variants, but the contribution of different β_2 receptor phenotypes to the overall prevalence of asthma appears to be minimal.[7]

Bronchoconstrictor Pathway

Stimulation of M_3 acetylcholine receptors (Fig. 29.2) results in the activation of a different G-protein (G_q) that in turn activates phospholipase C, stimulating the formation of IP_3. IP_3 binds to receptors on the sarcoplasmic reticulum, promoting the release of Ca^{2+} from intracellular stores. Myosin light chain kinase is activated by Ca^{2+} and in turn phosphorylates myosin chains and activates myosin adenosine triphosphatase (ATPase). As a result, cross-bridges are formed between actin and myosin and contraction of smooth muscle occurs.[5] IP_3 is then converted to inactive inositol diphosphate (IP_2) by IP_3 phosphatase. Other mediators of bronchoconstriction (e.g., tachykinin and histamine) exert their effects via similar mechanisms resulting in an increase in IP_3 production (see Table 29.1).[8]

There are many interactions between the IP_3 and cAMP signaling pathways. Activation of G_q also results in synthesis of diacylglycerol from phosphatidylinositol bisphosphate by phospholipase C. Diacylglycerol in turn activates protein kinase C, which phosphorylates many downstream proteins, including G-proteins and the intracellular domain of the β_2 adrenoreceptor itself. This causes the β_2 adrenoreceptor to become uncoupled from its G-protein, resulting in downregulation of the transduction pathway.[4,5] Frequent stimulation of the receptor results in desensitization to its agonist via a similar mechanism.[9]



• **Fig. 29.2** Schematic diagram of the parasympathetic bronchoconstrictor system in human airways. Reflex activation of parasympathetic nerves by a variety of stimuli (see text for details) results in acetylcholine *(ACh)* release. Acting via M_3 muscarinic cholinergic receptors, a G_q-protein activates phospholipase C, which converts phosphatidylinositol biphosphate *(PIP_2)* into inositol trisphosphate *(IP_3),* which promotes release of Ca^{2+} from intracellular stores in the stimulated cells. The increase in Ca^{2+} then activates the contractile machinery. *Ca^{2+},* Calcium ion.

Bronchoconstriction in Airway Disease

Bronchoconstriction as part of airway disease occurs as a result of complex interactions between proinflammatory cells and mediators. Mast cells are ubiquitous in airway epithelium and can be activated physically (e.g., by coughing) as well as by allergens and infection. Both allergens and infection exert their effects via immunoglobulin E, complement, and cytokines. The last of these cause chemotaxis and activation of other inflammatory cells, including neutrophils, macrophages, eosinophils, and lymphocytes, which in turn leads to augmentation of the inflammatory response.

Another key pathway in the generation of bronchoconstriction is modulated by the noncholinergic parasympathetic system described earlier. C-fiber nerve endings release inflammatory mediators, including tachykinins, which are thought to play an important part in the genesis of bronchial hyperresponsiveness.[8]

The physiologic complexity of bronchoconstriction presents many potential therapeutic targets for the treatment of asthma (see Chapter 30). Steroids are the mainstay of treatment. Their antiinflammatory action reduces mucosal edema and swelling as

well as smooth muscle tone, vascular permeability, and pulmonary vascular resistance. Glucocorticoids exert their effects by down-regulating synthesis of certain proteins, leading to a reduction in inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-11, prostaglandins, bronchoconstrictor receptors such as neurokinin receptors, and inflammatory enzymes such as cyclooxygenase 2. In addition, glucocorticoids increase antiinflammatory cytokines and the numbers of bronchodilator receptors such as β_2 adrenoreceptors.[10] Cytoplasmic glucocorticoid receptors consist of a single protein with two centrally bound zinc atoms. Agonists bind to the receptor within the cytoplasm, resulting in a conformational change that allows the receptor to enter the nucleus. The receptor then regulates DNA transcription by directly binding to specific regulatory DNA sequences and interacting with other transcription factors to modify gene expression. Steroid responsiveness varies between individuals and this might be due to the variable requirement for other transcription factors to interact with the glucocorticoid receptor.[11]

There is increasing recognition that the inflammatory process underlying asthma development originates from abnormal immune responses to infection or allergens, with important roles for several subtypes of T "helper" (Th) lymphocytes. An early, oversimplistic view of this claimed that asthma developed simply because of an imbalance between the activity of proinflammatory Th2 lymphocytes and their antiinflammatory Th1 counterparts, but more recently the focus has moved to regulatory T cells and natural type-2 helper cells that influence the activity of both Th1 and Th2 cells. Irrespective of the exact cellular mechanisms, the numerous cytokines by which these cells communicate provide great therapeutic potential. Monoclonal antibodies that reduce the activity of the main pro-inflammatory cytokines in asthma, IL-5 and IL-13, are already available and have shown good outcomes in clinical trials in some patients.[12,13]

Oxygenation

The partial pressure of oxygen (P_{O_2}) of dry air at sea level is 159 mm Hg (21.2 kPa). Oxygen is diluted by water vapor and expired carbon dioxide as it passes through the respiratory tract and then moves down its partial pressure gradient across the alveolar capillary barrier into the blood, then from arterial capillary blood into tissues and cells. P_{O_2} finally reaches its lowest level in the mitochondria, where it is consumed in oxidative phosphorylation. At this point, the P_{O_2} is probably within the range of 3.8 to 22.5 mm Hg (0.5–3 kPa), varying within different tissues and cell types. This stepwise reduction in P_{O_2} from air to mitochondria is known as the oxygen cascade, and any step in the cascade can be affected under pathologic circumstances to result in tissue hypoxia (see Chapter 23).

There are about 300 million alveoli in the adult human lung. These thin-walled air sacs form the basic unit of gas exchange and are approximately 0.3 mm in diameter at FRC. Alveoli begin to appear in the lung at the level of the respiratory bronchioles, the level at which gas movement ceases to be tidal and moves instead by diffusion. The walls of alveoli are very thin, approximately 0.5 μm, to allow easy diffusion of respiratory gases. For gas to enter pulmonary capillaries it must first traverse the alveolar-capillary barrier. This consists of the alveolar lining fluid, alveolar epithelial cell, interstitial tissue, basement membranes, and finally the pulmonary capillary endothelium. To minimize the distance between capillary endothelium and red blood cells (RBCs), the diameter of the pulmonary capillaries is small so that the RBCs must flatten to pass, bringing the RBC membrane into close contact with the capillary wall. Diffusion occurs quickly across the blood-gas barrier so that RBCs become fully saturated with oxygen within 0.25 second of entering the pulmonary capillary. This is only a third of the time the cell spends in the capillary in a resting subject and means that a diffusion barrier is rarely a cause of poor oxygen uptake; the only examples in humans are extreme hypoxia at altitude or severe exercise in elite athletes.

Ventilation and Perfusion Relationships

Matching ventilation and perfusion is critical to optimize oxygen transfer. Gas exchange is optimal when ventilation and perfusion are evenly distributed throughout the lung. In a contrasting and extreme example, if 100% of perfusion is to one lung and 100% of ventilation is to the other lung, no gas exchange occurs even though total ventilation and perfusion might be normal.

Distribution of Ventilation

Ventilation to different lung regions is influenced by several factors. The right lung is bigger than the left and therefore receives a greater proportion of total ventilation in the upright and supine positions. The effect of gravity is also important. Lung tissue can be considered as semifluid or gel-like within the chest cavity. The weight of tissue above compresses tissues below, making the density of tissues at the bases greater than at the apices. The dependent bases are therefore less expanded and so more compliant, which in turn means they are better ventilated. With the body in the lateral position, the lower, dependent lung is better ventilated than the upper, nondependent lung, and similarly, in the supine position, the posterior part of the lung is better ventilated than the anterior part. Gravity is not the only influence, and airway distribution also affects ventilation. Scanning techniques with the ability to measure ventilation in areas of lung only a few milliliters in volume show increased ventilation in central compared with peripheral lung regions.[14] This observation probably results from unequal branching patterns of the airways.

Distribution of Perfusion

The flow of blood through the pulmonary circulation equals the flow through the systemic circulation, from about 6 L/min under resting conditions to as much as 25 L/min during exercise. It is remarkable that such a range of flow can normally be achieved with minimal increase in pulmonary vascular pressures, owing to the considerably lower pulmonary vascular resistance (PVR) compared with that in the systemic circulation. PVR determines total blood flow to the lungs but the regional distribution of blood flow is not uniform. Flow progressively increases down the lung in an upright subject with flow per unit of lung volume increasing by 11% per centimeter of descent,[15] but as for ventilation, gravity is not the only factor.[14]

Total PVR is influenced by a variety of both passive and active factors. Passive factors include the following:

1. Transmural pressure. If extravascular pressure is greater than intravascular hydrostatic pressure, the vessel will collapse, obstructing blood flow. This situation occurs in some lung regions during positive-pressure ventilation and can increase regional PVR and reduce perfusion.
2. Lung volume. PVR is at its lowest at FRC. As lung volume increases, some pulmonary capillaries become narrowed and stretched, whereas a reduction in lung volume makes some capillaries more tortuous or kinked, both of which increase PVR.

3. Vascular architecture. The branching pattern of the pulmonary vasculature might be responsible for gravity-independent variation in blood flow, known as the *fractal hypothesis*. Two aspects of vascular structure contribute to variations in flow. Because of the exponential relationship between flow and radius, bifurcations of pulmonary arteries into two slightly different-sized vessels has a large effect on the flow rates in each.[14] In addition, pulmonary arteries are more numerous than pulmonary airways as a result of small extra branches, often given off at right angles, throughout the pulmonary arterial tree. Mathematical modeling indicates that these "supernumerary" branches contribute significantly to the heterogeneity of regional perfusion.[16]

Ventilation in Relation to Perfusion

Ventilation can be related to perfusion using the ventilation-perfusion ratio ($\dot{V}/\dot{Q}$). If alveolar ventilation is 4 L/min and pulmonary blood flow is 5 L/min, then the $\dot{V}/\dot{Q}$ ratio equals 0.8. If ventilation and perfusion of all alveoli were the same, then $\dot{V}/\dot{Q}$ would be 0.8 throughout the lung. But ventilation and perfusion are not uniform for all the reasons described, and alveoli range from nonventilated to unperfused with all possible combinations in between. Alveoli with no ventilation ($\dot{V}/\dot{Q}$ ratio of 0) have P_{O_2} and partial pressure of carbon dioxide (P_{CO_2}) values that are the same as those of mixed venous blood because the trapped air in the nonventilated alveoli equilibrates with mixed venous blood. Alveoli with no perfusion ($\dot{V}/\dot{Q}$ ratio of ∞) have P_{O_2} and P_{CO_2} values that are the same as humidified inspired gas because there is no gas exchange to alter the composition of the alveolar gas. All other alveoli have P_{O_2} and P_{CO_2} values in between those of mixed venous blood and inspired gas depending on their $\dot{V}/\dot{Q}$ ratio (Fig. 29.3).

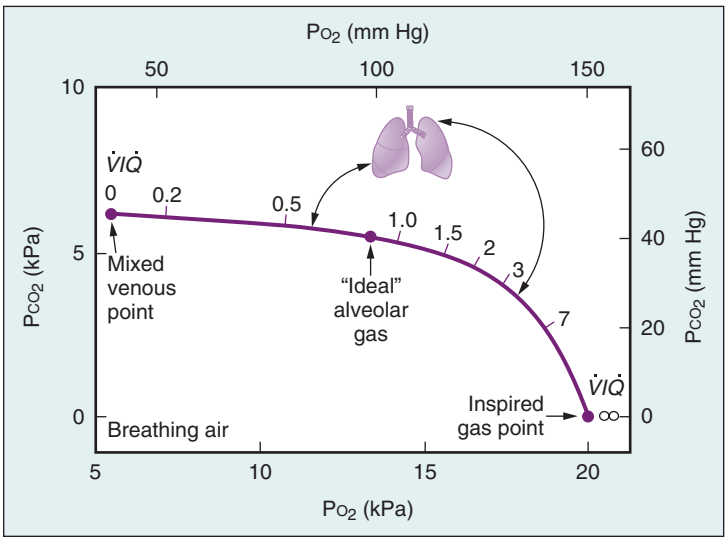
Shunt

Admixture of pulmonary venous blood with poorly oxygenated or mixed venous blood is an important cause of systemic arterial hypoxemia. Venous admixture refers to the degree of admixture of mixed venous blood with pulmonary end-capillary blood that would be required to produce the observed difference between the P_{O_2} of arterial and pulmonary end-capillary blood. There are several sources of venous admixture. Physiologic sources include the venae cordis minimae (Thebesian veins) that drain blood from the myocardium directly into the chambers of the left heart and the bronchial veins that drain into the pulmonary veins. Pathologic causes include right-to-left shunting in congenital heart disease, particularly conditions involving obstruction of the right ventricular outflow tract (e.g., tetralogy of Fallot). More commonly, pulmonary pathology causes increased venous admixture, usually resulting from pulmonary blood flow past nonventilated or poorly ventilated alveoli in conditions such as pneumonia, atelectasis, and acute lung injury.

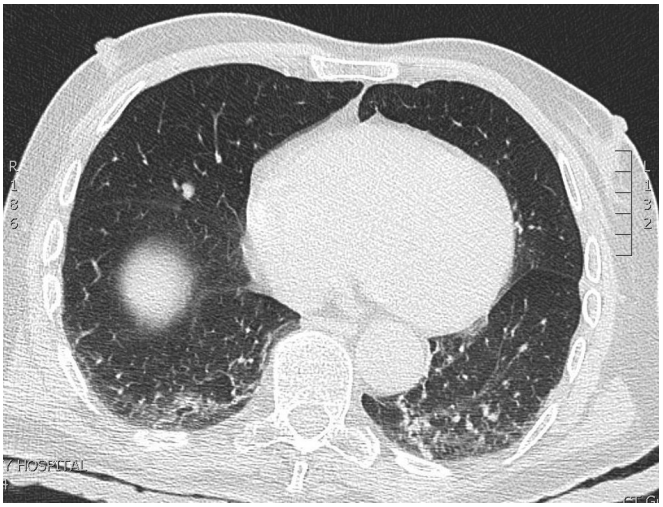
Effects of General Anesthesia

General anesthesia has a marked effect on $\dot{V}/\dot{Q}$ relationships. Following induction of anesthesia, changes in the dimensions of the thoracic cavity owing to muscle relaxation, in particular loss of tonic activity in the diaphragm, lead to a 10% to 20% reduction in FRC. As FRC approaches closing capacity, atelectasis occurs in the dependent parts of the lung (Fig. 29.4), resulting in areas of lung that are perfused but not ventilated ($\dot{V}/\dot{Q} = 0$), increasing shunt and therefore impairing oxygenation. Even in dependent areas without atelectasis, the $\dot{V}/\dot{Q}$ ratio is less than 1 and oxygenation poor. Atelectasis and areas with a low $\dot{V}/\dot{Q}$ ratio are more likely in patients whose closing capacity is already equal to or greater than FRC prior to anesthesia (e.g., in older patients, infants, and the obese).

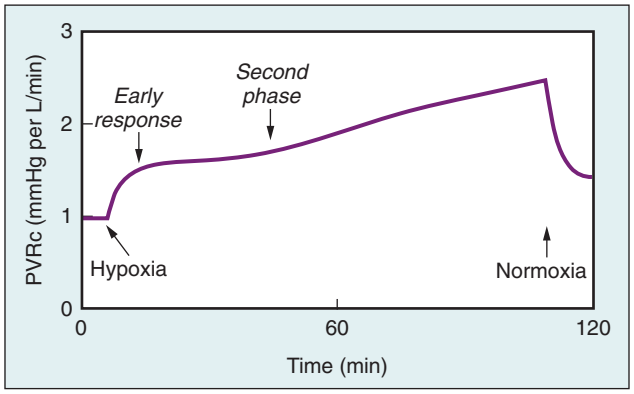
In nondependent areas of lung the converse problem occurs. These areas are, relative to dependent regions, well ventilated. General anesthesia commonly leads to low cardiac output and pulmonary hypotension, resulting in reduced perfusion to nondependent regions. As a result of these two effects, $\dot{V}/\dot{Q}$ ratios in nondependent regions are normally greater than 1, and there are some areas with ventilation but no perfusion ($\dot{V}/\dot{Q} = \infty$) which constitutes alveolar dead space. Without compensatory increases in ventilation, these regions of lung lead to reduced carbon dioxide elimination and give rise to the large difference between end-expiratory and arterial P_{CO_2} commonly seen during general anesthesia. Although $\dot{V}/\dot{Q}$ ratios throughout the lung as a whole remain normal during general anesthesia, there is increased scatter of $\dot{V}/\dot{Q}$ ratios in different lung regions, leading to impairment of both oxygenation and carbon dioxide elimination.



• **Fig. 29.3** Effect of different ventilation-perfusion ($\dot{V}/\dot{Q}$) ratios on alveolar partial pressure of oxygen (P_{O_2}) and partial pressure of carbon dioxide (P_{CO_2}). In regions where there is no perfusion ($\dot{V}/\dot{Q} = \infty$), alveolar gases are the same as inspired; in regions where there is no ventilation ($\dot{V}/\dot{Q} = 0$), alveolar gases are the same as mixed venous blood. All possible $\dot{V}/\dot{Q}$ ratios between these extremes are shown on the graph, illustrating a nonlinear relationship between $\dot{V}/\dot{Q}$ ratio and gas partial pressures. The arrows show typical $\dot{V}/\dot{Q}$ ratios at the apex and base of normal lungs in the upright posture.



• **Fig. 29.4** Computed tomography scan of the chest during general anesthesia with muscle relaxation. The slice shown is at the level of the dome of the right diaphragm, which is visible in the center of the right hemithorax. Patches of atelectasis in this supine patient can be seen throughout the dependent regions of both lungs.



• **Fig. 29.5** Hypoxic pulmonary vasoconstrictor response to prolonged hypoxia (end-tidal partial pressure of oxygen [P_{O_2}] 50 mm Hg). The early response is complete within a few minutes, then a more potent second phase begins after about 40 minutes. Note that when normoxia is restored, pulmonary vascular resistance corrected for cardiac output *(PVRc)* does not immediately return to baseline. (Modified from Talbot NP, Balanos GM, Dorrington KL, et al. Two temporal components within the human pulmonary vascular response to approximately 2 h of isocapnic hypoxia. *J Appl Physiol.* 2005;98:1125–1139.)

Active Control of Pulmonary Vascular Resistance

In addition to the passive changes in PVR already described, pulmonary blood vessels are also under active control. The pulmonary vasculature is normally kept in a state of active vasodilatation. There are many mechanisms involved in the active control of PVR. Some vasodilators (e.g., prostaglandins and vasoactive intestinal peptide) act directly on smooth muscle cells via the cAMP second-messenger system. In contrast, vasoconstrictors activate G-protein-coupled receptors, leading to increased IP_3. NO plays an important role in pulmonary blood vessels, and it is likely that NO acts as a final common pathway for relaxation of pulmonary vascular smooth muscle from a variety of different stimuli. Nitric oxide synthase (NOS) produces NO by converting L-arginine to L-citrulline. Pulmonary NOS exists in two forms: constitutive and inducible NOS. The inducible form (iNOS or NOS2) is produced by many cells in response to activation by inflammatory mediators. Constitutive NOS (cNOS or NOS3) is always present in some cells, including pulmonary endothelium, producing short bursts of NO in response to changes in Ca^{2+} levels. NO diffuses from the site of production to the smooth muscle cell, where it activates guanylyl cyclase to produce cGMP, which in turn activates protein kinase G. This system is similar to the cAMP pathway and causes relaxation by a combination of effects on cytosolic Ca^{2+} levels and the activity of enzymes controlling myosin activity.

Hypoxic Pulmonary Vasoconstriction

Vasoconstriction in response to hypoxia represents the fundamental difference of pulmonary blood vessels compared with systemic vessels. Hypoxic pulmonary vasoconstriction (HPV)[17] is mediated both by mixed venous (pulmonary arterial) and alveolar P_{O_2}, with the greater influence from the alveolus.

Regional HPV is beneficial as a means of diverting pulmonary blood flow away from areas of lung with a low oxygen partial pressure and is an important mechanism for optimizing $\dot{V}/\dot{Q}$ relationships. It is also important in the fetus to minimize perfusion of the nonventilated lungs. However, long-term HPV, either continuous or intermittent, can lead to remodeling of the pulmonary vasculature and irreversible pulmonary hypertension.

The pressor response to hypoxia results from constriction of small arterioles of 30 to 200 μm in diameter and begins within a few seconds of P_{O_2} reduction. In humans, hypoxia in a single lobe of the lung results in a rapid decline in perfusion of the lobe such that within 5 minutes regional blood flow is half that during normoxia. With prolonged hypoxia, HPV in humans is biphasic: the initial rapid response reaches a plateau after about 5 minutes, with the second phase occurring after around 40 minutes and reaching a maximal response after 2 to 4 hours (Fig. 29.5).[18]

Cellular Physiology of Hypoxic Pulmonary Vasoconstriction

Neural connections to the lung are not required as HPV occurs in isolated lung preparations and in humans following lung transplantation. Attempts to elucidate the mechanisms of HPV have been hampered by species differences, the multitude of systems affecting pulmonary vascular tone, and a lack of appreciation of the biphasic nature of the response.[19] Uncertainties remain regarding the exact cellular mechanisms of HPV, but there is now agreement that contraction of pulmonary artery smooth muscle cells (PASMCs) in response to hypoxia is an inherent property of these cells and that pulmonary endothelial cells act only to modulate the PASMC response.[20]

Molecular Physiology

Hypoxia leads to a small increase in intracellular Ca^{2+} concentration within the PASMCs, and also a rho-kinase–mediated increase in the Ca^{2+} sensitivity of the smooth muscle contractile proteins. The change in Ca^{2+} results from opening of L-type voltage-gated Ca^{2+} channels (Ca_v1), stimulated by hypoxia-induced inhibition of voltage-gated K^+ (K_v) channels. The molecular oxygen sensor that affects K_v channels remains controversial and might be an inherent

property of the K_v channels, although mitochondria, nicotinamide adenine dinucleotide phosphate oxidases, and reactive oxygen species are also involved.[19,21]

Modulation by the endothelial cell of the PASMC response to hypoxia can either enhance or inhibit HPV.[20] Inhibitors of HPV include prostacyclin and NO, both of which maintain some perfusion of hypoxic lung regions, although their role in normal lung is uncertain. For example, prostacyclin is a potent pulmonary vasodilator, but cyclooxygenase, which is required for its production, is inhibited by hypoxia and might therefore diminish its vasodilator effects. Similarly, basal NO secretion by endothelial cells might act to moderate HPV, but hypoxia also inhibits endothelial NO production and so enhances HPV. Molecules that enhance HPV include thromboxane A_2 and endothelin; the latter is released by endothelial cells in response to hypoxia.[22] It is a potent vasoconstrictor peptide, and has a prolonged effect on pulmonary vascular tone such that this mechanism is probably involved in the second slow phase of HPV (see Fig. 29.5). Two groups of endothelin receptors are described, ET_A and ET_B, and their relative expression varies between the central and peripheral pulmonary vasculature. Apart from its vasoconstrictor effects, endothelin also stimulates cellular proliferation of vascular endothelial cells and pulmonary fibroblasts, and so has an important role in the pulmonary vascular remodeling that accompanies long-term hypoxia.

Iron status affects the intensity of an individual's HPV response. Increased iron availability (achieved by intravenous infusion) attenuates HPV, whereas reducing iron availability by administration of desferrioxamine enhances the response.[23] This finding indicates that HPV in humans is at least partially mediated via hypoxia-inducible factor, a ubiquitous transcription factor that is activated by hypoxia to initiate a range of responses to protect the cell from damage. One of the crucial oxygen-dependent steps in this reaction requires iron as a cofactor, explaining why iron status influences HPV. These observations might be highly significant for patients given that normal subjects have widely varying iron status, depending on such factors as gender, diet, and chronic illness, and also open up the possibility of therapeutic interventions for pulmonary hypertension[24] or hypoxic critically ill patients.[25]

HPV is therefore a complex and poorly elucidated reflex. In normal subjects, HPV within the lung is inhomogeneous, with intense vasoconstriction in some areas and relative overperfusion elsewhere.[26] The degree of this inhomogeneity varies between individuals, and this has important implications when traveling to high altitude. Subjects susceptible to high-altitude pulmonary edema have a more intense and inhomogeneous HPV response.[26] Although this has never been studied, it raises the possibility that the same subgroup of patients would tolerate hypoxia related to lung disease poorly.

Control of Breathing

Early in fetal development the respiratory center forms within the brainstem and is responsible for subconscious rhythmic breathing throughout life. Breathing is controlled by a complex network of physical and chemical reflexes that can be overridden by voluntary control and interrupted by acts such as swallowing, sneezing, vomiting, hiccupping, and coughing. The control system can also be fine-tuned to accommodate for posture, speech, voluntary movement, and exercise. The respiratory pattern is generated within the medulla and coordinates the voluntary and involuntary demands of respiratory activity via multiple neuronal connections.

Respiratory Center

There are two main groups of respiratory neurons: the dorsal and ventral respiratory groups.

The dorsal respiratory group lies close to the nucleus tractus solitarius, which is the area of the brain where visceral afferents from cranial nerves IX and X terminate. This group consists mainly of inspiratory neurons and is responsible for timing of the respiratory cycle.

The ventral respiratory group is a column of respiratory neurons divided into four subgroups. The caudal group has both inspiratory and expiratory functions in addition to controlling the force of contraction of the contralateral inspiratory muscles. The rostral subgroup is composed mainly of the nucleus ambiguus and controls the airway dilator functions of the larynx, pharynx, and tongue. The pre-Bötzinger complex is believed to be the anatomic location of the central pattern generator (CPG), while the Bötzinger complex is within the nucleus retrofacialis and has widespread expiratory functions.

Central Pattern Generation

Unlike the heart, where inherent rhythm is initiated by a single pacemaker cell, respiratory rhythm begins with associated groups of neurons generating regular bursts of activity.[27] This activity can be recorded throughout the medulla but is concentrated in the pre-Bötzinger complex. Respiratory neuron networks that exhibit spontaneous activity achieve this by a combination of intrinsic membrane properties and excitatory and inhibitory feedback mechanisms. In practice, both inhibitory and excitatory neurotransmitters have a dual effect to (1) recruit other cells by direct activation and (2) modulate the spontaneous activity of a single cell by effects on its own membrane ion channels—for example, by slowing the rate at which an action potential travels along a dendrite.

Connections to the Respiratory Center

The pontine respiratory group, previously known as the pneumotaxic center, was believed to be important in controlling the timing of the respiratory cycle. It is no longer considered essential for generation of the respiratory rhythm but exerts fine control over medullary neurons—for example, setting the lung volume at which inspiration is terminated. The pons also coordinates input from other centers (e.g., the hypothalamus, cortex, and nucleus tractus solitaries), integrating cortical and peripheral sensory information, such as odors, temperature, and visceral and cardiovascular inputs with the respiratory rhythm. Voluntary interruption of breathing is possible within limits determined by arterial blood gas tensions. This is necessary for conscious activities such as speech. It is possible that cortical signals bypass the respiratory center, overriding it by acting directly on the lower motor neurons supplying respiratory muscles.

A number of different peripheral receptors also provide input to the respiratory center. Chemical and irritant receptors are found in the nasopharynx, larynx, and trachea. When stimulated by irritants such as smoke and gastric acid, a reflex is initiated that protects the lungs from inhalational injury, resulting in sneezing, coughing, laryngeal closure, apnea, or bronchoconstriction. The Paintal juxtapulmonary capillary receptors (J receptors) are small C-fiber endings in alveolar walls close to pulmonary capillaries. Stimulation can occur in response to pulmonary vascular congestion, pulmonary embolus, or exercise and results in rapid, shallow breathing; apnea; and mucus secretion.[28]

Pulmonary stretch receptors can be divided into two groups. Slowly adapting stretch receptors are situated in bronchial smooth

muscle and are stimulated by lung inflation, maintaining their firing rate when lung inflation is sustained and thus acting as a lung volume sensor. Rapidly adapting stretch receptors are located in the superficial mucosal layer of the airways and are stimulated by a change in tidal volume, respiratory frequency, or lung compliance. Stimulation of pulmonary stretch receptors leads to inhibition of inspiration in response to lung distention and a reduction in respiratory rate by increasing expiratory time. This reflex was first described in 1868 by Hering and Breuer, who noted that lightly anesthetized, spontaneously breathing animals ceased or decreased ventilation effort during sustained lung distention. Although this weak reflex has little clinical significance in adult humans, it is more pronounced in neonates and infants.[29]

Baroreceptors located in the carotid sinus and aortic arch are primarily concerned with regulation of the circulation, but can promote hyperventilation in response to a large decrease in arterial pressure.

Molecular Physiology

There are a variety of different neurotransmitters involved in the CPG and respiratory control. Excitatory transmitters include glutamate, which activates both N-methyl-D-aspartate (NMDA) and non-NMDA type receptors. Inhibitory transmitters such as glycine and gamma-aminobutyric acid (GABA) act via glycine and $GABA_A$ receptors to hyperpolarize and inhibit respiratory neurons.

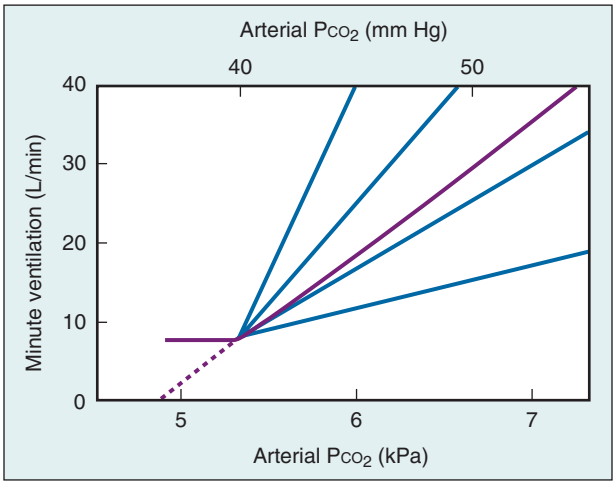
Neuromodulators influence CPG output but are not involved in rhythm generation. The exact role of neuromodulators is unclear but they are important for both normal and abnormal breathing. For example, opioids have a profound effect on breathing, suggesting the presence of opioid receptors in the respiratory center. However, the opioid antagonist naloxone has no effect on respiration in resting normal subjects. Other neuromodulators include acetylcholine, serotonin, and substance P. They exert their effects via final common intracellular signaling pathways within CPG neurons involving protein kinase A and protein kinase C, modulating the activity of GABA, glycine, and glutamate-regulated potassium ion (K^+) and chloride ion (Cl^-) channels.

Chemical Control of Ventilation

For many years it was believed that the respiratory center itself was sensitive to carbon dioxide. However, it is now known that both peripheral and central chemoreceptors are responsible for the effect of carbon dioxide on breathing, the latter accounting for about 80% of the total ventilatory response.[30] Because of their reliance on extracellular pH (see later text), the central chemoreceptors are regarded as monitors of steady-state arterial P_{CO_2} and tissue perfusion in the brain, while the peripheral chemoreceptors respond more to short-term and rapid changes in arterial P_{CO_2}.[31]

Central Chemoreceptors

Central chemoreceptors are located 0.2 mm below the ventrolateral surface of the medulla in the retrotrapezoid nucleus[32] inside the blood brain barrier (BBB). As arterial P_{CO_2} rises, so does the CO_2 content of cerebrospinal fluid (CSF). This occurs because the BBB is permeable to CO_2 but not to hydrogen ions. CO_2 diffuses across the BBB into the CSF, where it is hydrated to carbonic acid, which quickly ionizes to increase CSF hydrogen ion concentration and hence reduce pH. The mechanism by which a change in pH causes stimulation of chemoreceptor neurons remains controversial: the retrotrapezoid nucleus might contain pH-sensitive K^+ channels, and release of ATP has been proposed.[32] Increases in arterial P_{CO_2} lead to an increase in respiratory rate and depth of breathing until steady-state hyperventilation is achieved after a few minutes. The response is linear over the range that is usually studied, with alveolar ventilation increasing by around 2 L/min for each 1 mm Hg increase in arterial P_{CO_2} (Fig. 29.6). As P_{CO_2} continues to rise, the point of maximal ventilatory stimulation is reached, probably in the range of 100 to 200 mm Hg (13.3–26.7 kPa). Beyond this point, respiratory fatigue and CO_2 narcosis occur.



• **Fig. 29.6** The partial pressure of carbon dioxide *(P_{CO_2})* ventilation response. The response to carbon dioxide is highly variable between individuals as shown by the four *blue* response lines. The population average is shown in *purple,* and is hockey-stick shaped because when P_{CO_2} falls below the normal value, an awake subject continues to breathe despite the lack of respiratory drive from carbon dioxide. In an anesthetized subject, when this voluntary drive for respiration is lost, the *dotted line* shows the continuation of the slope to the point where it meets the *x*-axis and apnea occurs.

Decreasing P_{CO_2} produces a fall in alveolar ventilation, but once arterial P_{CO_2} is less than about 30 mm Hg (4 kPa), there are two possible physiologic responses. Some individuals reduce ventilation further, becoming apneic if P_{CO_2} continues to fall, while others continue to breathe regardless of the reduction in P_{CO_2}. This variable ventilatory response to low P_{CO_2} almost certainly arises from cortical control of respiration, maintaining breathing despite a lack of chemical drive, particularly when awake (see Fig. 29.6).

The P_{CO_2}/ventilation response curve is the response of the entire respiratory system to the challenge of raised P_{CO_2}. Apart from reduced sensitivity of the central chemoreceptors, the overall response can be blunted by partial neuromuscular blockade or by obstructive or restrictive lung disease. These factors must be taken into account when drawing conclusions from a reduced response; for example, severe airway obstruction will cause a blunted response to P_{CO_2} even when the central response is normal. Nevertheless, the slope of the P_{CO_2}/ventilation response curve remains one of the most valuable parameters in the assessment of the responsiveness of the respiratory system to CO_2 and its depression by drugs.

Peripheral Chemoreceptors

The peripheral chemoreceptors are the fast-responding monitors of arterial blood located in the carotid bodies close to the bifurcation of the common carotid artery.[33] The carotid bodies contain large sinusoids with a very high rate of perfusion, about 10 times that

predicted by their metabolic rate, which is itself very high. This results in a small arterial/venous P_{O_2} difference, which allows for a rapid (1- to 3-second) response to changes in arterial blood P_{O_2}. Increased ventilation in response to activation of peripheral chemoreceptors occurs in response to various stimuli:

1. Reduced arterial P_{O_2}. Glomus (type I) cells within the carotid body are in synaptic contact with neurons of the glossopharyngeal nerve. Discharge rate in the afferent nerves from the carotid body increases exponentially in response to falling arterial P_{O_2}.
2. Acidemia. Elevated arterial P_{CO_2} or hydrogen ion (H^+) concentration both stimulate ventilation; the magnitude of the stimulus is the same whether the change in pH is due to a respiratory or metabolic cause. Quantitatively, the change produced by elevated P_{CO_2} on the peripheral chemoreceptors is only about one-sixth of that caused by the action on the central chemosensitive areas. This response does, however, occur very rapidly and develops only when a "threshold" value of arterial P_{CO_2} is exceeded.[31]
3. Hypoperfusion. Stimulation of peripheral chemoreceptors by hypoperfusion can occur as a result of severe systemic hypotension, possibly by causing a "stagnant hypoxia" of the chemoreceptor cells.
4. Hyperthermia. An increase in body temperature increases the rate of firing from peripheral chemoreceptor neurons.

Chemical stimulation by a wide range of substances causes increased ventilation via the peripheral chemoreceptors. These substances fall into two groups. The first group consists of agents such as nicotine and acetylcholine that stimulate sympathetic ganglia. The second group of chemical stimulants consists of substances such as cyanide and carbon monoxide that block the cytochrome system and so prevent oxidative metabolism. Some drugs also stimulate respiration via the peripheral chemoreceptors, for example, doxapram.

Molecular Physiology

There is now general agreement that oxygen-sensitive K^+ channels are responsible for the hypoxic response of the peripheral chemoreceptor type I cells.[20,33,34] Hypoxia inhibits the activity of K^+ channels, altering the membrane potential of the cell and stimulating Ca^{2+} channels to open, allowing an influx of extracellular Ca^{2+} that stimulates transmitter release. Stimulation of the chemoreceptors by increased arterial P_{CO_2} is dependent on carbonic anhydrase, present in the type I cell, and there is therefore the possibility of both raised P_{CO_2} and decreased arterial pH acting through an increase in intracellular H^+ concentration, as in the central chemoreceptors.

Various neurotransmitters have been identified within the carotid body with dopamine, acetylcholine, and ATP being the most prominent. Norepinephrine, angiotensin II, substance P, and enkephalins have also been described, although the specific role of each is uncertain. Acetylcholine and ATP are the most likely neurotransmitters involved in signaling between type I cells and afferent nerves.[35] The other transmitters seem to have autocrine rather than neurotransmitter roles, in that their release into the carotid body tissues modulates the response of the cells to various stimuli.[35] For example, dopamine is abundant in type I cells and released in response to hypoxia; its presence causes inhibition of Ca^{2+} channels so it effectively "dampens" the acute response. Similarly, the α_2-adrenoceptor agonist clonidine reduces the ventilatory response to acute hypoxia, indicating that norepinephrine also has an inhibitory effect.[36] Angiotensin II increases the sensitivity of the K^+ channels to hypoxia, and can be produced locally within the carotid body in response to long-term hypoxia or poor carotid body perfusion, as seen in heart failure.[37]

The gain of the carotid bodies is under nervous system control. There is an efferent pathway in the carotid sinus nerve, which, on excitation, decreases chemoreceptor activity. Excitation of the sympathetic innervation to the carotid body causes an increase in activity.

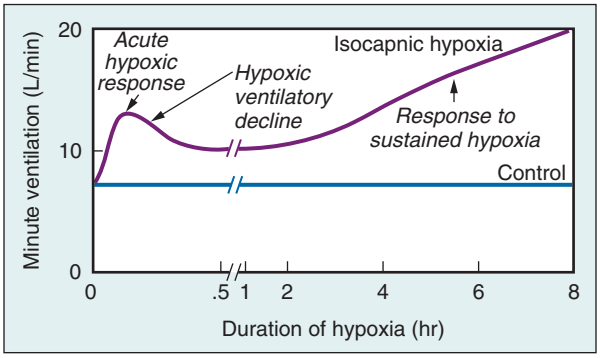
Ventilatory Response to Sustained Hypoxia

Moderate degrees of sustained hypoxia, with arterial oxyhemoglobin saturation (Sa_{O_2}) of about 80%, result in a triphasic physiologic response. The initial acute hypoxic response is an immediate and rapid increase in ventilation. Sudden imposition of hypoxia results in stimulation of ventilation within the lung-to-carotid body circulation time (about 6 seconds). Ventilation continues to increase for 5 to 10 minutes, rapidly reaching high levels. Shortly after the acute hypoxic response reaches a peak, there is a period of hypoxic ventilatory decline (HVD) during which the minute ventilation falls, reaching a plateau level, still above the resting ventilation, after 20 to 30 minutes (Fig. 29.7). The individual degree of HVD correlates with the acute hypoxic response: the greater the initial increase in ventilation, the greater the subsequent decline. Although not completely elucidated, the mechanism of HVD appears to have a significant central component, and HVD represents a change in ventilatory drive rather than a decline in the sensitivity of receptors to hypoxia.[38] Once HVD is complete, continued isocapnic hypoxia results in a second, slower rise in ventilation over several hours (see Fig. 29.7). Ventilation continues to increase for at least 8 hours and reaches a plateau by 24 hours. The most likely explanation for this is a direct effect of hypoxia on the carotid bodies, possibly mediated by angiotensin II.

Emerging Developments

Carbon Dioxide Oscillations and Control of Ventilation

For decades the traditional teaching on the roles of carbon dioxide and oxygen in respiratory control has remained unchanged despite



• **Fig. 29.7** Time course of the ventilatory response to sustained hypoxia (arterial oxygen saturation ≈ 80%). When arterial partial pressure of carbon dioxide is maintained at normal levels despite the changes in minute ventilation (isocapnia), the response is triphasic. The acute hypoxic response occurs within seconds, but lasts only for a few minutes, before hypoxic ventilatory decline returns the minute ventilation towards normal. Over several hours, a further and more pronounced ventilatory response occurs that reaches a plateau after 24 hours.

certain anomalies. For example, ventilation increases massively during exercise with no measurable change in arterial blood gas partial pressures. With resting ventilation, gas movement in and out of an alveolus is by diffusion, but as tidal volume increases, gas movement becomes cyclical. As a result, the P_{CO_2} of alveolar gas, and later arterial blood, begins to oscillate in phase with respiration, while the mean values remain unchanged. These oscillations of P_{CO_2} are sensed by the peripheral chemoreceptors and enhance respiratory drive, in effect providing positive feedback to breathing to maintain normal mean arterial P_{CO_2} even when metabolic production of carbon dioxide is very high. This system is believed to contribute to the ventilatory response to exercise and is particularly important if the subject is also hypoxic (e.g., at high altitude).[39]

Asthma Phenotypes and Targeted Therapies

Both host and environmental factors contribute to developing asthma, including a complex heritable component, with multiple genes involved in its development.[40] There are also genetic effects on a patient's responsiveness to treatment. The pharmacogenetics of the β_2 adrenoceptor have been described above and racial differences have also been observed. For example, individuals of African racial background are less responsive to short-acting bronchodilators compared with Mexican Americans and Puerto Ricans.[41] Other genes may modify the response to corticosteroids[42] and leukotriene receptor antagonists.[43] Understanding asthma genetics may also help develop biomarkers of disease phenotype and treatment; for example, genetic variation in the IL-6 receptor is associated with worse lung function and a more severe asthma phenotype.[44]

However, asthma is not a single disease, but more a heterogeneous group of underlying disease processes evidenced by a wide variety of presentations, physiologic characteristics, and patient outcomes.[44] As a result, the concept of asthma phenotyping has emerged, which involves integrating biological and clinical features with the ultimate goal of improving therapy.[45]

The most common phenotypes identified include the following:

- Allergic asthma. Onset in childhood, associated with a family history of atopy, sputum examination typically showing eosinophilic inflammation.
- Nonallergic asthma. Adult onset, not associated with allergy, sputum examination may reveal neutrophilia, eosinophilia, or contain few inflammatory cells.
- Late-onset asthma. Presents in adult life, more commonly in women, tends to manifest as nonallergic wheezing.
- Asthma with fixed airflow limitation. Patients with longstanding asthma develop fixed airflow limitation, thought to be secondary to airway remodeling.
- Asthma with obesity. Obese patients with prominent respiratory symptoms and little eosinophilic airway inflammation.

By classifying the characteristics of each phenotype, it is hoped that a more targeted approach to treatment and a better understanding of the clinical course for an individual patient may be possible. In patients with severe disease, some phenotype-guided treatments are already available. Eosinophilic inflammation, allergic processes, and obesity have been identified as phenotypes that may be helpful when considering both nonspecific (corticosteroids) and more immune-targeted therapies including anti–IL-5[12] and anti–IL-13[13] antibody treatments. From the phenotypes discussed earlier it can be seen that the age of onset of asthma is linked to differences in allergic tendency and eosinophilic airway inflammation. Assessing the level of eosinophilic or Th2 lymphocyte–induced inflammation has the potential to predict a patient's response to corticosteroid therapy and perhaps to more targeted treatments.[46] Guidance from the 2016 Global Initiative for Asthma (GINA)[47] now incorporates some phenotype-specific management for the treatment of severe asthma, but aside from this example there is no strong relationship between phenotype and response to therapy.[48]

TABLE 29.2 Summary of Structural Changes in the Airways of Patients With Asthma

Tissue	Changes in Asthma
Subepithelial fibrosis	Deposition of collagen fibers and proteoglycans under the basement membrane: seen in most patients with asthma even before symptom onset. Fibrosis can occur in other layers of the airway wall.[52]
Thickened airway smooth muscle	Consequence of hypertrophy and hyperplasia and contributes to increased thickness of airway wall.[49] Process may relate to disease severity.
Increased blood vessels in airway walls	Asthma patients have exaggerated influence of growth factors such as vascular endothelial growth factor, possibly mediated by Th2 cells.[50] Increased vascularity may contribute to increased airway wall thickness.
Mucus hypersecretion	Results from increased number of goblet cells in epithelium and increased size of submucosal glands.[51]

Remodeling of Airways

Repeated inflammation in small airways results in morphologic changes to airway smooth muscle, vascular, and epithelial cells (Table 29.2).[49–52] Hyperplasia of smooth muscle cells thickens the airway wall, even when the muscle is relaxed, and increases the degree of airway narrowing that occurs even with small amounts of muscle contraction. These structural changes not only affect airway mechanics, but can also contribute to inflammation themselves through the release of proinflammatory[53] and growth factors.[54] Autopsy and biopsy studies have linked increased amounts of smooth muscle to asthma severity, degree of airway obstruction, and bronchial hyperresponsiveness.[55] Fibrocytes, which may differentiate into myofibroblasts, are also increased in the blood and smooth muscle bundles of patients with asthma who have fixed airway obstruction and/or severe disease.[56] Airway remodeling in asthma patients may result in relatively irreversible narrowing of the airways.[57,58] The morphologic changes may represent attempted tissue repair in response to chronic inflammation or may occur independently themselves.[59] Remodeling can begin before asthma becomes severe, or is even diagnosed at all, and even though reducing airway inflammation with steroids can delay remodeling, drugs to reverse the structural changes are yet to be discovered.

Key Points

- The diaphragm is the principal muscle for inspiration and is responsible for 75% of tidal volume during resting inspiration in the supine posture. In upright postures activity of the intercostal muscles accounts for the majority of inspiration. Expiration is normally a passive process but when ventilation increases (e.g., in response to exercise), expiration becomes active with contraction of the internal intercostal and abdominal muscles.
- Most bronchial smooth muscle is found in the 12th to 16th generations of the airway. Four mechanisms are involved in controlling muscle tone in small airways: neural, humoral (via blood), direct physical and chemical, and local cellular. Neural control is the most important in normal lung.
- Overall ventilation and perfusion are well matched and approximately equal, but in smaller regions of lung there are discrepancies between the two that can adversely affect gas exchange. For example, during general anesthesia there is a wider than normal spread of $\dot{V}/\dot{Q}$ ratios throughout the lung that impairs both oxygenation and carbon dioxide elimination.
- Regional HPV is beneficial as a means of diverting pulmonary blood flow away from areas of lung with low P_{O_2} and is an important mechanism for optimizing $\dot{V}/\dot{Q}$ relationships. Long-term HPV, either continuous or intermittent, leads to remodeling of the pulmonary vasculature and irreversible pulmonary hypertension.
- Uncertainties remain regarding the exact cellular mechanism of HPV, but there is now agreement that contraction of pulmonary artery smooth muscle cells in response to hypoxia is involved.
- Breathing is controlled by a complex network of physical and chemical reflexes that can be overridden by voluntary control and interrupted by acts such as swallowing, sneezing, vomiting, hiccupping, and coughing. The respiratory pattern is generated within the medulla, which coordinates the voluntary and involuntary demands of respiratory activity via multiple neuronal connections.
- Reflex control of breathing occurs in response to both carbon dioxide and oxygen. Minute volume of ventilation increases in a linear fashion in response to increasing P_{CO_2}, a response that is highly variable between individuals. The response to hypoxia is exponential in nature such that below a P_{O_2} of approximately 60 mm Hg (8 kPa), the ventilatory response curve is very steep.

Key References

Dehnert C, Risse F, Ley S, et al. Magnetic resonance imaging of uneven pulmonary perfusion in hypoxia in humans. *Am J Respir Crit Care Med*. 2006;174:1132–1138. This study used contrast-enhanced magnetic resonance imaging to demonstrate that individuals who previously had high-altitude pulmonary edema had a more intense and patchy pulmonary vascular response to 2 hours of hypoxia (fraction of inspired oxygen [FIO_2] = 0.12). These were otherwise healthy subjects, but the prospect that patients who develop hypoxia are also likely to have such a variable pulmonary vascular response is likely to lead to therapeutic interventions in the future. (Ref. 26).

Del Negro CA, Hayes JA. A 'group pacemaker' mechanism for respiratory rhythm generation. *J Physiol*. 2008;586:2245–2246. The concept of neuronal groups generating rhythmic activity (a "group pacemaker") is quite a recent one and a departure from the conceptually simpler single "pacemaker neuron." This review considers the evidence that central pattern generation of respiratory rhythm is an example of a group pacemaker. (Ref. 27).

Galvin I, Drummond GB, Nirmalan M. Distribution of blood flow and ventilation in the lung: gravity is not the only factor. *Br J Anaesth*. 2007;98:420–428. For decades, physiologists have taught students that gravity is the main influence on both regional ventilation and perfusion in the lung, despite microgravity experiments in space clearly demonstrating that inhomogeneity of both still exists. This review covers the history of these studies and the various mechanisms underlying the current view that gravity, and the weight of the lung, is not the major determinant of regional $\dot{V}/\dot{Q}$ matching. (Ref. 14).

Talbot NP, Balanos GM, Dorrington KL, et al. Two temporal components within the human pulmonary vascular response to approximately 2 h of isocapnic hypoxia. *J Appl Physiol*. 2005;98:1125–1139. This study of human volunteers provides the first clear demonstration of the biphasic nature of hypoxic pulmonary vasoconstriction (see Fig. 29.5). This finding allowed the very different mechanisms of the two phases to be elucidated (oxygen-sensitive K_v channels for phase 1 and endothelin release for phase 2), and has significant implications for patients whose lungs are hypoxic, either through disease or anesthesia manipulations (e.g., during one-lung ventilation). (Ref. 18).

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Anatomy and Imaging: The Thoracic Wall, Intercostal Space, and Thorax

Jeffrey D. Swenson and John Skaggs

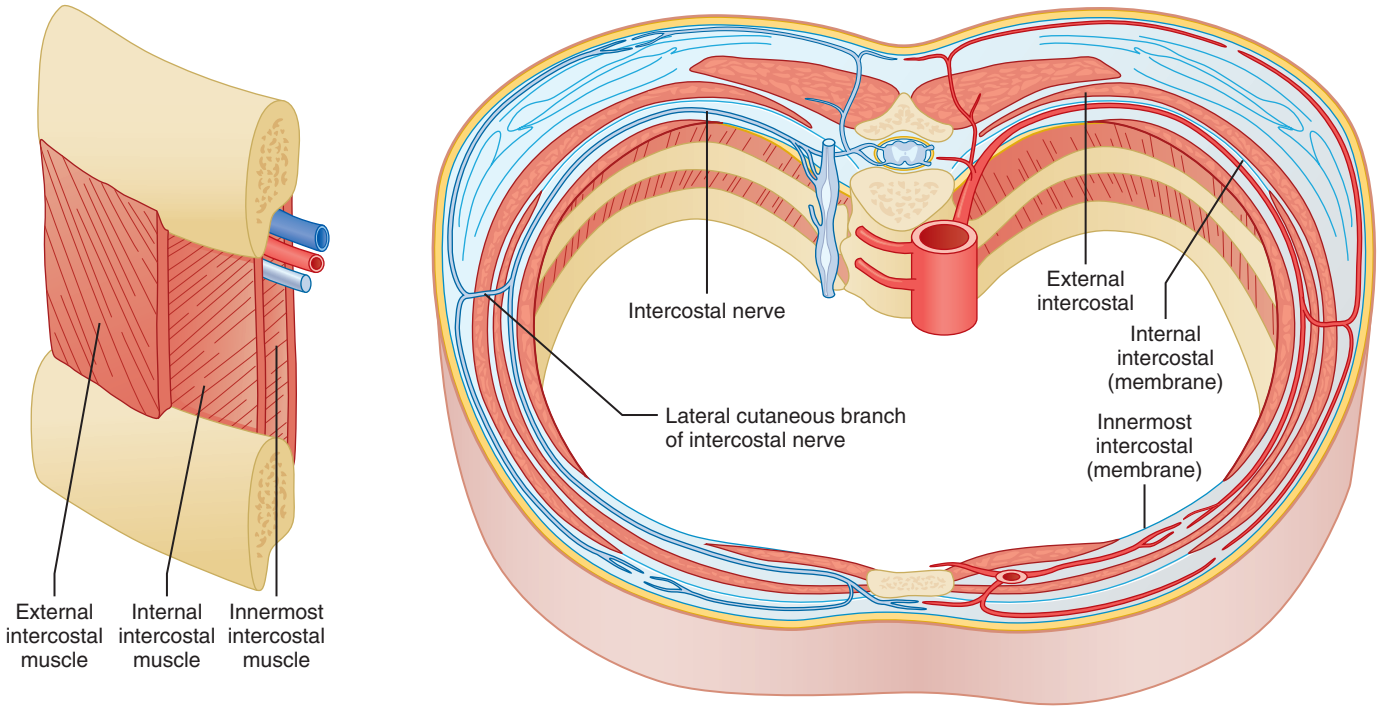
This special section on Anatomy and Imaging outlines important anatomic structures and imaging techniques for the thoracic wall, intercostal space, lungs, and bronchial tree. Key structures are reviewed in anatomic drawings, plain radiographs, computed tomography (CT) scans, ultrasound (US), and bronchoscopic images. Modern imaging techniques that enable "real-time" visualization of relevant clinical anatomy are emphasized.

The **left panel** of Fig. AI3.1 illustrates that the **external intercostal muscle** extends from the superior margin of the rib below to the inferior margin of the rib above but does not overlie the outer cortex of the rib. This important distinction can be used to differentiate the **external intercostal muscle** from other muscles that overlie the thoracic wall.

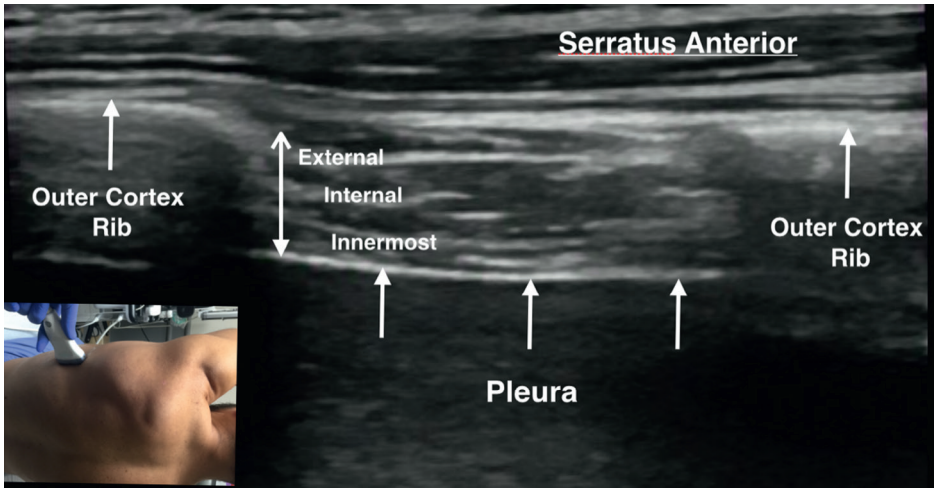
The drawing also highlights the location of the major **neurovascular bundle** supplying the intercostal muscles, ribs, and chest wall. Because of the neurovascular bundle's location inferior to the rib, chest tube thoracostomy is performed superior to the rib in the targeted intercostal space, thereby avoiding injury to the neurovascular bundle.

In the **right panel**, note the structural transition of the intercostal muscles between the anterior and posterior thoracic walls. The **internal intercostal muscle** transitions from a membranous layer in the posterior wall to a muscular layer in the anterior wall. By contrast, the **external** and **innermost intercostal muscles** exist as muscular layers in the posterior wall but transition to membranous layers in the anterior thoracic wall. This transition is important since US images of the intercostal space may not reveal 3 distinct muscular layers.

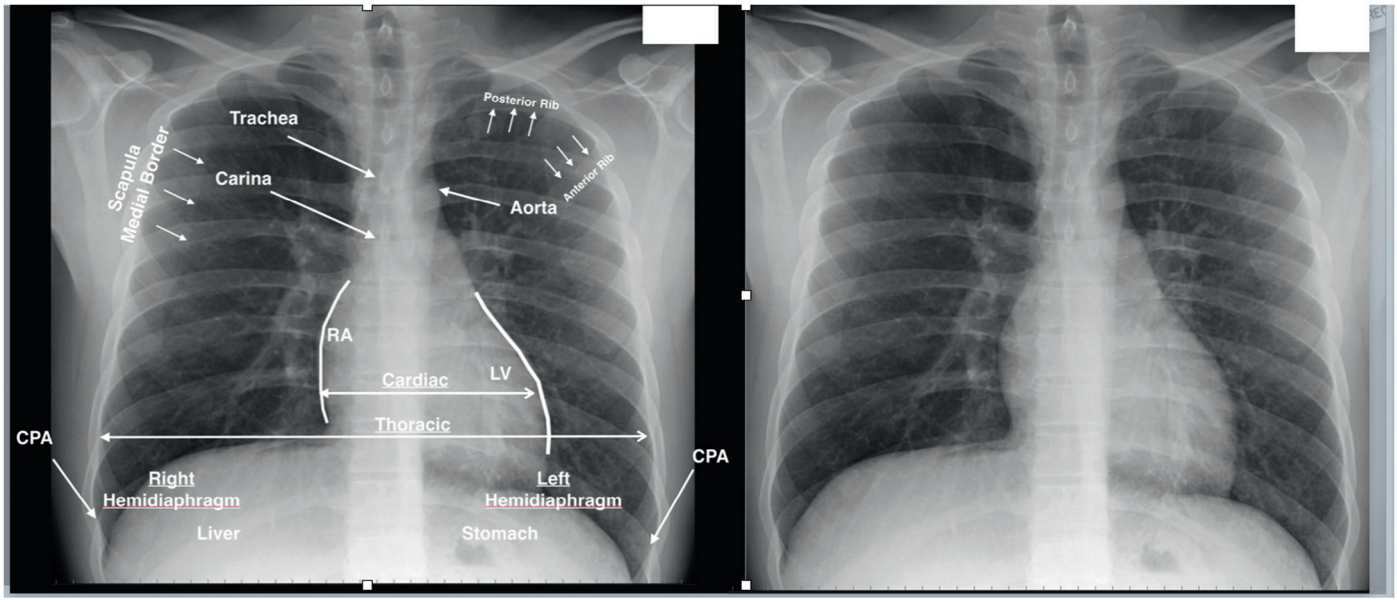
The drawing also highlights important features of the **intercostal nerve**. At approximately the level of the midaxillary line, the **intercostal nerve** gives rise to the **lateral cutaneous branch**. Thus, intercostal injections performed in the posterior thorax produce sensory changes across the entire chest wall. By contrast, injections performed anterior to the division of the **lateral cutaneous branch**



• **Fig. AI3.1** The intercostal muscles, nerves, and blood vessels, as represented in idealized anatomic drawings.



• **Fig. AI3.2** The posterior intercostal space, as viewed by ultrasonography.



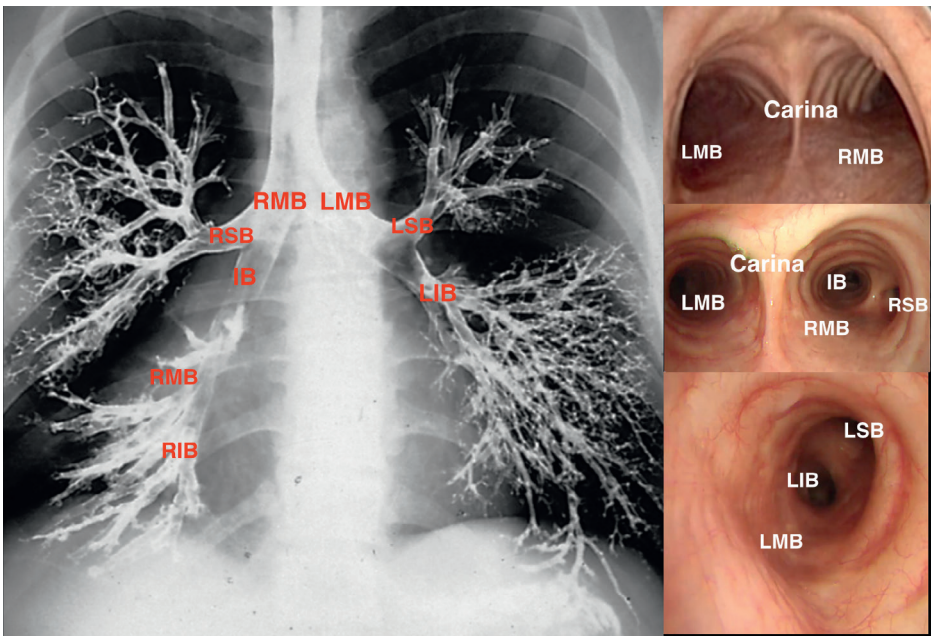
• **Fig. AI3.3** Thorax anatomy, as viewed in the normal chest radiograph.

produce limited sensory changes over the medial aspect of the anterior chest wall.

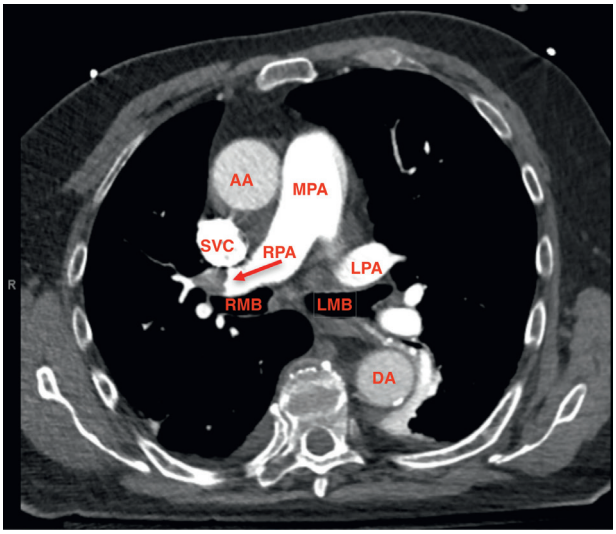
An ultrasound image of the posterior intercostal space between the 7th and 8th ribs is shown (Fig. AI3.2). The position of the transducer is demonstrated in the inset picture. A line with 2 arrowheads marks the confluence of the **innermost**, **internal**, and **external intercostal muscles** extending from the **pleura** to the **outer cortex** of the rib. Note that the **external intercostal** muscle does not extend over the **outer cortex** of the ribs. The **serratus anterior muscle** is superficial to the outer cortex of the ribs at this level. This image also shows the clear border of **pleura** deep to a confluence of the **external**, **internal**, and **innermost intercostals**. Note the position of the intercostal muscles relative to the outer cortex of the ribs and position of the **serratus anterior muscle** immediately superficial to the **outer cortex**.

Two normal posterior-anterior (PA) chest radiographs are shown (Fig. AI3.3). The image on the left has been labeled to highlight normal anatomic structures. The standard PA technique for radiographs of the chest is obtained with the patient upright and facing the digital image recorder. When examining a chest radiograph, it is important to know whether an alternative technique has been used (e.g., portable anterior-posterior film), since this may influence the interpretation.

Several important anatomic structures visible on the standard PA chest radiograph are demonstrated. The **trachea** is normally midline and passes slightly right of the aorta at the level of the **carina**. Lung markings extend to the chest wall, below the diaphragm, and behind the heart. The area overlying the **medial border of the scapula** may appear to be without lung markings; however, careful examination reveals lung markings in this region. The appearances of the **anterior and posterior ribs** are distinctive. The **posterior ribs** are more readily visible and oriented relatively horizontal to the thorax. By contrast, **anterior ribs** are less prominent and are angled medially and inferior relative to the thorax.



• **Fig. AI3.4** Bronchial anatomy, as visualized in a contrast bronchogram and by bronchoscopy.



• **Fig. AI3.5** The pulmonary arterial vasculature by computed tomographic angiography.

The **cardiac silhouette** shows the right border as the **right atrium** and the left border as the **left ventricle**. In a PA view, the ratio of the **cardiac** width to **thoracic** width should be less than 1 : 2. The **right and left hemi-diaphragms** are domed structures overlying the liver and stomach, respectively. The **right hemi-diaphragm** is slightly higher than the left. A stomach bubble may be visible below the **left hemi-diaphragm**. The **costophrenic angle (CPA)** should be a sharp structure visible in the right and left hemi-thorax between the chest wall and the dome of the diaphragm. The arch of the **aorta** is visible at the left mediastinal border as it passes posteriorly over the left mainstem bronchus and pulmonary vasculature. The descending **aorta** is visible behind the cardiac silhouette.

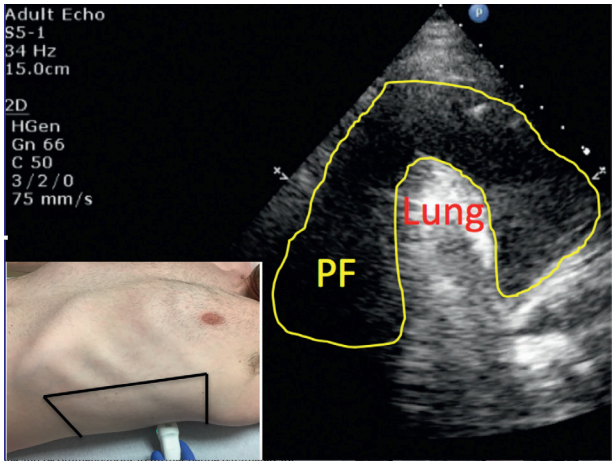
The **left panel** is a bronchogram with contrast material outlining the trachea and major bronchi (Fig. AI3.4). This image includes the **right main bronchus (RMB)**, **left main bronchus (LMB)**, **right superior bronchus (RSB)**, **intermediate bronchus (IB)**, **right middle bronchus (RMB)**, and **right inferior bronchus (RIB)**. The **left main bronchus (LMB)**, **left superior bronchus (LSB)**, and **left inferior bronchus (LIB)** are also displayed. Note the disparity in length between the **RMB** and **LMB**. The **RMB** is typically 2 to 2.5 cm in length as a result of the proximal origin of the **RSB**. In rare cases, the **RSB** may arise directly from the trachea. By contrast, the **LMB** is approximately 5 cm in length.

The **right upper**, **middle**, and **lower panels** are corresponding flexible bronchoscopic views of the structures seen in the bronchogram. The upper panel shows a view of the **RMB** and **LMB** from a position approximately 1 cm above the carina. In the right middle panel, the bronchoscope has been advanced to the carina. At this level, the **RMB** and **RSB** are completely visible. The entire length of the **LMB** can also be seen. The shorter distance between the carina and the orifice of the **RSB** is evident and has important implications for lung isolation procedures.

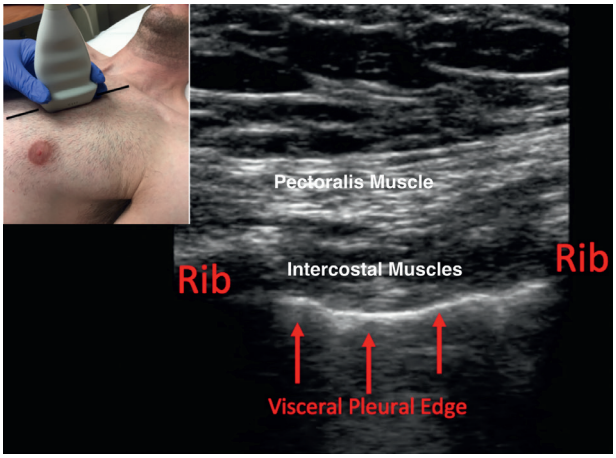
The right lower panel is a bronchoscopic view from a position 2 cm into the **LMB**. At this position, the **LSB** and **LIB** are visible.

Computed tomographic pulmonary angiography (CTPA) is used in patients with a high probability of pulmonary embolus (Fig. AI3.5). Ventilation–perfusion scans are now reserved for patients who have a contraindication to CTPA or where CTPA is unavailable. This particular CTPA image shows major vessels of the thorax, including the **superior vena cava (SVC)**, **ascending aorta (AA)**, **descending aorta (DA)**, **main pulmonary artery (MPA)**, **right pulmonary artery (RPA)**, and **left pulmonary artery (LPA)**. The **right main bronchus (RMB)** and **left main bronchus (LMB)** are also visible. The red arrow highlights a **thrombus** in the **RPA** that is visible as a filling defect in that vessel.

The image illustrates a point-of-care technique used to diagnose pleural effusion (Fig. AI3.6). The dependent (posterior-lateral)



• **Fig. AI3.6** The pleural space (with effusion) as viewed by ultrasonography.



• **Fig. AI3.7** Structures of the anterior, chest wall viewed by ultrasonography.

surface of the thorax is imaged using a phased array ultrasound transducer. The inset shows the transducer position used to acquire the image. The **lung** is displaced by **pleural fluid (PF)**, visualized as echogenic tissue. The displaced lung is outlined by a yellow border. Point-of-care evaluation of pleural effusion using surface ultrasound can provide both a qualitative and quantitative assessment with sensitivity and specificity equal to or exceeding that of conventional chest radiography.

A parasternal image of the thorax (using a linear ultrasound transducer) demonstrates the correct position of the transducer to evaluate potential pneumothorax (Fig. AI3.7). The **visceral pleural edge**, **ribs**, and **intercostal and pectoralis muscles** are labeled. During real-time ultrasound imaging, the **visceral pleural edge** has a characteristic sliding motion in the normal examination. When a pneumothorax is present, "lung sliding" is not seen. Pneumothorax is another important pathologic condition that can be rapidly diagnosed at the bedside using surface ultrasonography. Its sensitivity and specificity for diagnosing pneumothorax exceeds that of plain chest radiography but is somewhat less than that of computed tomography.

Physics: Blood Gas Measurement

Kai Kuck

OUTLINE

Background

Blood Gas Measurement Instrumentation

- Measurement of Oxygen Tension: Clarke (Polarographic) Oxygen Electrode
- Measurement of pH: Glass Electrode
- Measurement of pCO_2: the Severinghaus Electrode

Sampling For Blood Gas Analysis

Background

Assessment of arterial blood pCO_2, pH, and pO_2 is routinely performed during anesthesia and critical care.[1] In combination with respiratory gas measurements and pulse oximetry, it allows evaluation of cardiorespiratory function and metabolism. The most commonly used approaches require the sampling of arterial blood and in vitro analysis in a laboratory or point-of-care instrument. Understanding principles and limitations of the blood gas instrumentation is important to guide the correct interpretation of the measurements.

Blood Gas Measurement Instrumentation

Measurement of Oxygen Tension: Clarke (Polarographic) Oxygen Electrode

Most of the oxygen in blood is bound to hemoglobin. The small amount of unbound, dissolved oxygen is determined by the **oxygen tension**, abbreviated pO_2, which is the partial pressure of the dissolved oxygen. Reported in millimeters of a mercury column (mm Hg) or kilopascals (kPa), arterial pO_2 normally ranges between 70 and 100 mm Hg in subjects breathing air at sea level. Oxygen tension and oxygen saturation (the percent of hemoglobin bound to oxygen) are related to each other by the oxyhemoglobin dissociation curve (see Chapters 24 and 29 and Fig. P9.5).

Oxygen tension is conventionally measured by the polarographic oxygen electrode developed in 1956 by Leland Clark. It consists of a platinum cathode and a silver/silver chloride anode in a buffered electrolyte solution of potassium chloride. A gas permeable membrane separates the sensor from blood. Oxygen tension in blood equilibrates with the electrolyte solution (Fig. P7.1). At the anode, silver is oxidized and combines with the electrolytes to form silver chloride. The resulting electrons at the platinum cathode reduce oxygen, which combines with water to form hydroxide ions. The current from anode to cathode is measured and is proportional to the oxygen tension in the electrolyte solution and, thus, in the sample (blood). The electrochemical reaction requires a small voltage of 0.6 V to be applied externally. Both the electrodes and the electrolyte are changed through the electrochemical process such that the sensor must be replaced every few months. The electrochemical reactions in the **Clarke electrode** are temperature dependent and normally the electrode is kept at a constant temperature of 37°C (98.6°F), because temperature has an influence on pO_2. An experimentally determined correction for the temperature effect in whole blood has been described:

$$\frac{\Delta \lg p_{O_2}}{\Delta T} = 0.018 - 0.013 \tanh [4.37 \lg (p_{O_2}/19.2\ \text{kPa})]\text{K}^{-1}.$$

pO_2 is the pO_2 at 37°C (98.6°F), in kPa. If mm Hg is used for pO_2, the dividend 19.2 kPa should be changed to 144 mm Hg.

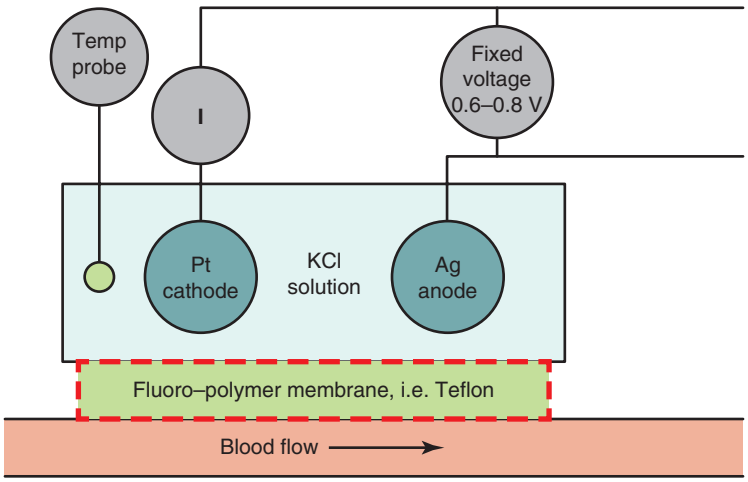
ΔT is the difference in °K between 37°C and the actual patient temperature

For example, a pO_2 of 95 mm Hg at 37°C is corrected to 84 mm Hg for a temperature of 35°C or to 121 mm Hg for a temperature of 41°C. Thus, correction for temperature is critical when patient temperature deviates substantially from normothermia.

Erroneous readings can result from perforations of the membrane, interference with other gases (e.g., the electrode can read falsely high in the presence of N_2O), depletion of the electrodes or the electrolyte, and contamination by proteins or blood products. Alternatives to the Clarke electrode include optical measurements (e.g., based on phosphorescent quenching). Some of these approaches lend themselves to placement on catheter tips for continuous in vivo measurements.

Measurement of pH: Glass Electrode

The **pH** is a logarithmic representation of the hydrogen ion concentration of a solution, (i.e., its acidity or alkalinity). It is dimensionless and expresses the negative of the logarithm of H^+ concentration (measured in mol/L or M). For example, the concentration of H^+ ions in water is 10^{-7} M, for a pH of $-\log(10^{-7}) = 7$. Values of pH larger than 7 indicate increased alkalinity and values of pH smaller than 7 indicate increased acidity. Normal



• **Fig. P7.1** A schematic diagram of the Clarke Polarographic Oxygen Electrode. (Modified from Langton JA, Hutton A. Respiratory gas analysis. *Continuing Education in Anaesthesia, Critical Care & Pain*, 2009;9(1): 19–23.)

values for pH in healthy humans range from 7.35 to 7.45 (note the lack of units).

The **pH glass electrode** operates on the principle that when two solutions of different hydrogen ion concentrations are separated by a glass membrane, the electrical potential difference between the solutions is proportional to their difference in hydrogen ion concentration. The pH glass electrode consists of two electrochemical cells. A silver/silver chloride measurement electrode is a bulb made of pH-sensitive glass containing a buffer solution titrated to a constant pH value. The outside of the pH-sensitive glass is exposed to the sample (blood) such that an electrical potential difference is created that is proportional between the blood pH and the pH of the buffering solution inside of the bulb. The potential difference is measured using a mercury/mercury chloride (calomel) reference electrode that is placed in buffered potassium chloride solution and is in contact with the blood through a semiporous membrane (Fig. P7.2). In contrast to the Clarke electrode, the pH glass electrode does not require an external voltage source and does not involve an exchange of ions or electrons. As a consequence, neither the electrodes nor the buffering solutions are consumed in the process of measurement.

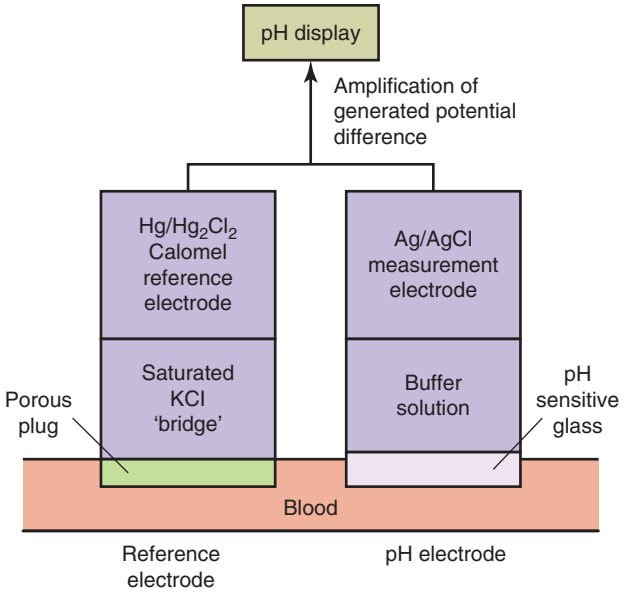
Both electrodes must be kept at 37°C and calibrated with buffer solutions of known pH. Just as with the Clarke electrode, results are reported with respect to a body temperature of 37°C (98.6°F). If the patient temperature deviates from 37°C, a temperature correction must be applied that has been experimentally determined for whole blood to be[2]

$$\frac{\Delta \text{pH}}{\Delta T} = -0.015\,\text{K}^{-1}.$$

ΔpH is the difference between the pH at 37°C and the pH at the patient temperature.

ΔT is the difference in °K between 37°C and the patient temperature.

For example, a pH of 7.4 at 37°C would have to be corrected to 7.43 for a patient temperature of 35°C or to 7.34 for a patient temperature of 41°C.



• **Fig. P7.2** A schematic diagram of the pH glass electrode. (From Magee PT. Physiological monitoring. In: Davey AJ, Diba A. *Ward's Anaesthetic Equipment*. Philadelphia: Saunders Elsevier; 2012.)

Measurement of pCO_2: the Severinghaus Electrode

The vast majority of CO_2 in the blood is carried as bicarbonate (HCO_3^-), with the remainder either as dissolved CO_2 or carbonic acid, H_2CO_3 in equilibrium:

$$CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows HCO_3^- + H^+.$$

The balance between these three compounds, including a weak acid (H_2CO_3) and a weak base (HCO_3^-), forms the buffer system that maintains stable blood pH. In arterial blood, the **Henderson-Hasselbach equation** describes this relationship as

$$pH = pK_{a\,H_2CO_3} + \log\left(\frac{[HCO_3^-]}{[H_2CO_3]}\right) = 6.1 + \log\left(\frac{[HCO_3^-]}{0.03 \times pCO_2}\right).$$

pK_a H_2CO_3 is the negative logarithm of the acid dissociation constant of carbonic acid equal to 6.1.
$[H_2CO_3]$ is the concentration of carbonic acid equal to $pCO_2 \times 0.03$ (mmol L^{-1})/mm Hg.
$[HCO_3^-]$ is the concentration of bicarbonate in mmol L^{-1} (mM).
p_{CO2} is the partial pressure of CO_2 dissolved in blood in mm Hg.

Normal values for pCO_2 range from 35 to 45 mm Hg. It is typically measured using the **Stow-Severinghaus** electrode. An early version of this measurement system was first described in 1956 by Stow and then later refined by Severinghaus.[3] It consists of a glass pH electrode (described earlier), in which the glass membrane is separated from the blood by another membrane that is selectively permeable to CO_2. To address the severe drift, a bicarbonate salt solution is placed between the CO_2 selective membrane and the pH-sensitive glass membrane (Fig. P7.3). Essentially, the CO_2 electrode lets the pCO_2 change pH and then uses the pH glass electrode to measure the resulting pH.

Usually, pH and pCO_2 are measured at the same time, allowing calculation of bicarbonate concentration. Measurement results are usually reported referenced to a patient temperature of 37°C. If the patient temperature differs from this value, the pCO_2 can be corrected[1] according to

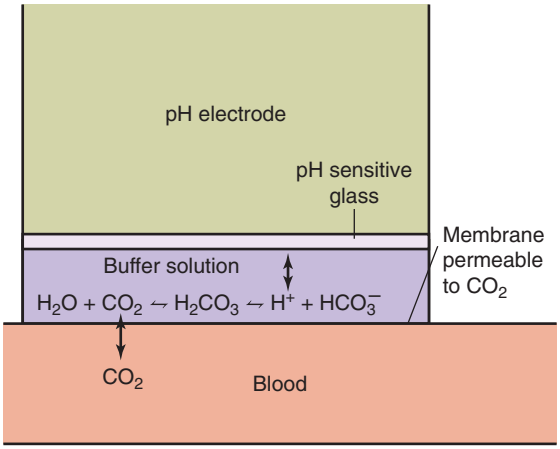
$$\frac{\Delta \lg p_{CO_2}}{\Delta T} = 0.021\,K^{-1}.$$

ΔT is the difference in °K between 37°C and the patient temperature.
pCO_2 is the partial pressure of CO_2 dissolved in blood (mm Hg).

For example, a pCO_2 of 40 mm Hg at 37°C would be corrected to 36 mm Hg for a temperature of 35°C or to 49 mm Hg for a temperature of 41°C. Developed by Severinghaus, an anesthesiologist, the carbon dioxide electrode has important historical significance in anesthesiology and constitutes an important advance in anesthesiology and critical care medicine.

Sampling for Blood Gas Analysis

Blood samples for blood gas analysis are typically obtained from the radial, brachial, or femoral artery. The process of obtaining a blood sample can introduce errors in blood gas measurement. For example, heparin used to anticoagulate the blood sample is acidic and can result in an incorrectly lower pH measurement. Air bubbles or air diffusing through a plastic syringe into the sample can alter the partial pressure of oxygen and CO_2. Finally, blood cells are metabolically active and continue to use oxygen and produce CO_2 while the sample is transported for analysis. If the sample cannot be analyzed expeditiously, it should be refrigerated at a temperature of 4°C.



• **Fig. P7.3** The Stow-Severinghaus CO2 electrode is created by modifying the measurement electrode of a pH glass electrode (described in Fig. P7.2). The pH sensitive glass membrane is covered by a CO2 permeable polymer membrane. A buffer solution between the glass and the polymer membrane helps to prevent sensor drift. (From Magee PT. Physiological monitoring. In: Davey AJ, Diba A. *Ward's Anaesthetic Equipment*. Philadelphia: Saunders Elsevier; 2012.)

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Physics: Regulators, Medical Gas Cylinders, and Pressure Measurement of Gases

Daniel Pulsipher and Kai Kuck

OUTLINE

Background

Medical Gas Cylinders
- Medical Gas Cylinder Safety
- Estimating the Remaining Volume

Pressure Measurement and Regulation of Gases

Background

Safe storage, transport and delivery of oxygen, and often of nitrous oxide and air, are essential for modern anesthesia.[1] The pressures required for efficient storage of medical gases are much higher than are safe for delivery directly to patients. Storage cylinders provide portability for patient transport and critical backup supply for anesthesia machines; thus, practitioners must be able to predict remaining available supply in full and partially filled medical gas cylinders. The physical properties of the gases explain differences in measured pressures as they are depleted from their respective cylinders.

Medical Gas Cylinders

Anesthesia machines are supplied oxygen, nitrous oxide, and air by medical gas supply systems from a bulk source through medical gas pipelines. These pipelines supply these gases near a pressure of 50 pounds per square inch (PSI) as measured on the gauge of a typical US anesthesia machine (**PSI Gauge**, or **PSIG)** using connectors that have different diameters for each gas (**Diameter Index Safety System [DISS]**) to assure connection of the different gas supply hoses to the correct anesthesia machine ports.[2] A reliable backup system is critical, as failure to deliver sufficient oxygen to a patient can be fatal. **Medical gas cylinders** are high-pressure storage containers that can provide onsite backup, reducing the probability of failure.

Medical Gas Cylinder Safety

There are multiple opportunities for accidents with medical gas cylinders owing to the high pressure at which the gases are stored, the oxidizing nature of the contents, or the delivery of an incorrect gas. Medical gas cylinders are commonly made of aluminum or steel alloys designed to withstand high pressures but exposure to extreme heat (fires) can increase internal pressures to unsafe levels. A safety measure used by suppliers is to fill the cylinders to a service capacity below maximum capacity. Tanks are also fitted with **pressure relief valves** that open under excessive pressure to decrease the risk of tank explosion from increased pressure owing to heat or overfilling. Gas filling stations are required to be dedicated to a specific gas—the manifold fittings are unique to that gas and cylinders are **color coded** for identification (Table P8.1).[3] Color, however, should not be the sole method used, as there are geographic differences; for example, colors used in the United States do not match International Organization for Standardization (ISO) standards used in many other countries, such that tank labels should also be referenced for proper identification. In the United States, for example, green = oxygen, yellow = air, and blue = nitrous oxide.

Medical gas cylinders are reusable and must undergo regular testing by the gas supplier to ensure continued safe use. There are multiple gas cylinder sizes available, with increasing capacity, A through M. The most common size used for anesthesia machines is gas cylinder size E. These gas cylinders are fitted to the **yoke hanger** (Fig. P8.1) on the back of anesthesia machines where a **pin index safety system (PISS)** is employed to ensure that the correct gas cylinder is connected to the corresponding gas-specific inlet (Fig. P8.2).

Estimating the Remaining Volume

When pipeline service fails or is unavailable, or when transporting a patient, it is important to be able to predict the remaining volume in a gas cylinder, which determines the time left at a specific gas flowrate before the gas cylinder will empty. If room temperature is significantly above the critical temperature of a gas, it will only exist in gaseous form as with oxygen and air. Therefore, for oxygen and air, the remaining volume compressed in a cylinder is directly proportional to the pressure in the cylinder. The internal pressure of a full E cylinder (internal volume of 5.1 L) filled with oxygen is 1900 PSIG (131 bar; bar is a metric unit of pressure that is ~ 1 atmosphere) at room temperature. The volume of compressed gas released into the atmosphere at an ambient pressure (sea level) of 14.696 PSI (1.013 bar) from a partially filled gas cylinder can be calculated using Boyle's Law:

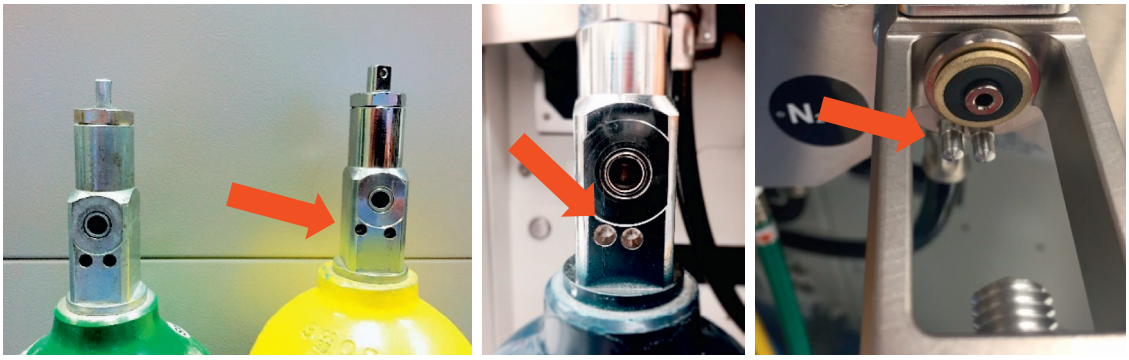
$$V = \frac{131\,bar \times 5.1\,L}{1.013\,bar} = 660\,L$$

In contrast, if the critical temperature of a gas is higher than room temperature, the gas may be stored as a liquid with the liquid and gas forms in equilibrium, as with nitrous oxide. In contrast to oxygen and air, for nitrous oxide the measured pressure stays near 745 PSIG until there is no remaining liquid in the cylinder available to enter the gas phase. Only when the pressure drops below this value can Boyle's Law be used to predict the volume of nitrous oxide that would be released at atmospheric pressure. Prior to depletion of nitrous oxide in the liquid phase, the volume available can be reliably predicted by knowing the weight of the cylinder as well as its empty weight (the "tare weight" of the empty cylinder should be stamped on the cylinder) using the conversion of 1 kg of liquid nitrous oxide to produce 534 L of gaseous nitrous oxide.

• **Fig. P8.1** Medical gas cylinders for oxygen, air, and nitrous oxide are fitted to the yoke hanger system on the back of anesthesia machines.

Pressure Measurement and Regulation of Gases

The high gas pressures in central storage tanks must be substantially reduced before they are delivered to patients or the anesthesia machine. A **regulator** reduces pressure to a much lower and constant pressure. Without a regulator, flowrate from a storage cylinder would diminish as internal pressure decreases with the release of gas. The oxygen cylinder often used for transporting patients with a mask or nasal cannula has a valve that incorporates a pressure regulator, flow dial, and **pressure gauge** (typically, a **PSIG** in the United States but there are often two scales—PSIG and bars or 100 kPa, the SI unit) representing the difference between the internal cylinder pressure and ambient pressure. The high-pressure gauge on the anesthesia machine is placed after the **check valve**



• **Fig. P8.2** The pin index safety system ensures that the correct gas cylinder is connected to the corresponding gas-specific inlet.

TABLE P8.1 Medical Gas Cylinders Color Coding for Content Identification

			FULL E-CYLINDER (4.25″×26″)		
	United States	International	State in Cylinder	Capacity (L)	Pressure at 70°F
O_2	Green	White	Gas	660	1900
Air	Yellow	White and black	Gas	625	1900
N_2	Black	Black	Gas	610	1900
He	Brown	Brown	Gas	500	1600
CO_2	Gray	Gray	Gas + liquid below critical temp 88°F	1590	838
N_2O	Blue	Blue	Gas + liquid below critical temp 98°F	1590	745

Note that the color coding systems are different between the United States and countries that have adopted the ISO standard.
From Dorsch JA, Dorsch SE. Medical gas cylinders and containers. In: Dorsch JA, Dorsch SE. *Understanding Anesthesia Equipment.* Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2007:1–24.

(ensures unidirectional flow and proper connection to the yoke hanger) and before the intermediate pressure regulator. This regulator reduces the pressure of the gas from the cylinder to ~ 45 PSI. When a gas cylinder is placed on the hanger yoke and the valve is opened, the machine pressure gauge reads the pressure of the cylinder contents. When the cylinder valve is subsequently closed, the check valve prevents flow back to the cylinder and maintains the previous pressure reading. With the pipeline pressure nominally higher than the downregulated tank pressure, the downstream regulator prevents pipeline flow back toward the pressure gauge. Therefore, the pressure gauge may continue to show a full tank pressure even if the full cylinder is removed, an empty one added, and its valve opened. It is important to open the oxygen cylinder valve only when checking the machine or when the reserve supply is needed. If the valve is left open, the cylinder supply may be depleted if pipeline pressures drop below the downregulated pressures of the tank, creating a dangerous situation if the central supply fails.

References

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3. Dorsch JA, Dorsch SE. Medical gas cylinders and containers. In: Dorsch JA, Dorsch SE, eds. *Understanding Anesthesia Equipment*. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2007:1–24.

Physics: Pulse Oximetry

Soeren Hoehne and Kai Kuck

OUTLINE

Background
Pulse Oximetry Probe
Principle
Limitations of Pulse Oximetry

Background

Hemoglobin oxygen saturation—or "oxygen saturation," as it is commonly referred to in clinical practice—is the proportion of total hemoglobin in blood that is oxyhemoglobin (i.e., hemoglobin bound to oxygen), expressed as a percentage and abbreviated SaO_2 (for arterial saturation) or SvO_2 (for venous saturation). Oxygen saturation is an important variable in determining blood oxygen content and oxygen delivery. First described in 1972 by Aoyagi in Japan,[1] pulse oximetry provides a continuous, noninvasive estimation of SaO_2 that previously could only be measured periodically by analyzing blood *ex vivo* in a blood gas analyzer after obtaining an arterial blood sample. Because of its perceived clinical utility, pulse oximetry quickly emerged as a standard monitor to assess the adequacy of oxygenation in perioperative and critical care settings. Understanding the scientific and technical concepts underpinning pulse oximetry is essential for the practitioner to apply the technology appropriately, including recognition of artifactual signals.

Pulse Oximetry Probe

The typical pulse oximetry (SpO_2) probe is a flexible clamp that houses a red and a near infrared **light-emitting diode** (**LED**) on one side and a photodiode on the opposite side to detect the small fraction of light transmitted by the tissues and blood.

Standard pulse oximeter probes (transmission probes) are placed on a finger, ear lobe, or toe, and have the light detector opposite the light source with the finger or body part in-between (Fig. P9.1). These transmission probes pass the light through the body part. A second, less common type of SpO_2 probe uses reflectance by directing the light onto the patient's skin and measuring the light that penetrates the skin and is then partially reflected back. Reflectance probes can be used on the forehead, for example. Reflectance probes consist of LEDs and a photodiode that are situated next to each other but are physically separated by a barrier.

Principle

When light passes through a substance, a certain amount of the light is absorbed. The **Beer-Lambert Law** explains that the amount of light absorbed (A) is linearly related to the specific absorbance coefficient (ε) for the substance at the wavelength (color) of the light, the length of the path that the light travels (l), and the concentration of the substance (c):

$$A = \varepsilon \times c \times l.$$

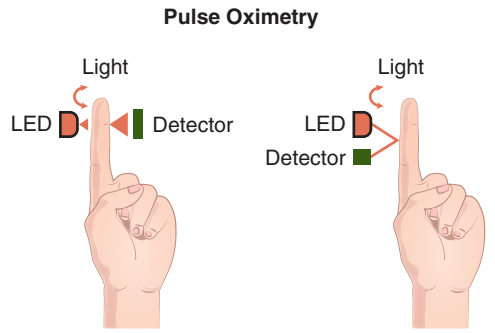
Pulse oximetry relies on the fact that oxygenated hemoglobin and deoxygenated hemoglobin differ in how much light they absorb at different wavelengths (Fig. P9.2). Typical wavelengths used in pulse oximetry are in the red (660 nm) and near infrared (940 nm) range.[2]

Although the underlying theory is well established, estimating the *absolute* concentration of arterial oxyhemoglobin is challenging from a technical perspective: The exact path length of the light cannot be determined easily owing to scattering of light by the tissues. Similarly, total hemoglobin concentration and the concentrations of oxygenated and deoxygenated hemoglobin are not known. Using only 2 wavelengths, conventional pulse oximetry cannot determine all of these unknown variables but can estimate only the *relative* concentration of oxyhemoglobin as a percentage of total hemoglobin (SpO_2). Modern pulse oximeters distinguish between venous and arterial saturation by relying on the fact that arteries exhibit pulsatile volume changes that coincide with the cardiac rhythm, while the volume of veins and tissue stay constant through the cardiac cycle (Fig. P9.3).

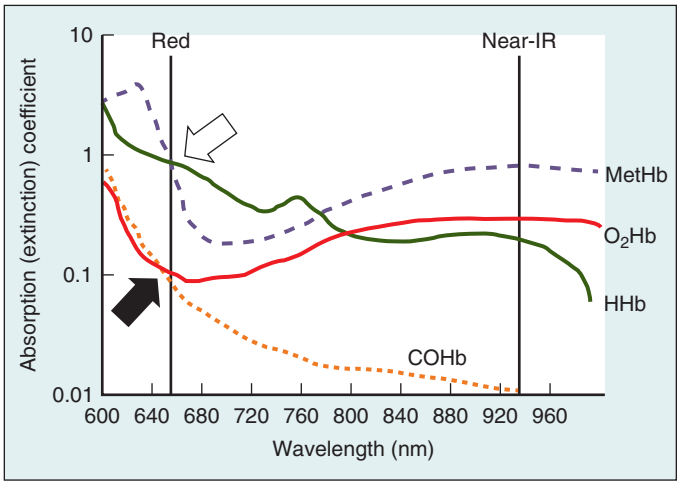
Borrowing concepts from electricity, the pulsatile absorption changes are often denoted as the "AC" part of the absorption signal and the constant offset of the absorption signal is often denoted as "DC" (AC and DC are derived from the terms *alternating current* and *direct current* used to describe oscillating and constant electrical currents, respectively).

The SpO_2 is estimated based on the "ratio of ratios" of the AC and DC parts of the red and the infrared absorption signals:

$$R = \frac{\left(\frac{A_{AC}}{A_{DC}}\right)_{red}}{\left(\frac{A_{AC}}{A_{DC}}\right)_{IR}}$$



• **Fig. P9.1** Typical pulse oximeter probe types. In a transmission type probe *(left)*, light from light-emitting diodes (LEDs) of 2 wavelengths is shone through a finger or other body part and detected on the side opposite from the LEDs. In a reflectance type probe *(right)*, the light is directed onto the patient's skin, penetrates the skin, and is then partially reflected back. The LEDs and the detector in a reflectance probe are situated next to each other but are physically separated by a barrier.



• **Fig. P9.2** Oxyhemoglobin (O_2Hb), deoxyhemoglobin (HHb), carboxyhemoglobin (COHb), and methemoglobin (MetHb) absorption spectra. The lines for red at 660 nm and near-IR (near infrared, 940 nm) indicate the 2 wavelengths used by conventional pulse oximeters' 2 light-emitting diodes. Note how similar the absorption by COHb and O_2Hb is at 660 nm *(black arrow)*. Also, the absorption by MetHb is very similar to that by HHb at 660 nm *(white arrow)*. These similarities contribute to the overestimation of arterial oxygen saturation by conventional pulse oximetry in patients with elevated levels of carboxyhemoglobin (e.g., from carbon monoxide poisoning or recent smoking) and to standard pulse oximeters reading 80% to 85% in patients with high levels of methemoglobin (e.g., from benzocaine toxicity). (Adapted from Chan ED, Chan MM, Chan MM. Pulse oximetry: understanding its basic principles facilitates appreciation of its limitations. *Respir Med*. 2013;107(6):789–799.)

where A_{AC} and A_{DC} represent the pulsatile and nonpulsatile components of the absorption signal and "red" and "IR" denote the wavelengths (660 nm and 940 nm, respectively) at which these absorption signals are measured. The Beer-Lambert Law relates this ratio linearly to SpO_2.

In most clinical circumstances, arterial oxygen saturation measured by pulse oximetry (i.e., **SpO_2**) is a very close approximation of the saturation measured by an arterial blood gas machine (i.e., **SaO_2**). SpO_2 can therefore be relied on clinically as a noninvasive measure of SaO_2. However, the different abbreviations for the same variable (i.e., SpO_2 and SaO_2) remind the practitioner that there are methodological and technical differences between the 2 approaches to measuring saturation that have clinical implications.

Advanced pulse oximetry technologies employ more than 2 wavelengths to measure other hemoglobin species (e.g., methemoglobin and carboxyhemoglobin); this approach emulates the methods used in blood gas analyzers. It is called *co-oximetry* because the method uses multiple wavelengths to distinguish between the multiple hemoglobin species that are typically reported on in an arterial blood gas analysis. Some pulse oximeters also use additional signal processing to derive additional variables, such as hemoglobin concentration, plethysmographic pulse pressure variation (to indicate fluid responsiveness), respiratory rate, and various indices of circulatory perfusion.

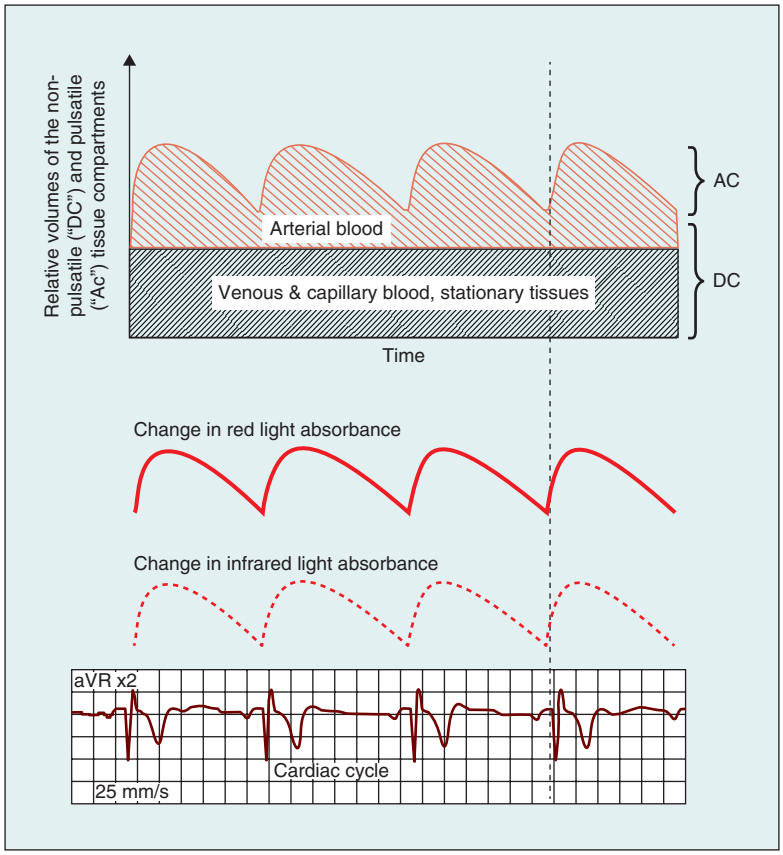
Limitations of Pulse Oximetry

When using pulse oximetry, signal loss or artifactual disturbance can occur when the probe is not correctly placed on the finger, when nail polish is present, or when dyes are present in the bloodstream. Similarly, severe hypotension, hypothermia, or shock can influence signal integrity. If a blood pressure cuff or tourniquet is positioned on the same arm as the pulse oximeter probe, the signal may be lost during cuff inflation. If the pulse oximeter probe is applied where venous pulsations can be expected (e.g., on the forehead), the resulting SpO_2 estimation might be erroneously low because it might partially reflect venous oxygen saturation. Ambient light and motion artifact are also common problems that impact accuracy of the pulse oximeter signal.

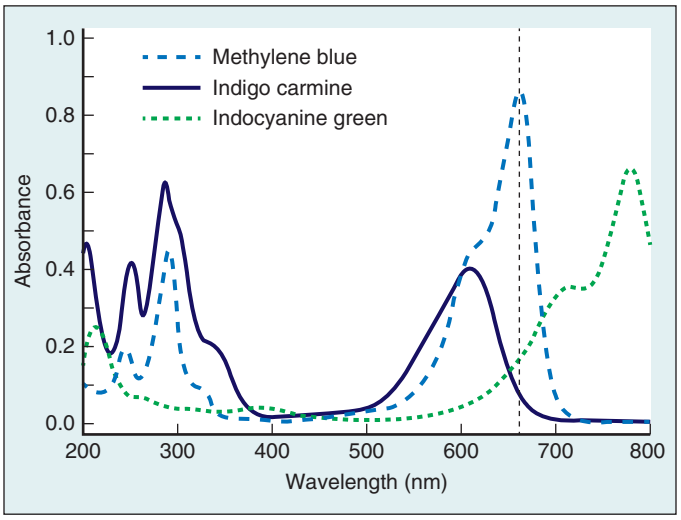
Abnormally high levels of other hemoglobin species (i.e., carboxyhemoglobin, methemoglobin) can also impact standard pulse oximetry readings. This is because the various hemoglobin species have overlapping absorption spectra with oxyhemoglobin, as shown in Fig. P9.2. For example, in patients with elevated levels of carboxyhemoglobin (e.g., from carbon monoxide poisoning or recent smoking), standard pulse oximetry overestimates arterial oxygen saturation. In cases of high levels of methemoglobin (e.g., from benzocaine toxicity), standard pulse oximetry readings converge to a false reading of 80% to 85%. The problems with standard pulse oximetry introduced by abnormally high levels of alternative hemoglobin species can be overcome by using multiple wavelengths of light (i.e., co-oximetry), as employed in blood gas analysis machines.

Dyes, sometimes injected intravenously for diagnostic purposes, can also adversely impact pulse oximetry readings. As with alternative hemoglobin species, intravenous dyes (e.g., methylene blue and indocyanine green) have absorption spectra that overlap with the oxyhemoglobin absorption spectrum (Fig. P9.4). For example, after injection of indocyanine green, there can be a brief artifactual decrease in the SpO_2 measurement until the dye is distributed from the bloodstream.[3]

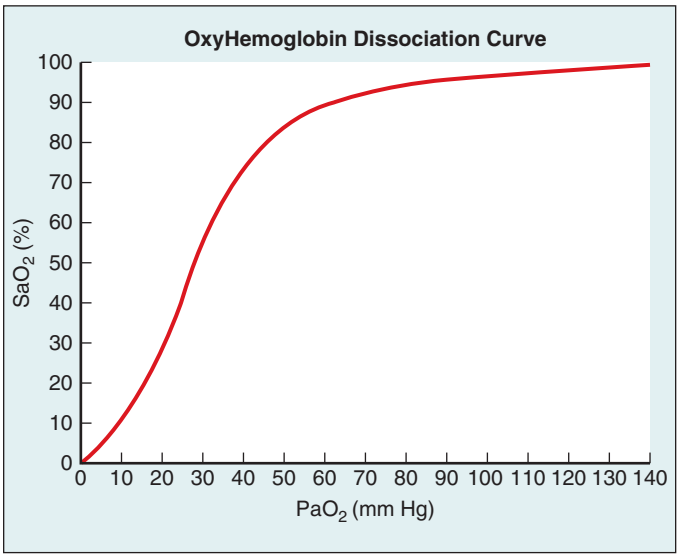
Because of the sigmoidal nature of the **oxyhemoglobin dissociation curve** (Fig. P9.5), SpO_2 is not a timely indicator of the adequacy of ventilation when patients are breathing supplemental oxygen. For example, if a patient becomes apneic while breathing 40% oxygen by face mask during procedural sedation, the SpO_2 will not decrease much until the patient has been apneic for several minutes.



• **Fig. P9.3** Volume pulses *(top)* and resulting light absorbance signals *(middle)*. Pulsatile arterial volume changes and relatively constant venous and tissue volumes along the light's pathway through tissue result in an absorption signal that has a constant (DC, direct current) component, and a pulsatile (AC, alternating current) component. (Adapted from Chan ED, Chan MM, Chan MM. Pulse oximetry: understanding its basic principles facilitates appreciation of its limitations. *Respir Med*. 2013;107(6):789–799.)



• **Fig. P9.4** Dyes (e.g., methylene blue, indocyanine green, among others) that are sometimes injected intravenously for diagnostic purposes (e.g., an intraoperative angiogram using indocyanine green) have absorption spectra that overlap with oxyhemoglobin and deoxyhemoglobin absorption spectra (see Fig. P9.2). As with alternative hemoglobin species, they also can adversely impact pulse oximetry readings. For example, after injection of indocyanine green, the clinician can expect a brief, artifactual decrease in the pulse oximeter reading until the dye has been more widely distributed from the bloodstream. (Adapted from Scheller MS, Unger RJ, Kelner MJ. Effects of intravenously administered dyes on pulse oximetry readings. *Anesthesiology*. 1986;65(5):550–552.)



• **Fig. P9.5** The oxyhemoglobin dissociation curve shows the relationship between the arterial hemoglobin oxygen saturation (SaO_2 in %) and the arterial partial pressure of oxygen (PaO_2, in millimeters Mercury [mmHg]). Note that the pO_2 can drop significantly while breathing supplemental O_2 before there is a noticeable change in SaO_2.

References

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2. Chan ED, Chan MM, Chan MM. Pulse oximetry: understanding its basic principles facilitates appreciation of its limitations. *Respir Med*. 2013;107:789–799.
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30

Pulmonary Pharmacology

CHARLES W. EMALA, SR.

CHAPTER OUTLINE

β_2-Adrenoceptor Agonists
- Structure-Activity
- Mechanism and Metabolism
- Clinical Pharmacology
- Drug Interactions
- Clinical Application

Anticholinergics
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- Mechanism and Metabolism
- Clinical Pharmacology
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Inhaled Corticosteroids
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Methylxanthines and Phosphodiesterase Inhibitors
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Leukotriene Receptor Inhibitors and 5-Lipoxygenase Inhibitors
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Monoclonal Antibodies
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Anesthetic Agents as Bronchodilators

Mucolytic Therapies
- Structure-Activity
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Emerging Developments
- Inhaler Propellants
- Smoking Cessation
- Novel Therapies

The most widely used medications in pulmonary medicine are those delivered via inhalation for small airway diseases, such as asthma, chronic obstructive pulmonary disease, and cystic fibrosis. Using the lung as a vehicle for drug delivery is well known to anesthesiologists who routinely deliver volatile anesthetics to the lungs for systemic distribution.

This chapter examines in detail pharmacologic approaches to the pulmonary system relevant to anesthesia; pulmonary pharmacology is discussed in the preceding chapter (Chapter 29). Three classes of medications are inhaled for therapeutic treatment of chronic lung diseases, including β_2-adrenoceptor agonists, anticholinergics (muscarinic receptor antagonists), and steroids. Although combinations of β_2-adrenoceptor agonists and steroids are now the most widely used therapies in bronchoconstrictive diseases, this was not always so. In 1896 medical textbooks advocated the smoking of "asthma cigarettes" made from the dried leaf or fruiting tops of the *Datura stramonium* plant, commonly known as jimson weed, devil's trumpet, or thorn apple. This plant contains tropane alkaloids such as atropine, hyoscyanine, and scopolamine that function as anticholinergics that would relieve reflex-induced bronchoconstriction. Modern use of anticholinergics has evolved with the introduction of inhaled ipratropium bromide in the 1980s.

Methylxanthines were first recognized as having therapeutic effects for asthma when coffee was recommended as early as the 1860s[1] and again in 1914 by Osler and McCrae.[2] By the 1940s intravenous aminophylline was recognized as effective for asthma even though today the mechanisms for this beneficial effect are not clearly established. The likely mechanisms involve elevation of cyclic adenosine monophosphate (cAMP) in airway smooth muscle owing to phosphodiesterase (PDE) inhibition, antagonism

Abstract

Pulmonary pharmacology is focused primarily on medications that effect the conducting airways of the lung responsible for gas exchange at the alveoli. The maintenance of patent airways occurs naturally in health but reduced luminal area can be acutely life threatening in disease states. The anesthesiologist is frequency confronted with patients suffering from asthma, chronic obstructive pulmonary disease or cystic fibrosis since over 10% of the population suffer from these diseases with bronchoconstrictive potential. Furthermore, instrumentation of the airway, which is a frequent component of airway management, can induce bronchoconstrictive reflexes. The reversal of acute bronchoconstriction relies heavily on inhaled agonists for the β2-adrenoceptor or antagonists of muscarinic receptors, but can also be facilitated by a number of anesthetic agents, particularly inhaled volatile anesthetic agents. The chronic maintenance of conducting away patency is largely achieved by avoiding lung inflammation which induces airway smooth muscle hypercontractile responses, airway epithelial damage and mucus production, airway nerve hyperexcitability and chronic airway remodeling causing fixed airway narrowing. These chronic effects are attenuated by a variety of inhaled corticosteroids and selective antagonists of leukotriene signaling. Emerging therapies for avoidance of airway inflammation include monoclonal antibodies targeting specific cytokines, cytokine receptors and immunoglobulins common in allergic lung inflammation.

Keywords

bronchoconstriction
bronchodilator
beta-adrenoceptor
cyclic AMP
muscarinic receptor
inflammation

of adenosine receptors, and/or systemic release of catecholamines. Nonetheless, the low therapeutic benefit versus toxicity ratio led to its elimination from first-line asthma therapies.

The β-adrenoceptor agonists (see Chapter 14) have been the mainstay of asthma maintenance and rescue therapy since the development of metered-dose inhalers (MDIs) in the 1950s, but in 1910 Melland described three cases of patients achieving dramatic relief of acute asthmatic symptoms by subcutaneous administration of epinephrine.[3] Inhaled epinephrine and isoproterenol were the initial therapeutics directed at β_2 adrenoceptors, but because of increased asthma death rates[4,5] agents that were more selective for β_2 adrenoceptors were introduced in the 1960s.

By the 1970s it was recognized that systemic steroids dramatically improved asthma maintenance therapy. But the devastating complications of long-term systemic steroid use led to the search for alternative therapies in patients with mild asthma and alternative routes of delivery of steroids for those with severe asthma. With the development of inhaled steroids, combination inhalers that combine selective β_2-adrenoceptor agonists with steroids became the mainstay of asthma therapy and ultimately culminated in the combination of long-acting β_2-adrenoceptor agonists (LABAs) with steroids. However, by the early 2000s it was recognized that LABAs alone are associated with increased asthma deaths. In 2009 this led to a warning from the U.S. Food and Drug Administration (FDA) that LABAs should not be used alone in the treatment of asthma, but should be used in combination with inhaled steroids. Studies continue to examine whether LABAs added to inhaled steroids are indeed superior to inhaled steroids alone.[6] A study of more than 11,000 adult patients with 6-month follow-up demonstrated no increased risk of serious asthma-related events in patients receiving fluticasone only compared to those receiving fluticasone with salmeterol, and patients receiving fluticasone with salmeterol had a 21% lower incidence of severe asthma exacerbations.[7] In a similar study of more than 6000 children, 4 to 11 years of age, salmeterol in a fixed-dose combination with fluticasone was associated with a risk of serious asthma-related events that was similar to the risk using fluticasone alone.[8]

Many inflammatory diseases are now being treated with monoclonal antibodies directed against specific immunoglobulins, cytokines, or cytokine receptors, and asthma is no exception. The biologic therapies have emerged as specific subtypes of asthma are defined by their specific pathophysiologic mechanism(s) (endotypes). The clearest molecular phenotyping emerging is the T helper 2 (Th2) lymphocyte–dominated response with its associated cytokines (interleukin [IL]-4, IL-5, IL-13)[9] and the more poorly characterized non-Th2 lymphocyte–dominated subtype that includes neutrophilic asthma.

β_2-Adrenoceptor Agonists

Structure-Activity

All short-acting β_2-adrenoceptor agonists (Table 30.1) are small molecules with a molecular structure very similar to the endogenous nonselective agonist epinephrine (Fig. 30.1). The LABAs salmeterol and formoterol have modified long side chains with additional aromatic moieties to increase their lipophilicity, which prolongs their duration at the site of action.

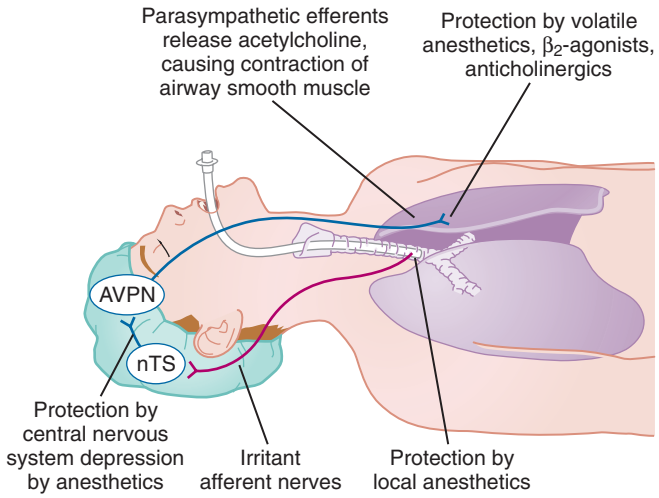
Mechanism and Metabolism

Among the hundreds of types of G-protein–coupled receptors (GPCRs) within cells, the biochemical understanding of

TABLE 30.1 β²-Adrenoceptor Agonist and Anticholinergic Drugs for Acute and Chronic Management of Chronic Obstructive Pulmonary Disease and Asthma

	Generic or Trade Name	Delivery Method
Short-Acting Inhaled β_2-Adrenoceptor Agonists		
Albuterol	Generic	Nebulization
	Proair HFA	MDI
	Proventil HFA	MDI
	Ventolin HFA	MDI
	Accuneb	Nebulization
Levalbuterol	Xopenex	MDI and nebulization
Metaproterenol	Generic	Nebulization
Pirbuterol	Maxair	MDI
Short-Acting Inhaled β_2-Adrenoceptor Agonists–Anticholinergic Combinations		
Albuterol + ipratropium bromide	Generic	Nebulization
	Duoneb	Nebulization
	Combivent	MDI
Long-Acting Inhaled β_2-Adrenoceptor Agonists		
Formoterol	Foradil Aerolizer	DPI
	Perforomist	Nebulization
Salmeterol	Serevent Diskus	DPI
Arformoterol	Brovana	Nebulization
Long-Acting Inhaled β_2-Adrenoceptor Agonists–Corticosteroid Combinations		
Salmeterol/fluticasone	Advair Diskus	DPI
	Advair HFA	MDI
Formoterol/mometasone	Dulera	MDI
Formoterol/budesonide	Symbicort	MDI
Short-Acting Oral β_2-Adrenoceptor Agonists		
Albuterol	Generic	Oral
	VoSpire ER	Oral
Metaproterenol	Generic	Oral
Terbutaline	Generic	Oral
Inhaled Anticholinergics		
Ipratropium bromide	Generic	Nebulization
	Atrovent HFA	MDI
Tiotropium bromide	Spiriva	DPI
Umeclidinium	Incruse Ellipta	DPI
Aclidinium	Tudorza Pressair	DPI
Long-Acting Inhaled β_2-Adrenoceptor Agonist–Long-Acting Inhaled Muscarinic Receptors Antagonists Combinations		
Vilanterol/umeclidinium	Anoro Ellipta	DPI
Formoterol/glycopyrrolate	Bevespi Aeorsphere	MDI
Indacaterol/glycopyrrolate	Utibron Neohaler	DPI
Olodaterol/tiotropium	Stiolto Respimat	MDI

DPI, Dry powder inhaler; *HFA*, hydrofluoroalkane propellant; *MDI*, metered-dose inhaler.



• **Fig. 30.1** Sites of action of major classes of anesthetics on reflex-induced bronchoconstriction. Irritation of the upper airway by foreign bodies, including endotracheal tubes or suction catheters, initiates an afferent irritant reflex arc that results in the release of acetylcholine from parasympathetic nerves onto muscarinic receptors on airway smooth muscle, resulting in bronchoconstriction. Anesthetics and other agents work at different levels of this irritant reflex to block bronchoconstriction. Local anesthetics can attenuate the initial afferent stimulus, whereas multiple classes of anesthetics (general, intravenous, local) can attenuate the glutamatergic and gamma-aminobutyric acid-ergic relay at the nucleus of the solitary tract to the airway vagal preganglionic neurons. Direct effects of volatile anesthetics, β_2-adrenoceptor agonists, or muscarinic receptor antagonists attenuate the effects of acetylcholine at the airway smooth muscle. *Ach,* Acetylcholine; *CysLT$_1$,* cysteinyl LT receptor 1; *GTP,* guanosine triphosphate; *[Ca^{2+}]$_i$,* intracellular calcium concentration.

β-adrenoceptor ligand binding, G-protein interactions, and mechanisms of receptor phosphorylation, desensitization, and internalization have served as the prototypical model for understanding their function. The effectiveness of β_2-adrenoceptors in asthma and chronic obstructive pulmonary disease (COPD) results from their combined effect at reducing inflammatory cell activation and directly relaxing airway smooth muscle. The role of β_2 adrenoceptors in bronchodilation is largely due to the multiple signaling mechanisms activated within airway smooth muscle cells that all favor smooth muscle relaxation. Classically, β_2 adrenoceptors couple the G_s-stimulatory G protein that activates adenylyl cyclase and synthesis of the second-messenger cAMP. cAMP activates several targets, including protein kinase A, that ultimately results in the opening of calcium ion (Ca^{2+})-activated potassium ion (K^+) channels and subsequent plasma membrane hyperpolarization, decreased intracellular entry of Ca^{2+}, and decreased sensitivity of the smooth muscle contractile proteins to Ca^{2+}.

The long-lasting effects of LABAs such as salmeterol and formoterol are thought to be accounted for by their binding to two sites within the β_2 adrenoceptor: the classic ligand binding site and an exosite on the receptor to which the hydrophobic tail binds irreversibly.[10] A second mechanism proposed to contribute to the prolonged duration of drug effect is that their high lipophilicity allows them to dissolve within the lipid bilayer of the airway smooth muscle cell to serve as an agonist depot.[11]

The majority (80%–100%) of albuterol is excreted in the urine; its primary metabolic route is sulfate conjugation by sulfotransferase 1A3. Salmeterol is extensively metabolized to α-hydroxysalmeterol (aliphatic oxidation) by cytochrome P450 3A4 (CYP 3A4) with 25% eliminated in the urine and the majority in the feces. The xinafoate moiety of salmeterol xinafoate has no pharmacologic activity and is highly protein bound (>99%) with an elimination half-life of 11 days. Formoterol is metabolized by glucuronidation and O-demethylation by CYP 2D6 and CYP 2C. About 60% of oral or intravenous formoterol is excreted in the urine and the remainder in the feces.

Clinical Pharmacology

Pharmacokinetics, Pharmacodynamics, and Therapeutic Effects

Inhaled β_2-adrenoceptor agonists are rapidly absorbed through the respiratory epithelium reaching the airway smooth muscle within a few minutes. The therapeutic effect of inhaled β_2-agonists depends on local tissue concentrations that are not reflected in plasma drug concentrations.[12] Regardless of the delivery device used, only about 10% of the inhaled dose actually reaches the peripheral airways to mediate bronchodilation.[13] The mean time for a 15% increase in forced expiratory volume at 1 sec (FEV_1) was 6 minutes following two albuterol inhalations with a peak effect occurring at 55 minutes with a mean duration of 2.6 hours.[14] A comparison of the racemic formulation to the levo (R–) enantiomer of albuterol given by nebulization to healthy volunteers demonstrated a shorter time to maximum plasma concentrations for the R-enantiomer (0.2 hours for R–, 0.3 hours for RS–) but a longer half-life (1.5 hours for RS–, 3.4 hours for R–).[15] Limited pharmacokinetic data are available for salmeterol because plasma concentrations often cannot be detected even 30 minutes after a therapeutic dose of 50 μg. Salmeterol-induced airway relaxation is slow in onset, prolonged in duration, and resistant to washout. After inhalation of 400 μg of salmeterol, plasma concentrations of 0.2 and 2 μg/L were achieved at 5 and 15 minutes in healthy volunteers.[16] In a separate study a second peak plasma concentration occurred 45 to 90 minutes after inhalation, likely reflecting gastrointestinal absorption of swallowed drug.[17] LABAs can require up to 30 minutes to first achieve bronchodilator effects with a duration of 12 hours.

Adverse Effects

The β agonists can produce dose-related cardiovascular effects (arrhythmias, tachycardia), hypokalemia, and elevations of blood glucose. Acute adverse effects are more common with oral compared with inhaled β_2 agonists and most commonly include tachycardia, nervousness, irritability, and tremor. Changes in the plasma concentrations of potassium and glucose are seen at doses far exceeding those used clinically.[18] Paradoxical bronchospasm has been reported with β agonists. An initial concern regarding an increased death rate in patients with asthma using salmeterol was raised in 1993 when 12 of 16,787 patients using salmeterol died, but this outcome was attributed to the severity of the patients' illnesses at the time of study entry.[19] The Salmeterol Multicenter Asthma study Research Trial (SMART), conducted at more than 6,000 sites enrolling more than 26,000 patients, was stopped after an interim data analysis revealed a small but significant increase in respiratory-related morbidity and mortality.[19] A meta-analysis of 19 trials involving more than 33,000 patients also revealed an increased risk of hospitalization for asthma exacerbations, life-threatening asthma attack, or asthma-related death.[20] Although the mechanism or mechanisms for these increased are unknown, speculations include the lack of antiinflammatory effect,

downregulation of β_2 adrenoceptors, or incorrect use of these LABAs as rescue inhalers. These findings led to a black box warning by the FDA that LABAs should not be used as monotherapy, and should be used only in patients whose asthma symptoms are not adequately controlled by low- to medium-dose inhaled steroids or whose disease severity warrants two maintenance therapies. Subsequently the FDA initiated a clinical trial protocol in cooperation with academic experts and manufacturers of LABAs that consists of five clinical trials: four in adults and one in children.[21] The initial studies are reassuring. showing no increased risk of serious asthma-related events in a trial involving more than 11,000 adults,[7] and in a separate trial of more than 6,000 children[8] randomly assigned to receive fluticasone alone or fluticasone combined with salmeterol for a 6-month period.

Drug Interactions

The β agonists can potentiate the hypokalemic effect of non–potassium-sparing diuretics. Serum levels of digoxin are reduced after the oral or intravenous administration of albuterol. The vascular effects of β agonists can be exacerbated by patients currently or recently taking monoamine oxidase inhibitors or tricyclic antidepressants. An increased risk of cardiovascular side effects can occur when salmeterol is used along with strong CYP 3A4 inhibitors.

Clinical Application

Common Applications

The use of LABAs in combination with inhaled steroids is an option for patients whose bronchospasm is not adequately controlled using monotherapy with low to medium doses of inhaled corticosteroids as recommended by the Global Initiative for Asthma (GINA)[22] and an expert report from the National Institutes of Health.[23] Conversely, use of inhaled LABAs without steroids is not approved by the FDA because of an increased rate of asthma deaths with this therapy. Short-acting β agonists are recommended as rescue therapy for break-through episodes of bronchospasm, and the frequency of use of rescue therapy is often used as an indicator of the adequacy of asthma maintenance therapy. Inhaled short-acting β agonists can be given to treat active wheezing in the preoperative or intraoperative period. They may also be administered prophylactically in patients at risk for bronchospasm, especially in those patients in whom intubation of the trachea is planned.

Rationale Drug Selection and Administration

The anesthesiologist will most commonly administer short-acting β_2-adrenoceptor agonists (e.g., albuterol) by inhalation via nebulization or MDIs either preoperatively or intraoperatively. Either modality can be connected to the inspiratory circuit of the anesthesia machine, but effective drug delivery to the airway smooth muscle is variable. This is affected by timing of drug administration relative to inspiration, and the volume of dead space (tracheal tube dimensions and anatomic dead space of the upper trachea/bronchi). Many studies have addressed the efficacy of delivering inhaled β_2 agonists in mechanically ventilated patients. Nebulization is more effective than MDIs.[24] A location 15 cm upstream from the tracheal tube on the inspiratory side of an anesthesia circuit was optimal in an in vitro model.[25] The mode of mechanical ventilation and the humidity of the circuit are also important factors in delivery; a dry circuit and spontaneous breaths under continuous positive airway pressure enhance delivery compared with continuous mandatory volume, assist control, or pressure control ventilator settings.[26] It is also possible to administer selective β_2-adrenoceptor agonists parenterally (e.g., terbutaline). Emergency treatment of bronchospasm in the emergency room uses inhaled short-acting β_2 agonists and systemic corticosteroids.[27] Rescue therapy from intractable bronchospasm can require intravenous epinephrine, but systemic administration of these therapies is associated with significant cardiovascular effects.

Anticholinergics

Structure-Activity

Inhaled anticholinergics (see Table 30.1) are a mainstay in the chronic management of COPD[28] and also are a component of some asthma regimens. Ipratropium bromide (nebulization or MDI) and tiotropium bromide (dry powder inhaler) (Fig. 30.2) antagonize the effects of acetylcholine released from airway parasympathetic nerves on M_3 muscarinic receptors on airway smooth muscle (Fig. 30.3).

Mechanism and Metabolism

Acetylcholine released from parasympathetic nerves traveling within the vagus nerve innervate the lung to act on M_2 and M_3 muscarinic receptors on airway smooth muscle. The nerve terminals also express autoinhibitory M_2 muscarinic receptors that respond to released acetylcholine to inhibit further neurotransmitter release. The M_3 muscarinic receptor on airway smooth muscle is a G-protein–coupled receptor (G_q) that activates phospholipase C to generate diacylglycerol and inositol phosphates from membrane phospholipids. Diacylglycerol activates a number of targets, primarily protein kinase C isoforms. Inositol phosphates elevate intracellular Ca^{2+} primarily via release from the sarcoplasmic reticulum. This entire signaling cascade is blocked upstream by ipratropium or tiotropium's antagonism of cell surface airway smooth muscle muscarinic receptors (see Fig. 30.2). Inhaled ipratropium is metabolized to eight metabolites that have little to no anticholinergic activity and are excreted in approximately equal proportions in feces and urine.

Clinical Pharmacology

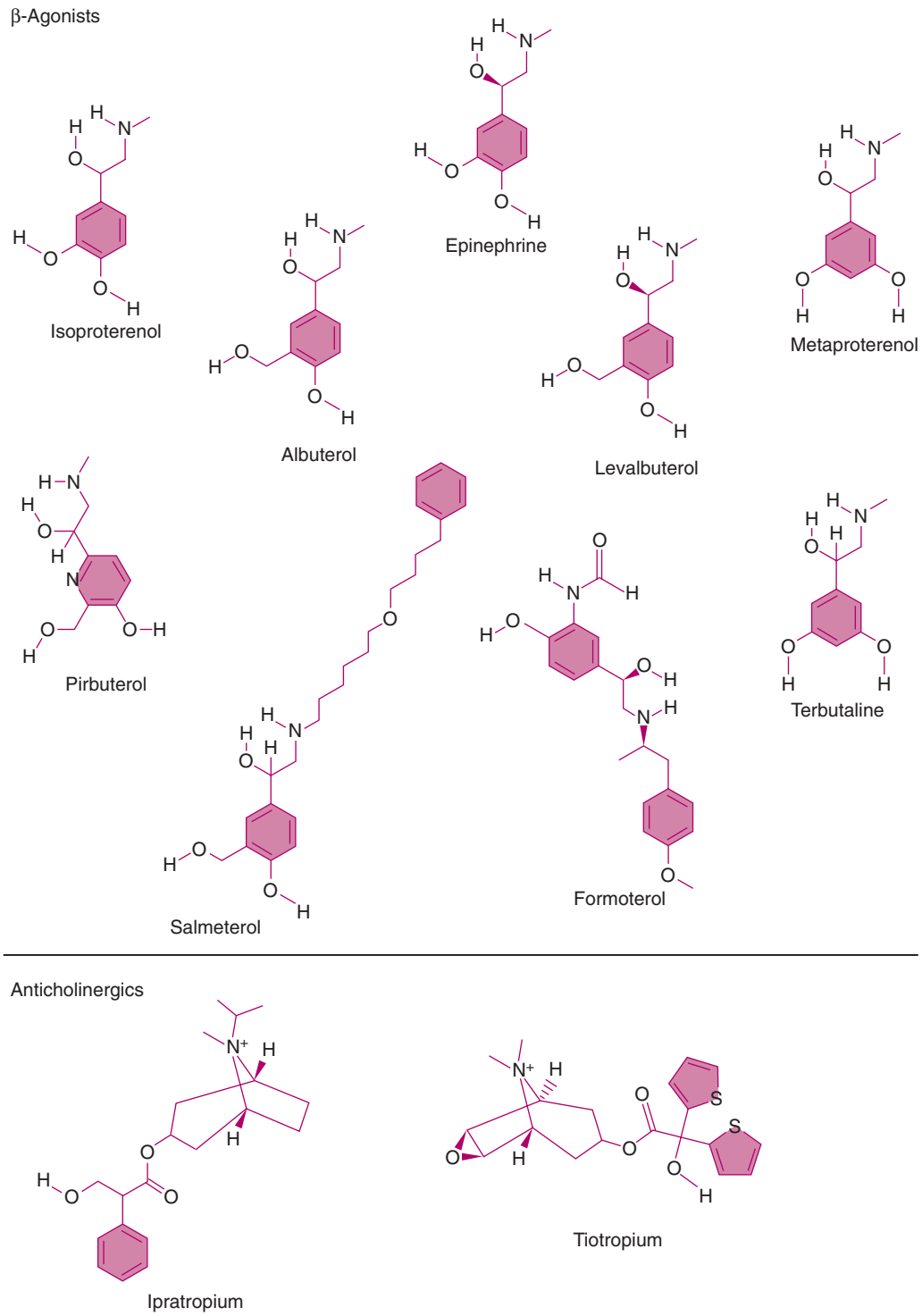
Pharmacokinetics, Pharmacodynamics, and Therapeutic Effects

Inhaled ipratropium (2 puffs, 18 μg/puff) has an initial onset of 15 minutes with a peak effect at 1 to 2 hours and duration of 3 to 6 hours. Tiotropium bromide (18 μg/capsule, 18 μg/day) has an onset of 30 minutes, a peak effect at 3 hours, and a duration of 24 hours. Only 7% of inhaled ipratropium is bioavailable; the elimination half-life is 3.5 hours by all routes of administration.

Inhaled anticholinergics are indicated for the relief of bronchoconstriction in COPD and asthma by blockade of the M_3 muscarinic receptor on airway smooth muscle. They can be used both prophylactically and as maintenance therapy. Their slower onset of action compared with inhaled β_2 agonists make them unacceptable as rescue therapy for acute exacerbations.

Adverse Effects

Anticholinergics inhibit mucosal secretions and thus dry mouth is common (antisialogogue effect). As with β agonists, paradoxical bronchospasm has been reported with ipratropium. Patients with



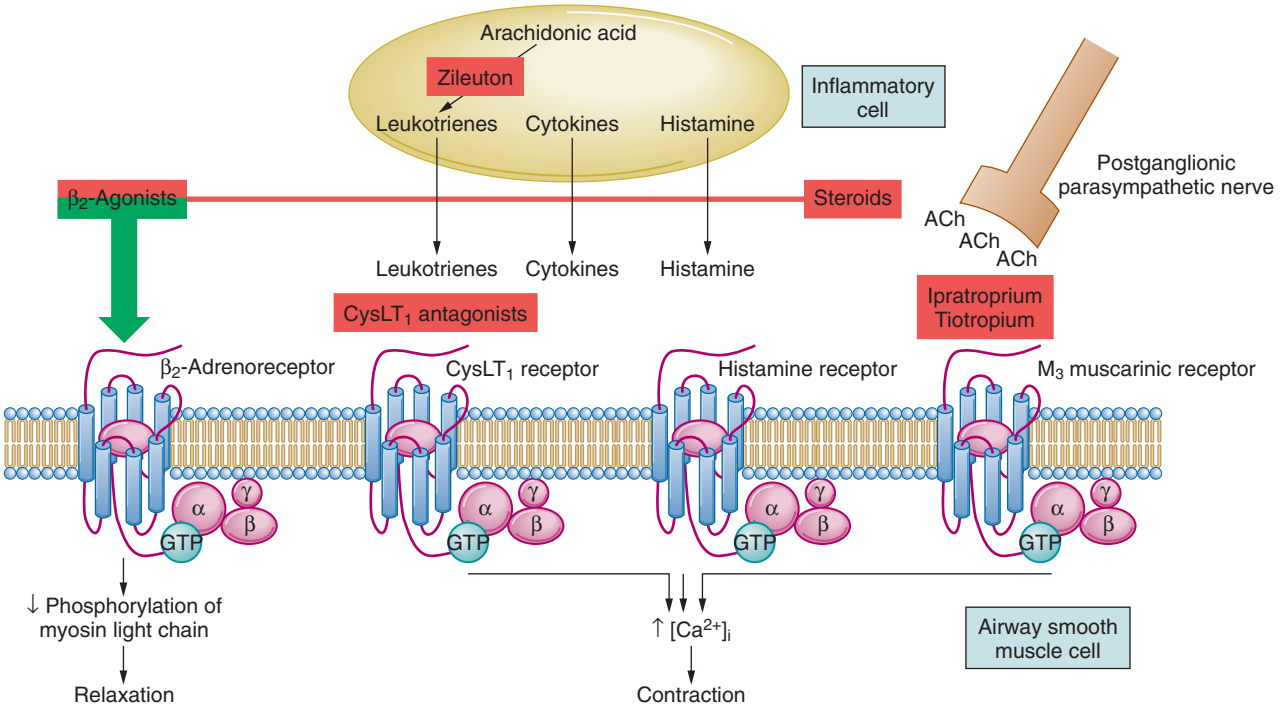
• **Fig. 30.2** Structures of β-receptor agonists and anticholinergics drugs used as bronchodilators.

COPD who are using ipratropium bromide have an increased risk of adverse cardiac events[29,30] that occur less commonly with tiotropium.[31] Inhaled anticholinergics increase the risk of acute urinary retention more than fourfold in men with benign prostatic hypertrophy as the result of effects on parasympathetic innervation to the detrusor muscles of the bladder. Inhaled ipratropium can also worsen acute narrow-angle glaucoma owing to its parasympathetic effects.

Clinical Application

Common Applications

Anticholinergics have been used to treat obstructive airway disease since the early use of the deadly nightshade (genus *Atropa*) and asthma cigarettes.[32] Although inhaled β_2-adrenoceptor agonists with steroids are often initial therapy for the bronchoconstrictive



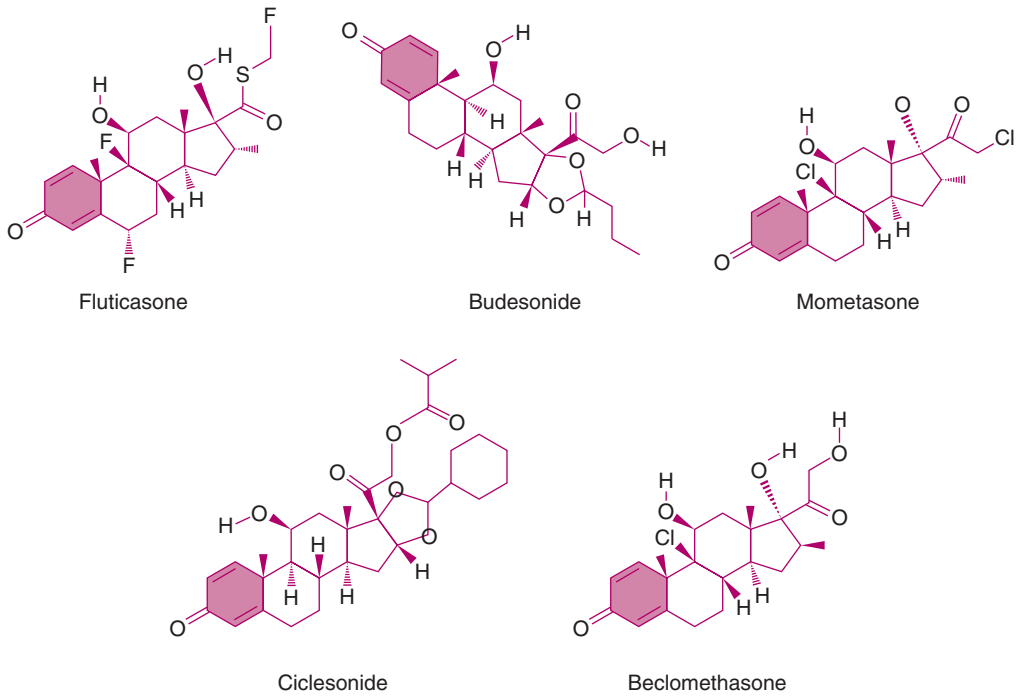
• **Fig. 30.3** Sites of action of major classes of pulmonary drugs on inflammatory and airway smooth muscle cells. Inflammatory cells in the airway release a wide variety of mediators that affect signal transduction of several types of cells in the airway (epithelium, smooth muscle, and nerves). 5-Lipoxygenase inhibitors (e.g., zileuton) block the synthesis of leukotrienes, whereas cysteinyl LT receptor 1 antagonists block the effect of leukotrienes on airway cells. Steroids nonspecifically block activation of many inflammatory cells in the airway responsible for cytokine production that alter signaling pathways of airway cells favoring edema, mucus secretion, and airway smooth muscle contraction. β_2-Adrenoceptor agonists both directly relax airway smooth muscle and block the activation of inflammatory cells. Muscarinic receptor antagonists block M_3 muscarinic receptors on airway smooth muscle as well as muscarinic receptors on epithelium and nerves. The determinants of airway smooth muscle contraction are an increase in intracellular calcium concentrations as well as the sensitivity of the contractile proteins to a given concentration of calcium (dictated by phosphorylation of the myosin light chain and termed *calcium sensitization*). *AVPN;* Airway vagal preganglionic neurons; *nTS,* nucleus of the solitary tract.

diseases asthma and COPD, there is evidence of equivalence or even superiority of inhaled anticholinergics in the treatment of COPD.[33] In the perioperative setting the choice of anticholinergic is mechanistically sound because the bronchoconstriction following airway irritation involves parasympathetic nerve release of acetylcholine onto M_3 muscarinic receptors on airway smooth muscle.

Instrumentation of the upper airway with an endotracheal tube or suction catheter is a potent stimulus for reflex-induced bronchoconstriction (see Fig. 30.1). This reflex originates in the airway wall where irritant nerve fibers travel in the vagal nerve to the nucleus of the solitary tract, which synapses via gamma-aminobutyric acid $(GABA)_A$ and glutamatergic receptors on airway-related vagal preganglionic neurons.[34] The efferent outflow from this brainstem nucleus travels back down the vagus to release acetylcholine onto M_3 muscarinic receptors on airway smooth muscle. The M_3 muscarinic receptor via G_q-coupling increases intracellular Ca^{2+}, resulting in smooth muscle contraction and airway narrowing. Thus anticholinergic blockade of M_3 muscarinic receptors is an ideal target to attenuate reflex-induced bronchoconstriction.

Four inhaled antimuscarinics are available: the relatively quick-onset short-duration ipratropium bromide, the intermediate-duration aclidinium, and the longer-duration tiotropium bromide[35] or umeclidinium. Ipratropium bromide is available in either nebulized or MDI formulations, making this an ideal preoperative or intraoperative treatment for a patient with bronchoconstriction induced by airway irritation. A newer inhaled anticholinergic drug, aclidiumium, produces bronchodilation for a similar duration as tiotropium[36,37] with preclinical evidence of a reduced risk of anticholinergic heart rate effects.[38]

Combination inhalers are now available for COPD that contain both a LABA and long-acting muscarinic receptor antagonist (LAMA). Studies in patients with COPD comparing the combination inhaler indacaterol/glycopyrrolate indicated improved lung function, dyspnea, symptoms, and health status compared with the use of either agent alone.[39] A meta-analysis compared combination LABA/LAMA bronchodilators with either LAMA alone or LABA/inhaled corticosteroid combinations in COPD patients. The LABA/LAMA combination had greater efficacy and comparable safety profiles compared with the LAMA alone or the combined LABA/inhaled corticosteroid. In contrast, the addition of inhaled tiotropium to patients with asthma maintained with LABA/inhaled corticosteroid failed to show a benefit of adding a LAMA to LABA/inhaled corticosteroid maintenance therapy in this disease state.[40]



• **Fig. 30.4** Structures of inhaled corticosteroids.

Inhaled Corticosteroids

Structure-Activity

The specific structures of the inhaled corticosteroids on a steroidal backbone are illustrated in Fig. 30.4. For a more detailed discussion of systemic corticosteroid pharmacology see Chapters 36 and 38.

Mechanism and Metabolism

Corticosteroids interact with intracellular steroid receptors that translocate to the nucleus and interact with transcription factor complexes to regulate inflammatory protein synthesis. The stimulation of gene transcription (transactivation) correlates with negative side effects of corticosteroids, whereas repression of transcription factors (e.g., nuclear factor kappa B [NF-κB] and activator protein 1 [AP-1]) is responsible for antiinflammatory effects.[41] Although steroids affect the inflammatory response of lymphocytes, eosinophils, neutrophils, macrophages, monocytes, mast cells, and basophils, particular attention has focused on the role of a subset of T lymphocytes in asthma. CD^+ Th2 cells that produce IL-4, IL-5, and IL-13 are particularly important in orchestrating the complex inflammatory events in asthmatic lungs and are inhibited by inhaled steroids. Mast cell and basophil numbers are increased and release of mediators (histamine, leukotrienes [LTs]) in asthmatic airways is enhanced. Although inhaled steroids also suppress these cells, more specific therapy with oral LT antagonists has allowed reduction in inhaled steroid use in some patients. Corticosteroids exhibit high first-pass metabolism by the liver via CYP 3A4 isoenzymes.

Clinical Pharmacology

Pharmacokinetics, Pharmacodynamics, and Therapeutic Effects (Table 30.2)

Beclomethasone dipropionate is a prodrug that is rapidly activated by hydrolysis to the active monoester 17-beclomethasone

TABLE 30.2 Inhaled and Systemic Steroids for Bronchospasm

Inhaled	Formulation	Delivery Method
Ciclesonide	Alvesco HFA	MDI
Mometasone	Asmanex Twisthaler	DPI
Budesonide	Generic	Nebulization
	Pulmicort Flexhaler	DPI
	Pulmicort Respules	Nebulization
Fluticasone	Flovent Diskus	DPI
	Flovent HFA	MDI
Beclomethasone	Qvar HFA	MDI
Systemic		
Methylprednisolone	Generic	Oral
	Medrol	Oral
Methylprednisolone sodium succinate	Generic	Parenteral
	Solu-Medrol	Parenteral
Prednisolone	Generic	Oral
	Orapred	Oral
	Pediapred	Oral
	Prelone	Oral
	Veripred 20	Oral
Prednisone	Generic	Oral
	Sterapred	Oral
Hydrocortisone sodium succinate	Solu-Cortef	Parenteral

DPI, Dry powder inhaler; *HFA,* hydrofluoroalkane propellant; *MDI,* metered-dose inhaler

monopropionate. The active metabolite has an affinity for the glucocorticoid receptor that is 25 times that of the parent compound. Ciclesonide is an inactive prodrug that is converted to an active metabolite desisobutyrylciclesonide in the lung. Much (40%–90%) of an inhaled corticosteroid is swallowed and therefore available for systemic absorption (and potential systemic side effects). Thus a low oral bioavailability of inhaled corticosteroids is desirable, ranging from 1% for fluticasone propionate to 26% for 17-beclomethasone monopropionate. In contrast to oral absorption, most drug deposited in the lung will be absorbed systemically and is not subjected to first-pass hepatic metabolism. Deposition and thus absorption from the lung is more a function of the efficiency of the delivery device than the properties of the drug itself. Fluticasone has only 1% oral bioavailability owing to first-pass metabolism but when delivered to the lung by dry powder inhalers or MDIs, total systemic bioavailability is 17% and 25%, respectively.[42] The transition from chlorofluorocarbons- to hydrofluoroalkane (HFA)-powered MDIs has resulted in unanticipated improvement in the delivery of smaller particles deposited deeper in the lung with less oropharnygeal deposition and thus less systemic absorption (see "Emerging Developments"). Most of the inhaled corticosteroids are (~70%) bound to plasma proteins and have half-lives of 3 to 8 hours owing to high extraction and metabolism by the liver.

The efficacy of inhaled corticosteroids in asthma has been shown in many studies, usually with comparable benefits to systemic steroids with fewer side effects. Patients with asthma discharged from the emergency room with 40 mg oral prednisone daily versus 600 μg inhaled budesomide 4 times a day exhibited similar rates of asthma relapse and similar improvements in FEV_1, asthma symptoms, and peak expiratory flow.[43] Personalized medicine may be able to predict respondents to specific therapies including inhaled corticosteroids.[44]

Adverse Effects

Many studies report no or minimal side effects on adrenal function, bone density,[45] or subcapsular cataracts, whereas some studies contend a dose-dependent effect of all inhaled steroids on these parameters.[46] A year-long study in adults receiving inhaled fluticasone or beclomethasone[47] and a 12-week study in children[48] receiving inhaled fluticasone showed no effect on bone density.

Drug Interactions

Numerous reports exist of clinically significant Cushing syndrome and adrenal insufficiency in both children and adults secondary to the combination of fluticasone propionate or budesonide with a CYP 3A4 inhibitor (e.g., ketoconazole, itraconazole, ritonavir).[49] Most patients were using high doses of inhaled corticosteroids. Plasma concentrations of mometasone furoate and a metabolite of ciclesonide increased with ketoconazole administration.

Clinical Application

Common Applications

Inhaled corticosteroids are commonly recommended as initial therapy for asthma. The introduction of inhaled steroids in the 1970s revolutionized therapy for bronchospastic diseases by allowing the delivery of steroids directly to the airway with a reduction in the systemic toxicity of chronic oral steroid ingestion. Although the precise mechanisms of asthma remain poorly understood, a significant component of asthma involves a complex interplay between inflammatory and structural cells of the airway. Inhaled glucocorticoids are the most effective antiinflammatory drugs for the treatment of asthma. Inhaled corticosteroids reduce symptoms,[50] frequency of exacerbations, airway hyperresponsiveness,[51] airway inflammation, and asthma mortality.[52] A review of clinical studies suggests that inhaled fluticasone was more efficacious that inhaled budesonide as monotherapies, and that either a combination of fluticasone/salmeterol or budesonide/formoterol was more effective than corresponding monotherapies with inhaled corticosteroids or inhaled LABAs.[53] However, the ongoing controversy regarding the uncertain risk-benefit of adding inhaled LABAs to inhaled glucocorticoids for asthma therapy led to an unprecedented series of clinical trials coordinated between the FDA and drug manufacturers of LABAs. Combined analysis of four trials by members of the joint oversight committee concluded that combination therapy with a LABA plus an inhaled glucocorticoid was not associated with a higher risk of serious asthma-related events compared to treatment with an inhaled glucocorticoid alone.[6,6a] Combination inhaled corticosteroids and LABAs are also useful in COPD.[54,55]

Methylxanthines and Phosphodiesterase Inhibitors

Structure-Activity

Theophylline is a close structural analog of caffeine on a purine backbone. Aminophylline is two theophylline molecules combined with a 1,2 ethanediamine moiety. Roflumilast is a halide-modified benzamide molecule synthesized from 3-(cyclopropylmethoxy)-4-hydroxybenzaldehyde. The x-ray crystal structure of roflimulast bound within the catalytic sites of PDE4 has been solved,[56] showing with unprecedented mechanistic molecular detail the target site of a drug newly added to clinical medicine.

Mechanism and Metabolism

Methylxanthines have antiinflammatory and bronchodilating effects. Although these drugs are PDE inhibitors in vitro, this is not likely to occur at the therapeutic levels achieved.[57] Methylxanthines release catecholamines from the adrenal gland,[58] which might contribute to their beneficial effect in asthma, and also are nonselective antagonists of four known adenosine receptor subtypes (A_1, A_{2a}, A_{2b}, and A_3).[59] Additional mechanisms that have been proposed for the beneficial effects of methylxanthines in bronchoconstrictive diseases include modulation of intracellular Ca^{2+} flux through ryanodine receptors,[60] modulation of histone deacetylase activity, and increased peroxisome proliferator–activated receptor γ expression.

Roflumilast represents a new class of oral medication introduced in 2011 for severe COPD. Roflumilast, a specific type IV PDE inhibitor, inhibits degradation of cAMP in cells of the airway (airway smooth muscle, epithelium, and inflammatory cells) and elsewhere that express the PDE4 isoenzyme. Roflumilast and its active metabolite N-oxide roflumilast are highly selective inhibitors of PDE4 (which is turn is highly selective for cAMP), and are inactive against isoforms 1, 2, 3, 5, and 7. The selectivity of roflumilast is distinct from that of the PDE inhibitors used in heart failure (milrinone, inamrinone, and cilostazol) that target cAMP-selective PDE3 and from the inhibitors used for erectile dysfunction (sildenafil and tadalafil) that target the cGMP-selective PDE5. The selectively of roflumilast for PDE4 is suggested to

produce fewer side effects than nonselective (PDE types III, IV, and V) inhibition by theophylline.

Theophylline is extensively (>70%) metabolized in the liver by N-demethylation by CYP 1A2 primarily to 3-methylxanthine. Theophylline is also 8-hydroxylated to 1,3-dimethyluric acid, which is subsequently N-demethylated to 1-methyluric acid. In neonates it is directly 7-methylated to caffeine. About 10% is excreted in the urine unchanged. Many drug classes affect its metabolism and thus serum concentrations (see later text).

Roflumilast is metabolized in the liver by CYP 3A4 and 1A2 to roflumilast N-oxide (also a potent PDE4 inhibitor) and then O-deacylated and glucuronidated for urinary excretion.

Clinical Pharmacology

Pharmacokinetics, Pharmacodynamics, and Therapeutic Effects

Theophylline is 40% protein bound with a volume of distribution of 0.5 L/kg. Oral theophylline is well absorbed from the gastrointestinal tract, resulting in 90% to 100% bioavailability with peak serum levels occurring within 1 to 2 hours of ingestion. Sustained-release formulations are available owing to the relatively short half-life of 8 hours in healthy adults. The elimination half-life varies widely—from 30 hours in premature neonates to 3.5 hours in children, 8 hours in nonsmoking adults, 5 hours in smoking adults, and 24 hours in those with New York Heart Association class III-IV congestive heart failure. The intravenous dose required to achieve a therapeutic concentration of 10 to 20 μg/mL varies fourfold in an otherwise healthy adult population. For rapid treatment of acute bronchospasm a loading dose followed by maintenance infusion is frequently used. In children the rate of clearance of theophylline is 40% greater than adults.

Following oral administration of roflumilast, the time to peak plasma concentration is 1 hour, with nearly 99% protein bound. With daily dosing, steady-state levels are achieved in 4 days with a mean plasma half-life of 17 hours.

The role of methylxanthines as antiinflammatory and bronchodilator drugs in asthma and COPD is well established. However, methylxanthines are also respiratory stimulants and have been evaluated in central apnea, obstructive sleep apnea, and periodic breathing (Cheyne-Stokes respiration).[61] Clinical trials show a benefit in central sleep apnea but not obstructive sleep apnea.[62] In animal studies roflumilast did not protect against LTD4– or serotonin-induced bronchoconstriction, and there is no evidence that roflumilast is bronchodilatory in humans with COPD. This suggests that its primary therapeutic benefit is due to its antiinflammatory effects via PDE4 inhibition in airway inflammatory cells.

Adverse Effects

Adverse reactions are uncommon at serum theophylline levels below 20 μg/mL. Adverse reactions at serum concentrations between 20 and 25 μg/mL include nausea, vomiting, diarrhea, headache, and insomnia. Symptoms of overdosage at concentrations more than 30 μg/mL include seizures, tachyarrythmias, congestive heart failure, tachypnea, hematemesis, and reflex hyperexcitability. Methylxanthine use during anesthesia was also problematic owing to the release of catecholamines in combination with volatile anesthetics that sensitized the myocardium to their arrythmogenic effects (e.g., halothane).[63] Morever, aminophylline does not add additional bronchodilatory effect to the bronchodilation achieved by maintenance levels of volatile anesthetics.[64]

Drug Interactions

Many medications can increase the serum concentrations of theophylline, thereby enhancing their potential for toxicity; these medications include cimetidine, mexiletine, ticlopidine, propranolol, ciprofloxacin, alcohol, allopurinol, disulfiram, erythromycin, and estrogens. Cigarette and marijuana smoking and medications that induce liver metabolic enzymes (e.g., carbamazepine, phenytoin, thiabenzadole) reduce theophylline serum concentrations.

Special Populations

Theophylline should be used with caution in patients with active peptic ulcer disease, seizure disorders, cardiac arrhythmias, compromised cardiac function, angina, hypertension, hyperthyroidism, or liver disease.

Clinical Application

Common Applications

Theophylline is among the most widely prescribed medication for the treatment of asthma worldwide, but it is recommended as second- or third-line therapy behind inhaled corticosteroids and inhaled β agonists because of its potential for systemic toxicity. By the 1980s several studies reported that inhaled β_2 agonists were superior to aminophylline or theophylline in acute asthmatic exacerbations.[65] Aminophylline and theophylline formulations are less commonly used as maintenance therapy in the United States because of their low therapeutic index.

Leukotriene Receptor Inhibitors and 5-Lipoxygenase Inhibitors

Structure-Activity

LTs are synthesized from arachidonic acid by 5-lipoxygnase. They are so named owing to their source from leukocytes and the presence of three conjugated double bonds in their structure. The discovery that the slow-reacting substance of anaphylaxis was a mixture of LTs released from mast cells and basophils sparked the search for antagonists of LT receptors. Independent medicinal chemistry strategies were used to identify both of the antagonists in current clinical use (Table 30.3). Montelukast was discovered by modifying a quinoline with LT structural elements. Zafirlukast was based on a compound incorporating components from both FPL 55712 and the natural LTs.[66]

Mechanism

The cysteinyl LTs—LTC_4, LTD_4, LTE_4, and LTB_4—are products of plasma membrane phospholipids that increase smooth muscle contraction, microvascular permeablility, and airway mucus secretion. These LTs mediate their airway effects primarily through the cysteinyl LT receptor 1 ($CysLT_1$) receptor subtype that is widely expressed on mast cells, monocytes, macrophages, eosinophils, basophils, neutrophils, T and B lymphocytes, airway smooth muscle cells, microvascular endothelial cells, bronchial fibroblasts, and pluripotent hematopoietic stem cells.[67,68] The enzyme 5-lipoxygenase converts arachidonic acid to LTA_4, an upstream precursor to the active cysteinyl LTs. This enzyme is inhibited by the only 5-lipoxygenase inhibitor approved for asthma, zileuton. Montelukast

TABLE 30.3 Targeted Antiinflammatory Therapies for Bronchospasm

Leukotriene	Generic or Trade Name	Mode of Action
Leukotriene Receptor Antagonists		
Zafirlukast	Accolate	Leukotriene D4 and E4 receptor antagonist
Montelukast	Singulair	Cysteinyl leukotriene receptor antagonist
5-Lipoxygenase Inhibitor		
Zileuton	Zyflo	Inhibits leukotriene synthesis
Cell Release Inhibitors		
Cromolyn	Intal	Stabilizes mast cell membrane
Biologics (Antibodies)		
Omalizumab	Xolair	Antibody to IgE
Mepolizumab	Nucala	Antibody against IL-5
Reslizumab	Cinqair	Antibody against IL-5
Emerging Biologics (Antibodies)		
Benralizumab		Antibody to IL-5 receptor
Dupilumab	Dupixent	Antibody IL-4/IL-13
Tralokinumab		Antibody to IL-13
Lebrikizumab		Antibody to IL-13
Pitrakinra	Aerovant	Antagonist to IL-4 receptor
Anrukinzumab		Antibody to IL-13
Secukinumab	Cosentyx	Antibody to IL-17

IgE, Immunoglobulin E; *IL*, interleukin.

and zafirlukast are antagonists of the $CysLT_1$ receptor; they directly block the effect of LTC_4, LTD_4, and LTE_4 on this receptor.

Clinical Pharmacology

Pharmacokinetics, Pharmacodynamics, and Metabolism

Montelukast and zafirlukast are rapidly absorbed after oral administration and are more than 99% bound to albumin. They achieve peak plasma concentrations within 3 to 5 hours and undergo extensive metabolism by cytochrome P450 subtypes in the liver. Zileuton causes an increase in liver enzymes in 2% of patients and so should be avoided in patients with active liver disease or persistent elevation of liver enzymes.

Drug Interactions

Certain anticonvulsants (phenytoin, carbamazepine, oxycarbazepine, phenobarbital) and rifamycin can decrease plasma concentrations of montelukast. Coadministration of zafirlukast with warfarin increases prothrombin time by 35%. Coadministration of zafirlukast with oral theophylline or aspirin reduces zafirlukast plasma concentrations. Zileuton is a weak inhibitor of CYP 1A2 and has been shown to increase theophylline and propranolol concentrations, and it can increase prothrombin times in patients coadministered warfarin.

Clinical Application

Common Applications

LT receptor antagonists and 5-lipoxygenase inhibitors[69,70] are commonly used as adjuvant therapy in asthma.[71] The potential toxicity of this therapy appears less than that of inhaled steroids, and LT receptor antagonists can allow reduced steroid use. They are effective as additional therapy for acute asthma. An investigational intravenous formulation of montelukast has an onset within 10 minutes and improves bronchoconstriction for at least 2 hours.[72]

Monoclonal Antibodies

Structure-Activity

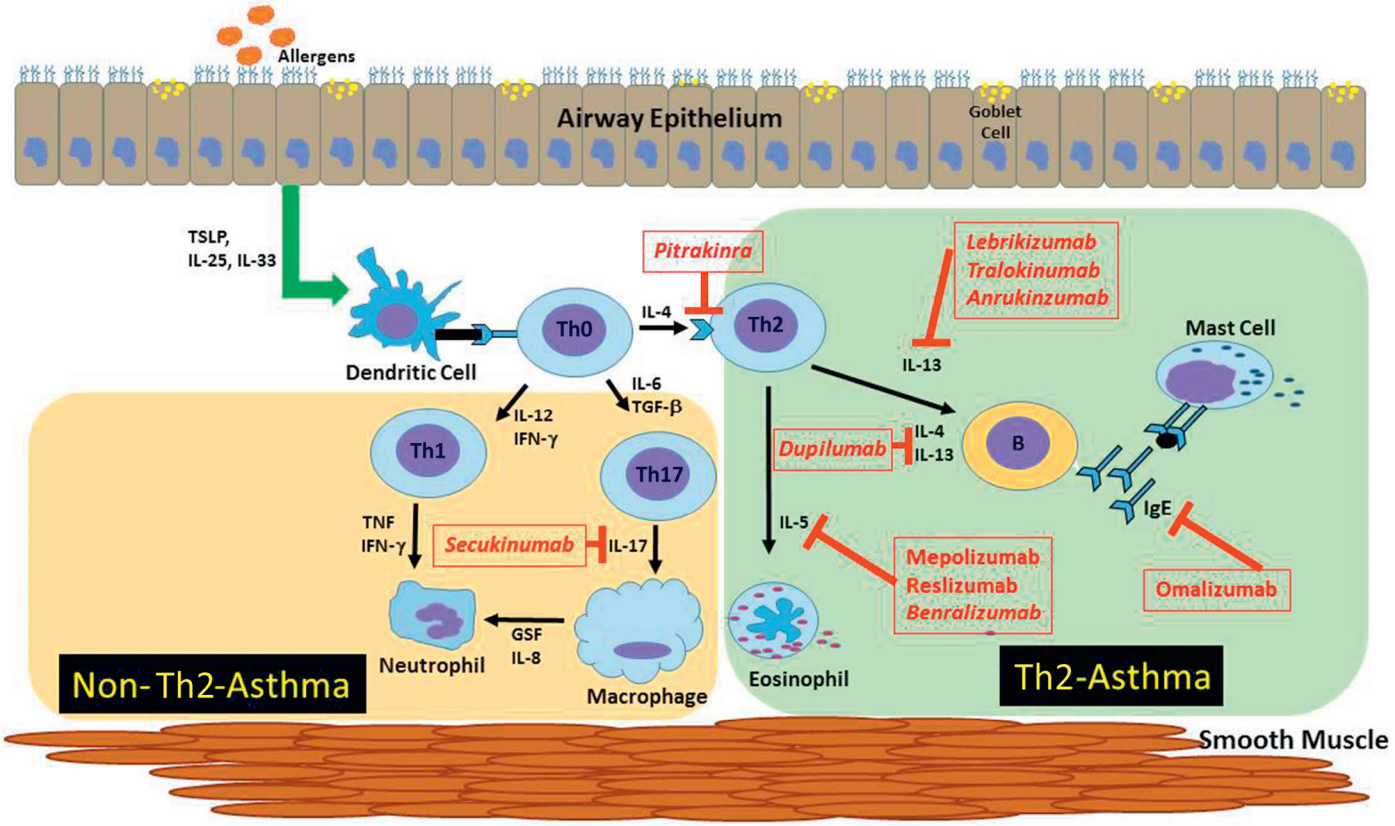
Asthma is a heterogeneous collection of clinical syndromes that share the characteristic of reversible small airways obstruction. Asthma occurs in 8% to 10% of the U.S. population, and 10% of this group have severe asthma defined as requiring high-dose inhaled or systemic steroids (≥880 μg of inhaled fluticasone propionate or equivalent) in combination with a second long-term inhaled therapy. Patients with severe asthma are further characterized by those with a Th2 phenotype (eosinophilia, high IL-4, IL-5, IL-13), but nearly 40% of those with severe asthma have a non-Th2 phenotype that involves Th17 cells and neutrophils. Emerging biologic therapies target specific cytokines, particularly those of the Th2 subtype. Approved therapies include antibodies against immunoglobulin (Ig) E (IgE; omalizumab) and IL-5 (mepolizumab and reslizumab). These biologics are reserved for patients with severe asthma, but a significant clinical challenge remains in identifying the molecular asthmatic endotype of a given patient who could potentially benefit from these therapies.[73] An additional challenge with these therapies is the need to administer them parenterally (typically monthly) in a monitored clinical setting.

Omalizumab was the first clinically available biologic in this class and is a recombinant human $IgG_1\kappa$ monoclonal antibody (150 kDa) that selectively binds to human IgE. It is effective as an adjuvant therapy in adults with moderate to severe asthma. This antibody binds to the constant region of circulating IgE molecules, preventing their binding to the high-affinity (FceRI) and low-affinity (FceRII) IgE receptors on mast cells, basophils, B lymphocytes, dendritic cells, and macrophages, thereby impairing mediator release from these cells. One IgE molecule has two antigenic binding sites for omalizumab, and omalizumab in turn has two antigen binding sites; thus IgE/anti-IgE complexes are formed with molecular masses of 500 to 1000 kDa.

Mepolizumab and reslizumab are clinically approved biologics that are monoclonal antibodies directed against the cytokine IL-5, a key orchestrator of inflammation in Th2- dominant asthma and an activator of eosinophils (Fig. 30.5).

Mechanism and Metabolism

As an anti-IgE antibody, omalizumab binds to circulating IgE molecules, interrupting the allergic cascade. It is effective in treating patients with allergic asthma that exhibit a high concentration of IgE molecules. Neutralizing IgE molecules prevents activation of degranulation in many IgE-presenting cells, including mast cells and basophils, and thus prevents release of histamine, LTs, and cytokines involved in the inflammatory component of reactive airway disease.



• **Fig. 30.5** Immunosignaling mechanisms in asthma. Th2-mediated asthma is primarily mediated by IL-4, IL-5, IL-13, and IgE targeted by monoclonal antibodies omalizumab (anti-IgE) or mepolizumab and reslizumab (anti-IL-5). Non–Th2-mediated asthma is modulated by Th1 and TH17 lymphocytes, which in turn activate neutrophils and macrophages. Monoclonal antibodies indicated by *italics* are in development for clinical use. *GSF,* Granulocyte-stimulating factor; *IgE,* immunoglobulin E; *IL,* interleukin; *INF,* interferon; TGF, transforming growth factor-β; *Th,* T helper (lymphocyte); *TNF,* tumor necrosis factor; *TSKP,* thymic stromal lymphopoietin.

The IgE/anti-IgE small immune complexes do not precipitate in the kidney and are easily cleared by the liver reticuloendothelial system and endothelial cells. Intact IgG is also excreted in the bile with serum elimination half-life of 26 days. Mepolizumab monoclonal antibody ($IgG_1\kappa$) and the reslizumab monoclonal antibody ($IgG_4\kappa$) bind circulating IL-5, which is a key mediator of eosinophilic production, maturation, recruitment, survival, and activation.

Clinical Pharmacology

Pharmacokinetics, Pharmacodynamics, and Therapeutic Effects

Omalizumab is administered subcutaneously every 2 to 4 weeks based on serum IgE levels and body weight. Absorption is slow after subcutaneous injection with peak serum concentrations achieved at 7 to 8 days with 62% bioavailability. Serum free IgE levels are reduced within 1 hour of the initial dose of omalizumab. In addition to a reduction in serum free IgE levels, omalizumab reduces expression of high-affinity IgE receptors on inflammatory cells and reduces circulating numbers of eosinophils. The beneficial effects of omalizumab in patients with severe persistent asthma include improvements in the respiratory system and quality of life,[74] a reduction in emergency room visits,[75] and reduction in steroid use[76] and rescue asthma medications.

Mepolizumab is administered as a subcutaneous injection (100 mg) every 4 weeks in a monitored clinical setting because of uncommon but potentially serious adverse effects. Reslizumab (3 mg/kg) is administered as an intravenous infusion every 4 weeks over a period of 20 to 50 minutes.

Adverse Effects

A concern across this class of therapeutics is the need for parenteral administration and an incidence of anaphylaxis that requires their administration in a monitored health care setting. Anaphylaxis has been reported in 0.2% of patients receiving omalizumab occurring as early as the first dose and as late as 1 year after the initiation of therapy. Although concerns were raised about a small increase in malignant neoplasms and a case of lymphoma in early studies with omalizumab, subsequent review by independent oncologists reported no causal relationship between omalizumab and cancer development.[76] Fever, arthralgia, and rash sometimes accompanied by lymphadenopathy occur in some patients 1 to 5 days after omalizumab injections. Parasitic infections are more common in patients receiving omalizumab compared with controls.[77]

Hypersensitivity reactions have been reported with mepolizumab, presenting as anaphylaxis, angioedema, bronchospasm, hypotension, urticarial, or rash. Although these reactions typically occur within hours of administration, some reactions have occurred days after administration. More common reactions include headache and soreness at the site of injection. Anaphylaxis has been reported in 0.3% of patients receiving reslizumab, sometimes occurring as soon as the second injection.

Clinical Application

Common Applications

Omalizumab is used as adjuvant therapy in patients older than 6 years with severe persistent asthma who have elevated serum IgE levels and positive skin tests or in vitro reactivity to a seasonal aeroallergen when symptoms are not adequately controlled with an inhaled corticosteroid. Antibodies against IL-5 (mepolizumab and reslizumab) are indicated in patients with severe asthma using high-dose inhaled corticosteroids (defined as >880 µg fluticasone proprionate or equivalent) along with an additional therapies, and who have had two or more exacerbations in the past year and blood eosinophil counts higher than 150 cells/µL.

Anesthetic Agents as Bronchodilators

Most volatile anesthetics are potent bronchodilators,[78] yet the mechanism by which this occurs is unknown. With the exception of desflurane,[79,80] volatile anesthetics dose-dependently dilate bronchial airways and protect against reflex-induced bronchoconstriction during intubation in both patients with asthma and those with COPD.[81] The mechanism of direct airway smooth muscle relaxation by inhaled anesthetics includes reduction in Ca^{2+} sensitivity of contractile proteins[82] and interruption of G-protein coupling of procontractile receptor agonists (e.g., acetylcholine).[83]

The intravenous anesthetics vary in their ability to blunt bronchoconstriction induced by tracheal intubation. Historically ketamine was the induction drug of choice for patients with asthma due to its release of catecholamines with their effect on airway smooth muscle β_2 adrenoceptors. In the mid-1990s it was recognized that propofol is very protective against bronchoconstriction during intubation in both patients with asthma[84] and those with COPD[85] compared with thiobarbiturates or etomidate. A direct clinical comparison between propofol and ketamine for bronchoprotective effects has not been done. The mechanism of bronchoprotection afforded by intravenous anesthetics is incompletely understood but might include direct interaction of anesthetics with $GABA_A$ receptors expressed on airway smooth muscle.[86] Intravenous,[87] epidural,[88] and inhaled[89] local anesthetics have all been shown to inhibit histamine-induced bronchoconstriction.

Mucolytic Therapies

Structure-Activity

Inhaled mucolytics allow direct deposition of drugs to reduce mucus viscosity in pulmonary diseases, primarily cystic fibrosis (Table 30.4). Acetylcysteine by inhalation serves as a sulfhydryl donor to cleave disulfide bounds in mucus, reducing its viscosity. Acetylcysteine is also used orally as an antidote for acetaminophen overdose. Dornase alfa is recombinant human deoxyribonuclease I produced in cultured Chinese hamster ovary cells. The 37-kDa native human enzyme cleaves DNA from dead leukocytes, reducing the overall viscosity of pulmonary secretions.

TABLE 30.4 Mucolytics, Surfactants, and α^1-Proteinase Inhibitors

Mucolytics	Formulation	Mode of Action
Acetylcysteine	Mucomyst	Reduced viscosity of mucus by cleavage of disulfide bonds
Dornase alfa	Pulmozyme	Reduced viscosity of mucus by cleavage of leukocyte DNA
Surfactant Substitutes		
Poractant alfa	Curosurf	Reduced surface tension in alveolus
Calfactant	Infasurf	Reduced surface tension in alveolus
Beractant	Survanta	Reduced surface tension in alveolus
α_1-Proteinase Inhibitors	Aralast Glassia Prolastin-C Zemaira	Inhibit neutrophil elastase in α_1-proteinase inhibitor genetic deficiency, protecting protein components of alveolar wall

Mechanism and Metabolism

Respiratory mucins contain disulfide bonds that contribute to the structure of mature mucins and are the target of sulfhydryl donors such as acetylcysteine. Tenacious airway secretions of cystic fibrosis arise in part from dying and dead leukocytes responding to airway infection and inflammation. The DNA of these dying cells contributes to the viscosity of secretions and is the substrate for degradation by dornase alfa. Acetylcysteine is rapidly deactylated or oxidized in vivo to form cysteine or diacetylcysteine, respectively.

Clinical Pharmacology

Pharmacokinetics, Pharmacodynamics, and Therapeutic and Adverse Effects

Inhalation of dornase alfa in patients with cystic fibrosis results in measurable DNAse activity in sputum within 15 minutes. Inhalation of 10 mg of dornase alfa 3 times a day for 6 days does not raise serum DNAse levels above endogenous levels.[90] Inhaled acetylcysteine has been associated with stomatitis, bronchoconstriction, nausea, vomiting, fever, rhinorrhea, and drowsiness. Bronchoconstriction responds to bronchodilators,[91] but gas exchange can initially worsen owing to thin secretions traveling to more distal airways.[92] Acetylcysteine delivery through a bronchoscope or endotracheal tube should be followed by suctioning to prevent deterioration in gas exchange.[93]

Clinical Application

Common Clinical Applications

Inhaled acetylcysteine (by nebulization or direct tracheal instillation) is indicated for viscous, increased or inspissated secretions in patients with chronic COPD, tuberculosis, primary amyloidosis of the lung, or cystic fibrosis. Dornase alfa is effective in lowering the

viscosity of pulmonary secretions with high DNA content such as in cystic fibrosis. Twice-daily use of dornase alfa reduces the incidence of pulmonary infections requiring parenteral antibiotics by 29%.

Emerging Developments

Inhaler Propellants

The propellants in most inhalers were chlorofluorocarbons until an international agreement entitled The Montreal Protocol on Substances that Deplete the Ozone Layer led to a ban on this propellant and its replacement with HFAs. Substantial new technology was involved to make HFAs suitable for MDIs.[94] This provided the opportunity to improve the performance of inhaled β_2-agonist formulations and enhanced the ability of inhaled steroids to reach smaller peripheral airways.[95] Ultralong-acting β_2-adrenoceptor agonists (olodaterol[96] and sibenadet[97]) that achieve effective bronchodilation for 24 hours are in development. Clinical trials continue to determine whether the risks of LABAs are mitigated by the concurrent use of inhaled corticosteroids.[6]

Smoking Cessation

Although the topic is not traditionally a part of pulmonary pharmacology, perioperative smoking cessation therapy is an emerging part of anesthesia practice.[98] As part of a multidisciplinary team, anesthesiologists are increasingly participating in individualized efforts to promote smoking cessation in perioperative patients.[99] Often regarded as the single most preventable cause of premature death in industrialized societies, smoking is also a major underlying factor in excess postoperative morbidity and mortality.[100] Studies suggest that a coordinated smoking cessation program instituted perioperatively when patients are motivated about personal health can be effective in helping smokers to quit the habit.[101,102] Some advocate that anesthesiologists should play a lead role in this process.[103,104] This mandates that anesthesiologists must be conversant with drug and nondrug therapies applied to assist patients in smoking cessation. The anesthesiologist, as a perioperative physician, has the opportunity to participate in interventions that have long-term impacts on patients' pulmonary health. The stress of the perioperative period has been recognized as a "teachable moment," a time in the patient's life where they may be most receptive to advice regarding smoking cessation.[105]

Novel Therapies

It has long been recognized that clinical asthma is a mixture of disease phenotypes such that a variety of mechanisms may lead to airway hyperresponsiveness.[106] Future pharmacologic therapy will undoubtedly make use of better phenotypic and genotypic characterization in individual patients. This may allow more directed therapy, particularly in the area of antiinflammatory therapies where nonspecific steroid approaches may be replaced by targeting specific immunomodulatory mediators such as elevated IgE (e.g., omalizumab) or specific interleukins (e.g., IL-13).[107,108]

A nonpharmacologic therapy directed at airway smooth muscle hyperresponsiveness is bronchial thermoplasty. The belief is that eliminating airway smooth muscle from mid-sized airways by heat destruction will improve asthma symptoms. This invasive procedure requires repeated bronchoscopies and has resulted in some short-term pulmonary complications, but long-term improvements in the use of rescue medications, prebronchodilator FEV_1, and quality-of-life measurements.[109] A blinded randomized trial reported an improvement in scores on an asthma quality-of-life questionnaire, but no statistical change in several secondary effectiveness endpoints, including FEV_1 (before or after bronchodilator), symptom-free days, or rescue medication use.[110] A randomized controlled trial demonstrated an improvement in asthma-specific quality of life with a reduction in severe exacerbations and emergency room visits.[111,112]

Key Points

- Inhaled corticosteroids are the preferred initial therapy for the management of asthma.
- Use of long-acting β_2-adrenoceptor agonists has been associated with increased risk of asthma-related death.
- Anticholinergics block acetylcholine released from parasympathetic nerves acting on muscarinic receptors on airway smooth muscle. Anticholinergics are more efficacious in chronic obstructive lung disease than in asthma.
- Tracheal intubation or suctioning can induce reflex-induced bronchoconstriction via a reflex arc that can be blocked at different levels by local anesthetics, intravenous anesthetics, or volatile anesthetics.
- Propofol is the preferred intravenous anesthetic for induction in patients with asthma or chronic obstructive lung disease.
- Volatile anesthetics, with the exception of desflurane, are potent bronchodilators.
- Personalized therapy for asthma is evolving with the introduction of monoclonal antibodies directed against IgE or interleukin 5.

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controversy and planned clinical trials to assess the safety of using long-acting β_2-adrenoceptor agonists as combined therapy with inhaled corticosteroids. (Ref. 6).

Chu EK, Drazen JM. Asthma: one hundred years of treatment and onward. *Am J Respir Crit Care Med*. 2005;171:1202–1208. This historical review summarizes the origins of pharmacologic therapy for hyperreactive airway disease. (Ref. 32).

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Lazarus SC. Clinical practice. Emergency treatment of asthma. *N Engl J Med*. 2010;363:755–764. This publication describes the current recommended therapy for treating acute bronchospasm in the emergency room, which is applicable to other acute care settings such as the operating room and intensive care unit. (Ref. 27).

Pizov R, Brown RH, Weiss YS, et al. Wheezing during induction of general anesthesia in patients with and without asthma: a randomized blinded trial. *Anesthesiology*. 1995;82:1111–1116. This publication established propofol as the preferred intravenous anesthetic for anesthetic induction in asthmatics. (Ref. 84).

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31

Liver and Gastrointestinal Physiology

RANDOLPH H. STEADMAN, MICHELLE BRAUNFELD, AND HAHNNAH PARK

CHAPTER OUTLINE

Liver
- Anatomy
- Blood Supply
- Liver Function
  - *Storage*
  - *Filtering and Cleansing*
  - *Metabolism of Nutrients*
  - *Synthesis of Coagulation Factors*
  - *Bile Secretion*
- Bilirubin and Jaundice
- Liver Regeneration
- Portal Hypertension
- Hepatic Drug Metabolism and Excretion
- Anesthetic Pharmacology and the Liver
- Liver Disease: Etiologies and Severity
- Cirrhosis and Perioperative Risk: Nonhepatic Surgery
- Hepatic Surgery

Gastrointestinal Tract
- Anatomy
- Properties of the Gastrointestinal Tract
- Respiration and Pharyngeal Swallowing
- Lower Esophageal Sphincter
- Neural Control
  - *Enteric Nervous System*
  - *Parasympathetic Stimulation*
  - *Sympathetic Stimulation*
- Hormonal Control
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  - *Gastric Secretions*
  - *Pancreatic Digestive Enzymes*
  - *Bicarbonate*
- Absorption of Nutrients
  - *Glucose*
  - *Fats*
- Gastrointestinal Disorders
- Anesthetic Pharmacology and the Gastrointestinal Tract

Emerging Developments
- Tissue Engineering

In perioperative management, the hepatic and gastrointestinal (GI) systems usually receive consideration after the cardiovascular and respiratory systems. However, potential perioperative problems such as aspiration, ileus, and nausea and vomiting are common and significant. Additionally, end-stage liver disease—often associated with multisystem organ failure—can be life threatening. It is incumbent in anesthesiology to understand the physiologic basis of these conditions to minimize associated complications and optimize patient outcomes.

Liver

The liver weighs approximately 1.5 kg, or about 2% of total body weight in an adult. Functionally, the liver metabolizes carbohydrates, proteins, fats, hormones, and foreign substances. In addition, it filters and stores blood; stores vitamins, glycogen, and iron; and produces bile and blood coagulation factors.

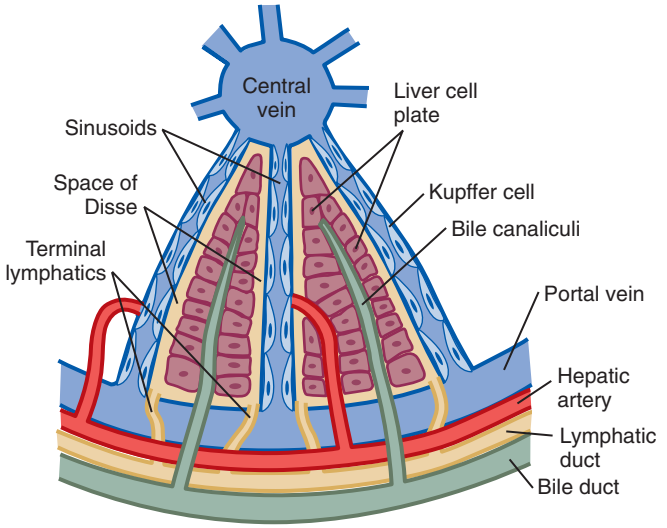
Anatomy

The functional unit of the liver is the lobule, or liver acinus, a structure roughly 1 × 2 mm that consists of plates of hepatocytes located in a radial distribution about a central vein (Fig. 31.1). Bile canaliculi are located between the plates and collect bile formed in the hepatocytes. The canaliculi drain into bile ducts located at the periphery of the lobule next to portal venules and hepatic arterioles. The bile ducts join to form the common hepatic duct. The cystic duct from the gallbladder and the pancreatic duct join the common hepatic duct before entering the duodenum. The sphincter of Oddi controls the flow of bile into the small intestine.[1,2]

Portal venules empty blood from the GI tract into the hepatic sinusoids, the space between the plates of hepatocytes that serve as the capillaries of the liver. Hepatic arterioles supply well-oxygenated blood to the septa located between the plates of hepatocytes and the sinusoids. The liver typically contains between 50,000 and 100,000 lobules.

The large pores of endothelium lining the sinusoids allow plasma and its proteins to move readily into the tissue spaces surrounding hepatocytes, an area known as the space of Disse, or perisinusoidal spaces. This fluid drains into the lymphatic system. The liver is responsible for generating about half of the lymph.

Macroscopically the liver is divided unequally into right and left lobes by the falciform ligament (Fig. 31.2A). More recently a segmental, or surgical, anatomy has been described, known as the



• **Fig. 31.1** The structure of the liver lobule, or acinus. Hepatocytes radiate outward from the central vein. Blood enters the lobule from the periphery via the portal vein and hepatic artery and then flows by the plates of hepatocytes before entering the central vein. Bile flows in the opposite direction.

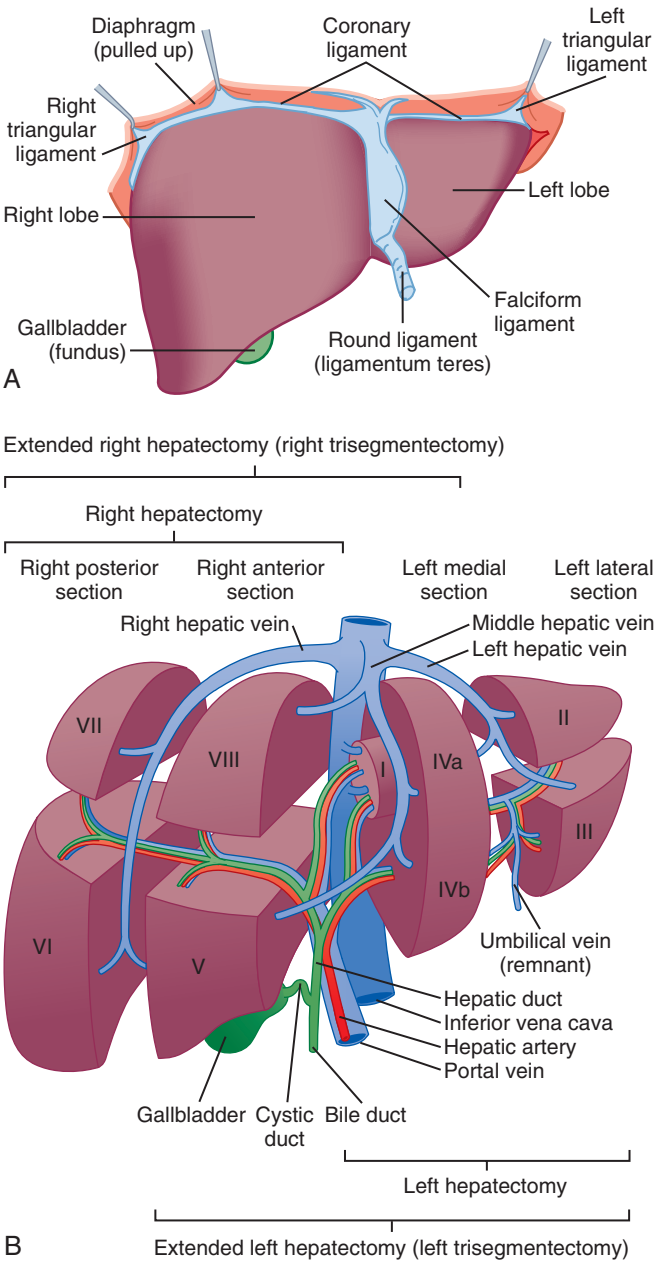
Couinaud classification. The liver is divided into eight segments based on the anatomy of the portal and hepatic veins (Fig. 31.2B).

Blood Supply

The liver receives almost 25% of cardiac output via a dual supply. The portal venules conduct blood from the portal vein that drains the GI tract. The portal vein supplies 75% of liver blood flow, about 1 L/min. The hepatic arterioles supply 25% of blood flow. Each system contributes about 50% of hepatic oxygen supply (Fig. 31.3).

The high hepatic blood flow is due to low vascular resistance in the portal vein. The average portal vein pressure is 9 mm Hg, whereas hepatic venous pressure averages 0 mm Hg for a 9-mm Hg perfusion pressure gradient. However, when hepatocytes are injured and replaced by fibrous tissues, blood flow is impeded, resulting in portal hypertension, the hallmark of cirrhosis. Sinusoidal pressures greater than 5 mm Hg are abnormal and define portal hypertension (see later text).[3] Sympathetic innervation from T3 to T11 controls resistance in the hepatic venules. Changes in compliance in the hepatic venous system help regulate cardiac output and blood volume. In the presence of reduced portal venous flow, the hepatic artery can increase flow by as much as 100% to maintain hepatic oxygen delivery. The reciprocal relationship between flow in the two afferent vessels is termed the *hepatic arterial buffer response*.[4]

The microcirculation of the liver lobule is divided into three zones that receive varying oxygen content.[5] Zone 1 receives oxygen-rich blood from the adjacent portal vein and hepatic artery. As blood moves through the sinusoid, it passes from the intermediate zone 2 into zone 3, which surrounds the central vein. Zone 3 receives blood that has passed through zones 1 and 2, reducing the oxygen content. Pericentral hepatocytes have a greater quantity of cytochrome P450 (CYP) enzymes and are the site of anaerobic metabolism. Hypoxia and reactive metabolic intermediates from biotransformation affect this zone more prominently than other zones.



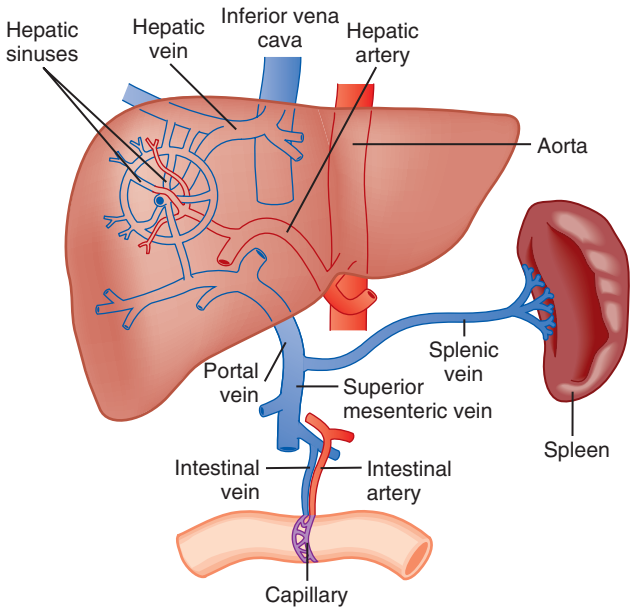
• **Fig. 31.2** Liver anatomy. A, Surface anatomy of the liver depicting the right and left lobes, separated by the falciform ligament. B, The Couinaud segments of the liver and the accompanying vascular structures. The segments resected during various partial hepatectomies are illustrated.

Volatile anesthetics decrease hepatic blood flow; however, newer agents (isoflurane, desflurane, and sevoflurane) reduce flow less than older agents such as halothane.[6,7]

Liver Function

Storage

Owing to its ability to distend, the liver is capable of storing up to 1 L of blood. Thus the liver serves as a reservoir capable of accepting blood, as in the presence of heart failure, or releasing blood at times of low blood volume. The liver also stores vitamins, particularly vitamins B_{12} (1-year supply), D (3-month supply), and A (10-month supply). Excess body iron is transported via



• **Fig. 31.3** The splanchnic circulation.

apoferritin to the liver for storage as ferritin, which is released when circulating iron levels are low. Thus the liver apoferritin system serves for iron storage and as a blood iron buffer.

Filtering and Cleansing

Kupffer cells, a type of reticuloendothelial cell, line the venous sinusoids. Kupffer cells are macrophages that phagocytize bacteria that enter the sinusoids from the intestines. Less than 1% of bacteria that enter the liver pass through to the systemic circulation.

Metabolism of Nutrients

The liver is involved in energy production and storage from nutrients absorbed from the intestines. The liver helps regulate blood glucose concentrations through its glucose buffer function. This is accomplished by storing glucose as glycogen, converting other carbohydrates (principally fructose and galactose) to glucose, and synthesizing glucose from glucogenic amino acids and from glycerol derived from triglycerides (gluconeogenesis).[8] In patients with altered liver function, glucose loads are poorly tolerated, and blood glucose concentration can rise severalfold higher than postprandial levels found in patients with normal hepatic function.

The liver synthesizes fat, cholesterol, phospholipids, and lipoproteins. It also metabolizes fat efficiently, converting fatty acids to acetyl coenzyme A (CoA), an excellent energy source. Some of the acetyl-CoA enters the citric acid cycle to liberate energy for the liver. The liver generates more acetyl-CoA than it consumes, so it packages the excess as acetoacetic acid for use by the rest of the body via the citric acid cycle. The majority of cholesterol synthesized in the liver is converted to bile salts and secreted in the bile. The remainder is distributed to the rest of the body where it is used to form cellular membranes. Fat synthesis from protein and carbohydrates occurs almost exclusively in the liver, and the liver is responsible for most fat metabolism.

The liver also plays a key role in protein metabolism. The liver synthesizes all of the plasma proteins with the exception of gamma globulins, which are formed in plasma cells. The liver is capable of forming 15 to 50 g of protein per day, an amount sufficient to replace the body's entire supply of proteins in several weeks. Albumin is the major protein synthesized by the liver and is the primary determinant of plasma oncotic pressure. The liver also synthesizes the nonessential amino acids from ketoacids, which it also synthesizes.

The liver can deaminate amino acids, a process required before their use for energy production or conversion to carbohydrates or fats. Deamination results in the formation of ammonia, which is toxic. Intestinal bacteria are an additional source of ammonia. The liver is responsible for the removal of ammonia through the formation of urea.

Synthesis of Coagulation Factors

Blood clotting factors, except factors III (tissue thromboplastin), IV (calcium), and VIII (von Willebrand factor), are synthesized in the liver. Vitamin K is required for the synthesis of the calcium ion (Ca^{2+})-binding proteins prothrombin (factor II) and factors VII, IX, and X (see Chapter 43).

Bile Secretion

Hepatocytes produce roughly 500 mL of bile daily. Between meals the high pressure in the sphincter of Oddi diverts bile to the gallbladder for storage (Fig. 31.4). The gallbladder holds 35 to 50 mL of bile in concentrated form. The presence of fat in the duodenum causes release of the hormone cholecystokinin from duodenal mucosa, which reaches the gallbladder via the circulation and stimulates gallbladder contraction. Bile contains bile salts, bilirubin, and cholesterol. Bile salts serve as a detergent, solubilizing fat into complexes called micelles, which are absorbed. Bile salts are returned to the liver via the portal vein, completing the enterohepatic circulation. Bile salts are needed for fat absorption, and cholestasis can result in steatorrhea and vitamin K deficiency.

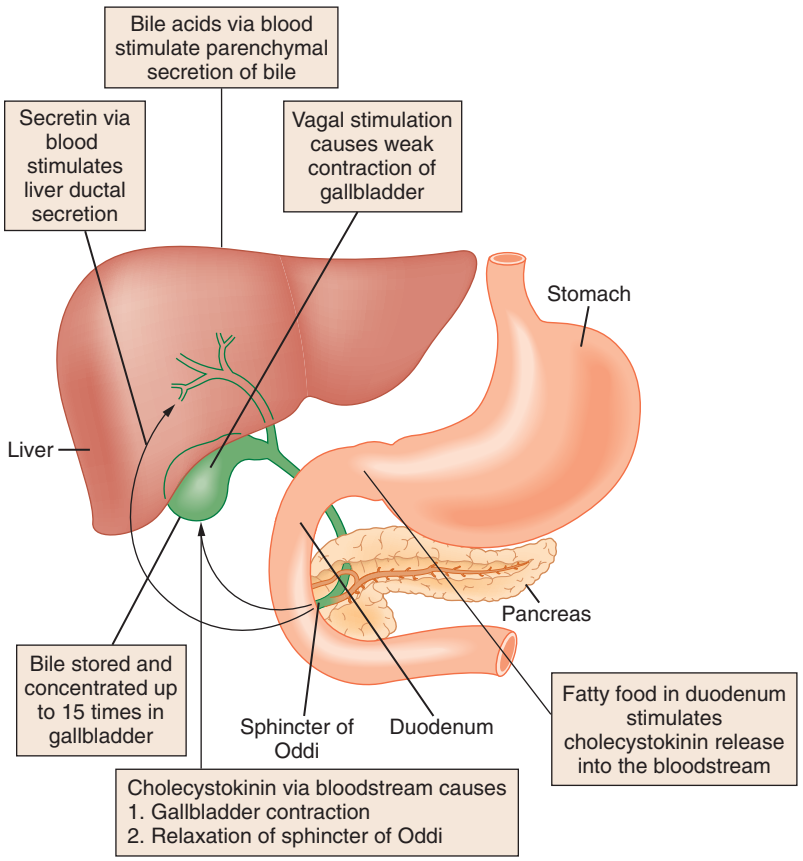
Bilirubin and Jaundice

Bilirubin is the major end product of hemoglobin breakdown, which occurs when red blood cells reach the end of their 120-day life span. After phagocytosis by reticuloendothelial cells, hemoglobin is split into globin and heme. The heme releases iron and a four-pyrrole nucleus that forms biliverdin, which is converted to free, or unconjugated, bilirubin. Unconjugated bilirubin is conjugated in the liver, primarily with glucuronic acid, before it is secreted into bile for transport to the intestines. In the intestines, a portion of conjugated bilirubin is converted to urobilinogen by bacteria. Some urobilinogen is reabsorbed from the intestines into the blood, but most is excreted back into the intestines. A small amount is excreted into urine as urobilin. Urobilinogen that remains in the intestines is oxidized to stercobilin and excreted in feces.

Jaundice is the yellow-green tint of body tissues that results from bilirubin accumulation in extracellular fluid. Skin discoloration is usually visible when plasma bilirubin reaches three times normal values. Bilirubin accumulation can occur as the result of increased breakdown of hemoglobin (hemolysis) or obstruction of bile ducts. Hemolytic jaundice is associated with an increase in unconjugated (indirect) bilirubin, whereas obstructive jaundice is associated with increases in conjugated (direct) bilirubin.[9]

Liver Regeneration

The liver has the unique ability to restore itself after injury or partial hepatectomy. As much as two-thirds of the liver can be removed with regeneration of the remaining liver in a matter of



• **Fig. 31.4** Neural and hormonal factors that regulate bile secretion.

weeks.[10] Control over this process is not completely understood, but hepatocyte growth factor, produced by mesenchymal cells in the liver, is involved. Other growth factors, such as epidermal growth factor and cytokines, tumor necrosis factor, and interleukin (IL)-6 can also stimulate regeneration. The mechanism responsible for returning the liver to a quiescent state might involve transforming growth factor β, a known inhibitor of hepatocyte proliferation. The signal for cessation of regeneration appears to be related to the ratio of liver to body weight.[10,11] In the presence of inflammation, as with viral hepatitis, regeneration is significantly impaired.

Portal Hypertension

Ongoing inflammation results in fibrosis that constricts blood flow in the sinusoids, creating increased portal pressures. Portal hypertension is formally diagnosed by measurement of the hepatic venous gradient (HVG), defined as the difference between hepatic venous and portal venous pressures. Because direct measurement of portal venous pressures is not easily accomplished, it is estimated by the wedge pressure of the hepatic veins as measured by a balloon catheter introduced into (typically) the right hepatic vein. The difference between that wedge pressure and the free pressure in the hepatic vein is the HVG, normally 1 to 5 mm Hg. Subclinical portal hypertension appears when the HVG rises to 6 to 9 mm Hg. When HVG reaches 10 to 12 mm Hg, portal hypertension becomes a systemic condition affecting hemodynamics, fluid balance, renal function, and cognition.[12]

Resistance to portal blood flow causes collateral vessels to develop between portal and systemic veins. With increased pressure in the splenic vein, collateral vessels to esophageal veins develop. These enlarge and protrude into the esophageal lumen, producing esophageal varices. Variceal size and HVG predict both the likelihood of rupture and ability to control variceal bleeding and rebleeding.[13] Within 2 years of diagnosis of portal hypertension, approximately 30% of patients have a variceal hemorrhage.[14] The 6-week mortality after variceal hemorrhage is 30%, which increases to 50% with a second episode of bleeding. Prophylaxis to prevent bleeding includes nonselective β blockers, long-acting nitrates, endoscopic obliteration, and endoscopic ligation.[15]

Portal hypertension results in portosystemic shunting. Shunted blood circumvents the filtering system of the liver. This results in the entry of drugs, ammonia, and other toxins normally handled by the liver into the systemic circulation; hepatic encephalopathy often ensues.[16] Splanchnic vasodilatation reduces renal perfusion, resulting in renal failure (hepatorenal syndrome). During the early stages of acute renal injury the kidneys can be functionally normal and the changes reversible. In the absence of improvement in liver function, renal injury can become permanent.[17]

Systemic vasodilatation leads to hyperdynamic circulation characterized by low normal blood pressure, low systemic vascular resistance, and high cardiac output. Response to vasoconstrictors is often attenuated owing to endogenous vasodilators, an ineffective splanchnic reservoir, and increased sympathetic tone.[18]

Hepatic Drug Metabolism and Excretion

The liver metabolizes and excretes many drugs into the bile. The liver is also responsible for metabolism of a number of hormones, including thyroxine and the steroids estrogen, cortisol, and aldosterone.

Intrinsic hepatic clearance of a compound divided by the hepatic blood flow determines the extraction ratio. The extraction ratio indicates the efficiency with which various drugs are cleared. Efficiently extracted drugs include many opioids, β blockers (except atenolol), calcium channel blockers, and tricyclic antidepressants. Poorly extracted drugs include warfarin, aspirin, ethanol, and phenobarbital. Elimination of poorly extracted drugs is limited by intrinsic clearance and/or protein binding rather than hepatic blood flow, whereas elimination of highly extracted drugs is dependent on blood flow (see Chapter 4).

Anesthetic Pharmacology and the Liver

Volatile anesthetic agents decrease hepatic blood flow. Agents currently in use—isoflurane, sevoflurane, and desflurane—affect hepatic blood flow less than older agents. Despite reductions in hepatic blood flow, liver function testing fails to show alterations of hepatic function after administration of current inhaled anesthetics.[19,20] Fewer data exist on the effects of inhaled anesthetics on patients with chronic liver disease. Central neuraxial blockade decreases hepatic blood flow proportionally to the decrease in systemic blood pressure. Hepatic blood flow can be restored by administration of vasopressors.

Hepatic dysfunction affects the pharmacokinetics of intravenous anesthetics through alterations in protein binding (as the result of reduced plasma proteins), increases in the volume of distribution, and reductions in hepatic metabolism.[21,22] The pharmacodynamic effects of opioids and sedatives can be enhanced in patients with end-stage liver failure who have encephalopathy. Although opioids have been used successfully to treat biliary colic, they can also produce spasm of the sphincter of Oddi.[23] Glucagon, opioid antagonists, nitroglycerin, and atropine reverse this effect. Intermediate-duration neuromuscular blocking agents that undergo hepatic elimination have a prolonged duration of action in the presence of liver disease. Atracurium and cisatracurium are not dependent on hepatic elimination, so dosing alterations are not required in patients with hepatic disease (see Chapter 22).

Liver Disease: Etiologies and Severity

The most common causes of hepatic cirrhosis are hepatitis C, alcoholic liver disease, and nonalcoholic fatty liver disease. Other causes include biliary cirrhosis, autoimmune disease, hemochromatosis, drug-induced liver disease, metabolic disorders, and hepatocellular cancer.[24] Biliary cirrhosis is associated with several forms of cholestatic disease, including primary biliary cirrhosis, sclerosing cholangitis, and biliary atresia. Nonalcoholic fatty liver disease (also called steatohepatitis), an increasingly recognized cause, is associated with obesity, type 2 diabetes mellitus, and the constellation of risk factors known as the metabolic syndrome.[25] The severity of cirrhosis can be graded using the Child-Turcotte-Pugh (CTP) scoring system (Table 31.1).[26] Patients with the most severe disease have a CTP score of 10 points or more (class C). These patients have exceedingly high perioperative mortality (up to 75%).[27] Class B (7–9 points) patients also have significant perioperative mortality (30%). Preoperative risk modification, through treatment of encephalopathy and ascites, appears to reduce risk.[28]

An alternative mortality risk stratification for patients with liver disease undergoing nonhepatic surgery is the Model for End-Stage Liver Disease (MELD) score. The MELD score was developed to predict 90-day mortality in patients undergoing transjugular intrahepatic portosystemic shunt procedures.[29] It has since been validated for risk stratification of patients with liver disease in a number of different settings, including patients awaiting liver transplantation. The MELD score is used to allocate donor grafts to liver transplant candidates with the greatest urgency (highest predicted 90-day mortality).[30] It is calculated as follows: MELD = 3.78 × ln bilirubin (mg/dL) + 11.2 × ln INR + 9.57 × ln creatinine (in milligrams per deciliter) + 6.43, where ln INR is the natural logarithm and INR is the international normalized ratio. In January 2016, serum sodium (Na) was added to the MELD score to account for the impact of hyponatremia on wait list mortality, particularly at lower MELD scores.[31] The resulting formula is MELD-Na = MELD + 1.32 × (137 − Na) − [0.033 × MELD × (137 − Na)].[32] Online calculators are convenient and commonly used to ascertain the MELD score.[33]

TABLE 31.1 Modified Child-Turcotte-Pugh Scoring System[a]

Parameters	1 Point	2 Points	3 Points
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4–6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3
Bilirubin (mg/dL)[b]	<2	2-3	>3
Ascites	Absent	Slight-moderate	Tense
Encephalopathy	None	Grade I-II	Grade III-IV

[a]Class A = 5.6 points, B = 7 to 9 points, and C = 10 to 15 points.
[b]For cholestatic diseases (e.g., primarily biliary cirrhosis), the bilirubin level is disproportionate to the impairment in hepatic function and an allowance should be made. For these conditions, assign 1 point for a bilirubin level less than 4 mg/dL, 2 points for a bilirubin level of 4 to 10 mg/dL, and 3 points for a bilirubin level more than 10 mg/dL.
Modified from Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60:646–649.

Cirrhosis and Perioperative Risk: Nonhepatic Surgery

Patients with cirrhosis frequently require nonhepatic surgery for abdominal wall hernias, peptic ulcer disease, biliary, small bowel, colon and pancreatic disease, in addition to cardiac, vascular and orthopedic surgery. In the perioperative period cirrhosis can decompensate owing to the effects of surgery and anesthesia, which results in decreased hepatic blood flow and an increased risk of bacterial infection.[34] Risk factors for perioperative mortality and morbidity include the severity of liver disease as determined by the CTP or MELD score, and the anatomic location of procedure, with upper abdominal surgery associated with considerable risk.

A pioneering study included 140 peripheral, intraabdominal, and intrathoracic procedures in 131 patients whose MELD scores ranged from 6 to 43. Overall 30-day mortality was 16%, which correlated with MELD score and was confined to nonperipheral procedures.[35] Abdominal surgery carries more risk than nonabdominal surgery owing to significant reductions in hepatic blood flow.[35,36] A more recent study, which included 138 patients with cirrhosis undergoing general surgical procedures, found an overall hospital mortality of 28%. As in other series, mortality was stratified by CTP group, with mortality highest in CTP class C patients.[37]

Laparoscopic surgery, which is controversial because of the requirement for pneumoperitoneum, appears to reduce perioperative risk.[38]

Hepatic Surgery

Hepatic resection surgery, most commonly for hepatocellular carcinoma and metastatic cancer, evolved over the past several decades of the 20th century. In a single-center series, the overall mortality was 4%, although subgroups with cirrhosis and biliary obstruction had higher mortality (9% and 21%, respectively).[39] This improvement in survival after hepatic resection is attributed to a number of factors, including improved patient selection, volumetric studies designed to assess predicted remnant liver mass, portal vein embolization (to decrease the mass of resected tissue and stimulate regeneration of the liver remnant), and use of intraoperative ultrasound to delineate vascular anatomy and the extent of pathology.[40] Additionally, the success of liver transplantation, with a 5-year patient survival of 73%, has given rise to a generation of hepatobiliary surgeons skilled in liver resection.[41] Since 2000, perioperative mortality for hepatic resection has not seen further reductions, remaining at about 3%, because of expanded indications for surgery in a patient population that is older and more likely to have cirrhosis.[42]

Liver transplantation is recognized as definitive management for patients with acute and chronic liver failure. The liver is the second most commonly transplanted organ, after the kidney. Anesthetic management for patients undergoing liver transplantation is challenging because of unpredictable, sometimes massive, blood loss; coagulation abnormalities; electrolyte and acid-base disturbances; and hemodynamic, pulmonary, renal, neurologic, and infectious derangements.[43]

Gastrointestinal Tract

The GI, or alimentary, tract provides the body with substrates for energy needs and essential nutrients through food digestion and absorption. Water, electrolytes, vitamins, and nutrients are supplied to the body via the exclusive function of the GI tract. Control of the process requires local, nervous system, and hormonal input.

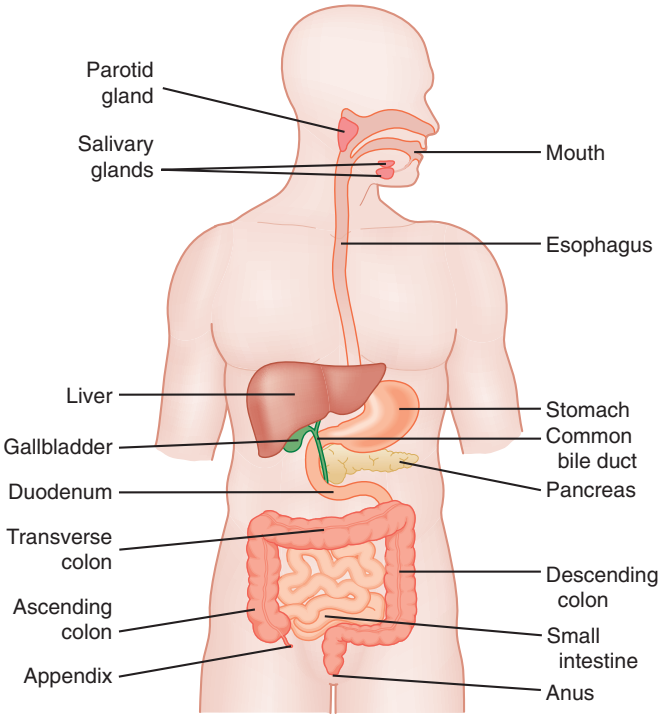
Anatomy

The anatomy of the digestive tract consists of one continuous tube connected with the external environment. It is separated into distinct sections, each adapted to specialized functions (Fig. 31.5). A typical cross section of the gut consists of multiple layers (Fig. 31.6). Moving from the outside to within, the gut is made up of the serosa, a longitudinal muscle layer, a circular muscle layer, submucosa, and mucosa. The enteric nervous system plexuses lie within the gut layers. As a barrier to the external environment, an epithelial layer lines the innermost portion of the gut.

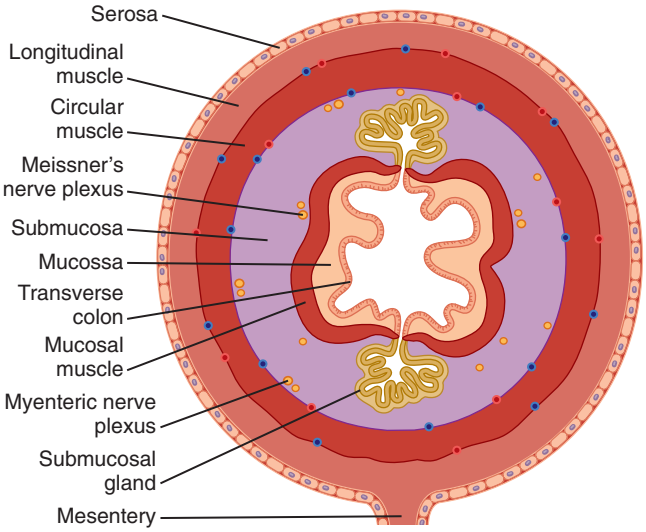
Properties of the Gastrointestinal Tract

Food moves forward in the alimentary tract by peristalsis. This movement consists of a contractile ring that encircles the gut, moving solids and liquids in front of the contractile ring forward. Peristalsis is stimulated by distention of the gut, chemical or physical irritation of the epithelial lining in the gut, and strong parasympathetic nerve signals.[44]

Chyme is a semifluid mixture consisting of a mixture of food and stomach secretions. In the stomach and when initially expelled from the stomach, chyme is highly acidic with a pH of around 2.



• **Fig. 31.5** The alimentary tract.



• **Fig. 31.6** A cross section of the intestines.

In the duodenum, pancreatic secretions of bicarbonate help to raise its pH (see later text).

Respiration and Pharyngeal Swallowing

Swallowing occurs as a negligible interruption of about 6 seconds to the respiratory cycle. Even while talking, the act of swallowing is so rapid that it poses no threat to respiration.

Lower Esophageal Sphincter

Located between the esophagus and stomach, the smooth muscle of the lower esophageal sphincter, also known as the *gastroesophageal*

sphincter or *cardiac sphincter*, remains constricted with an intraluminal pressure of about 30 mm Hg, whereas the higher portions of the esophagus remain normally relaxed.[45] Tonic constriction prevents the reflux of acidic stomach contents. Initiated by swallowing, a peristaltic wave helps coordinate the passage of food into the stomach, causing a "receptive relaxation" of the lower esophageal sphincter. Esophageal reflux is prevented by the valvelike mechanism of the distal end of the esophagus, which resists reflux of stomach contents as a result of high intraabdominal pressure.

Achalasia is a disorder in which the lower esophageal sphincter loses the ability to relax in response to swallowing. The esophagus distends, which can lead to chronic regurgitation and aspiration. Another disorder that can lead to reflux is Zenker's diverticulum, a weakness at the junction of the thyropharyngeus and cricopharyngeus muscles in the hypopharynx.

Neural Control

Enteric Nervous System

Important in controlling GI movement and secretion, the enteric nervous system is composed of an outer plexus (myenteric or Auerbach's plexus) and an inner submucosal plexus (Meissner's plexus). The outer plexus lies between the longitudinal and circular muscle layers of the gut and exerts main control over GI movements (see Fig. 31.6). The inner plexus is the main control for GI secretion and local blood flow.

The myenteric plexus extends throughout the entire length of the gut as a linear chain of interconnected neurons. Lying within intestinal smooth muscle, the myenteric plexus focuses on muscle control. Upon stimulation, the plexus causes an increase in gut wall tone and in intensity of rhythmical contractions. Although it is associated mostly with excitatory muscle activity, there is also an inhibitory function of the myenteric plexus. Possibly through secretion of vasoactive intestinal polypeptide (or some other inhibitory peptide), the myenteric plexus can inhibit intestinal sphincter muscles such as the pyloric sphincter and the ileocecal valve, which normally impede the movement of gut contents.[46] As a part of the inner wall, the submucosal plexus focuses on controlling local muscle intestinal secretion, local absorption, and local contraction.

Parasympathetic Stimulation

The cranial and sacral division of the parasympathetic system stimulates activity of the enteric nervous system. The cranial parasympathetic nerves originate almost entirely in the vagus nerves; however, some also exist at the mouth and pharyngeal regions of the tract. These nerves innervate the esophagus, stomach, pancreas, and a part of the intestines.[45]

The sacral parasympathetic nerves run from the second through fourth sacral segments of the spinal cord (S2-S4) and pass through to the distal half of the large intestine to end in the anus. Concerned mainly with defecation reflexes, these fibers supply the sigmoidal, rectal, and anal regions of the GI tract.[47,48]

Sympathetic Stimulation

The sympathetic innervation of the GI tract originates in segments T5 to L2 of the spinal cord. Preganglionic fibers pass from the spinal column to the sympathetic chains. From the chains, sympathetic nerve fibers enter various outlying sympathetic ganglia such as the celiac ganglia and other mesenteric ganglia. These ganglia relay sympathetic stimulation via postganglionic fibers to all parts of the gut by releasing mainly norepinephrine and a smaller amount of epinephrine (see Chapter 13).

In contrast to the parasympathetic system, the sympathetic nervous system primarily inhibits GI tract activity. The strength of stimulation is proportional to the amount of secreted norepinephrine, which causes a range of inhibition from slight to very strong inhibition capable of causing a cessation of movement.[47,48] Hence, patients undergoing emergency surgery should be considered at risk for aspiration of stomach contents.

Hormonal Control

GI hormones are important for the physiologic control of gut motility. Key hormones, along with their stimuli, site of secretion, and actions, are listed in Table 31.2.

Splanchnic Circulation

The blood supply of the GI system is a part of an extensive system called the *splanchnic circulation.* This system supplies and drains multiple organs, including the gut, spleen, pancreas, and liver. The arterial supply includes the celiac, superior mesenteric, and inferior mesenteric arteries. Venous drainage of the visceral organs occurs via the splenic, superior mesenteric, and inferior mesenteric veins. Splanchnic blood reaches the liver via the portal vein, which is a confluence of the splenic and superior mesenteric veins.

Stomach Emptying

The rate of stomach emptying varies depending on the signals from the stomach and the duodenum. The duodenum is the primary regulator of the rate at which chyme enters the small intestine.

Enterogastric Nervous Reflex

The enterogastric nervous reflex of the duodenum inhibits stomach emptying. Food entering the duodenum elicits various nervous reflexes that regulate the rate of stomach emptying. Factors initiating this reflex include (1) duodenal distention, (2) irritation of duodenal mucosa, (3) acidity of chyme, (4) osmolality of chyme, and (5) presence of certain breakdown products in chyme.[45]

Three parallel nerve circuits control stomach emptying: the gut enteric nervous system from the duodenum to the stomach; extrinsic nerves that travel to the prevertebral sympathetic ganglia and return to the stomach by the inhibitory sympathetic nerve fibers; and the vagus nerves to the brain that inhibit excitatory signals sent to the stomach. Altogether, these affect stomach emptying by inhibiting the propulsive contractions of the pyloric pump and by increasing the tone of the pyloric sphincter.[49]

The association between abdominal mesenteric manipulation and cardiovascular perturbations is well established.[50,51] The proposed mechanism is afferent sympathetic stimulation from mesenteric traction, resulting in systemic vasodilation that provokes a compensatory increase in cardiac output.[51] Although bradycardia is frequently invoked as part of this response, the change in heart rate is variable. The existence of a reflex arc has been suggested in which stimulation of the celiac plexus results in inhibition of sympathetic activity, leading to increased vagal tone and bradycardia. However, bradycardia in response to mesenteric traction has not been consistently demonstrated in controlled studies.

TABLE 31.2 Key Gastrointestinal Hormones

Hormone	Stimuli for Secretion	Site of Secretion	Action
Gastrin	Protein Distention Nerve (Acid inhibits release)	G cells of the antrum, duodenum, and jejunum	Stimulates Gastric acid secretion Mucosal growth
Cholecystokinin	Protein Fat Acid	I cells of the duodenum, jejunum, and ileum	Stimulates Pancreatic enzyme secretion Pancreatic bicarbonate secretion Gallbladder contraction Growth of exocrine pancreas Inhibits Gastric emptying (stomach contraction) Appetite
Secretin	Acid Fat	S cells of the duodenum, jejunum, and ileum	Stimulates Pepsin secretion Pancreatic bicarbonate secretion Biliary bicarbonate secretion Growth of exocrine pancreas Inhibits Gastric acid secretion
Gastric inhibitory peptide	Protein Fat Carbohydrates	K cells of the duodenum and jejunum	Stimulates Insulin release Inhibits Gastric acids secretion Gastric motility
Motilin	Fat Acid Nerve	M cells of the duodenum and jejunum	Stimulates Gastric motility Intestinal motility

Modified1from Hall JE. *Guyton and Hall Textbook of Medical Physiology.* 12th ed. Philadelphia: Saunders Elsevier; 2011.

Secretory Functions

The secretory function of the digestive glands is highly specialized to correspond with the food type and amount of food present in the gut. Secretions consist of digestive enzymes for the breakdown of food and mucus for the protection and lubrication of the GI tract. Estimated amounts and pH of daily secretions are listed in Table 31.3.

Autonomic Stimulation

The parasympathetic nervous system stimulates an increase in alimentary glandular secretion. The glossopharyngeal and vagus parasympathetic nerves innervate glands of the upper tract; these include the salivary glands, esophageal glands, gastric glands, pancreas, and Brunner's glands in the duodenum. Glands in the large intestine also receive parasympathetic innervation. Other glands of the gut secrete in response to local neural and hormonal stimuli rather than as a result of nerve innervation.

Sympathetic stimulation to alimentary tract glandular secretion is less straightforward than parasympathetic stimulation. Sympathetic stimulation has a dual effect, causing a slight increase in glandular secretion if stimulated alone, but with preexisting parasympathetic or hormonal stimulation, sympathetic stimulation reduces secretions. This results from vasoconstriction of blood vessels that supply the glands.[52]

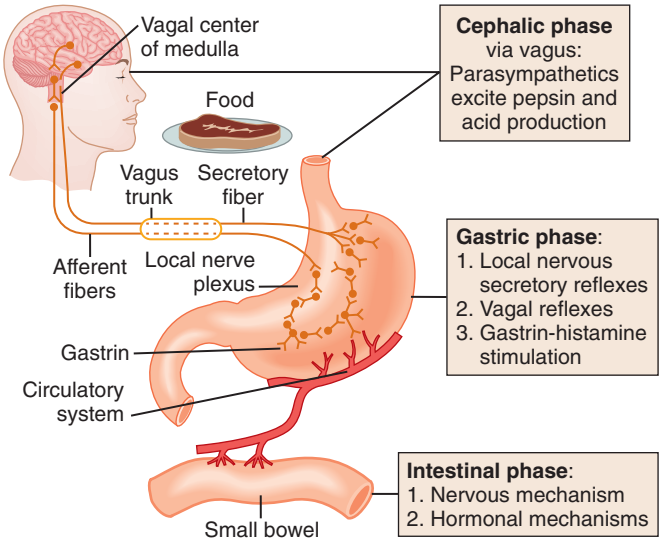
TABLE 31.3 Daily Secretion of Intestinal Juices

	Daily Volume (mL)	pH
Saliva	1000	6.0–7.0
Gastric secretion	1500	1.0–3.5
Pancreatic secretion	1000	8.0–8.3
Bile	1000	7.8
Small intestine secretion	1800	7.5–8.0
Brunner's gland secretion	200	8.0–8.9
Large intestinal secretion	200	7.5–8.0
Total	6700	

Modified from Hall JE. *Guyton and Hall Textbook of Medical Physiology.* 12th ed. Philadelphia: Saunders Elsevier; 2011.

Gastric Secretions

The stomach mucosa contains oxyntic or gastric glands and pyloric glands. Oxyntic glands secrete hydrochloric acid, pepsinogen, intrinsic factor and mucus; and pyloric glands secrete mucus and the hormone



• **Fig. 31.7** Phases of gastric secretion and their regulation.

gastrin.[45] The pyloric glands contain G cells (or gastrin cells) that secrete gastrin in a large form (G-34) and a smaller form (G-17) when stimulated by protein-containing foods in the antrum of the stomach. Gastrin is released into the blood and rapidly transported to the enterochromaffin-like cells of the stomach. This rapid transport is a result of the rapid mixing of gastric juices in the stomach. Histamine is also rapidly released into the deep oxyntic glands stimulating gastric hydrochloric acid secretion (Fig. 31.7).[53,54]

Pancreatic Digestive Enzymes

The pancreas secretes enzymes that are important for the digestion of proteins, carbohydrates, and fats. For the digestion of proteins, the pancreas releases the proteases trypsin, chymotrypsin, and carboxypolypeptidase. Carboxypolypeptidase is capable of breaking down some proteins entirely to their constituent amino acids. Trypsin and chymotrypsin split proteins into smaller, various-sized peptides. Fats are digested by pancreatic lipase, cholesterol esterase, and phospholipase. Pancreatic lipase breaks down triglycerides to fatty acids and glycerol. Cholesterol esterase and phospholipase hydrolyze cholesterol esters and phospholipids, respectively. Pancreatic amylase breaks down carbohydrates (including starch and glycogen), randomly cleaving carbohydrate chains into disaccharides and trisaccharides.

The proteolytic digestive enzymes released by the pancreas are inactive forms (proenzymes) when synthesized (thus preventing autodigestion of the pancreas). Release into the intestinal tract and interaction with various components of the intestinal fluid activates the enzymes by proteolytic processing. Trypsinogen can be activated by the enzyme enterokinase, which is released by the intestinal mucosa when contacted by chyme, or by previously secreted and activated trypsin (autoactivation).

Bicarbonate

In addition to digestive enzymes, the pancreas releases large amounts of bicarbonate that neutralize the acidity of chyme as it enters the duodenum. Pancreatic secretions also contain digestive enzymes and water. Pancreatic enzymes are secreted from the acini of the pancreatic glands, whereas bicarbonate ions and water are secreted from the epithelial cells of the ducts that lead from the acini. Concentrations of bicarbonate can reach 145 mM, allowing neutralization of hydrochloric acid released into the stomach.[55]

Absorption of Nutrients

Most nutrient absorption occurs in the small intestinal mucosa in the valvulae conniventes (folds of Kerckring). The stomach lacks such a highly increased surface area, allowing only the absorption of highly lipid-soluble substances, such as alcohol and aspirin, through its epithelium. Villi and the brush border of microvilli contribute to the high absorptive properties of the small intestine by adding to the total absorptive area. Daily absorption from the small intestine consists of several hundred grams of carbohydrates, 100 g or more of fat, 50 to 100 g of amino acids, 50 to 100 g of salt ions, and 7 to 8 L of water.[45]

Glucose

Glucose is mostly absorbed by a sodium ion (Na^+)-dependent glucose cotransporter mediated by a coupled secondary active transport process. This cotransporter uses an electrochemical potential difference instead of adenosine triphosphate to function. The pumping of Na^+ through the basolateral membrane into the extracellular compartment by sodium-potassium adenosine triphosphatase uses adenosine triphosphate to reduce Na^+ within the cell. The cotransporter allows Na^+ to move down its concentration gradient into the cell from the intestinal lumen, along with a glucose molecule. After glucose enters cells, it moves by facilitated diffusion into the bloodstream. The initial active transport of Na^+ out of the epithelial cell provides the electrochemical motive force for moving glucose from the intestinal lumen into the bloodstream.[45]

Fats

Digestion of fats yields monoglycerides and fatty acids. These hydrophobic molecules travel through the alimentary tract in the form of bile micelles, which are soluble in chyme. When they reach the microvilli of the intestinal cell brush border, monoglycerides and fatty acids diffuse through the membrane into epithelial cells. Within epithelial cells, fatty acids and monoglycerides are used to synthesize new triglycerides. These triglycerides are released as chylomicrons and travel through the thoracic lymph duct to be released into the bloodstream.[56]

Gastrointestinal Disorders

Table 31.4 lists GI and neurologic disorders, many of which have anesthetic implications. Risks from these conditions include aspiration, diabetes mellitus, malabsorption with malnutrition, and nausea/vomiting.

Aspiration is a concern in patients who have eaten recently, have acid reflux disease, or have disorders of GI motility. Cricoid pressure, or the Sellick maneuver, is the posterior displacement of the cricoid cartilage, intended to close the esophagus and decrease the risk of aspiration. However, cricoid pressure lowers resting lower esophageal sphincter pressure, so the benefit is confined to the physical barrier created. Questions exist about the efficacy of the mechanical effect owing to the lateral displacement of the esophagus, which is exacerbated by posterior pressure on the cricoid cartilage. Despite little evidence supporting benefit, the use of cricoid pressure is well entrenched. Because it can worsen the view with laryngoscopy, it should be abandoned if difficulties with intubation or ventilation are encountered.[57,58]

TABLE 31.4 Gastrointestinal Disorders

GI Disorder	Type of Disorder	Description	Cause	Abnormalities	Clinical Relation
Disorders of swallowing and of the esophagus	Myasthenia gravis or botulism	Prevents normal swallowing	Paralysis of swallowing muscles Failure of neuromuscular transmission Deep anesthesia	Complete abrogation of swallowing action Failure of glottis to close Failure of soft palate and uvula to close the posterior nares → food reflux into nose	Patients under deep anesthesia may aspirate owing to blocked reflex mechanism of swallowing
	Achalasia	Failure of lower esophageal sphincter to relax during swallowing	Damage in neural network of myenteric plexus in lower two-thirds of esophagus	Lower esophagus remains spastically contracted Food fails to pass from esophagus to stomach Prolonged constriction can cause ulceration of esophageal mucosa	Balloon inflated on the end of a swallowed esophageal tube to stretch the blocked esophagus Antispasmodic drugs to relax smooth muscle
Disorders of the stomach	Achlorhydria (and hypochlorhydria, diminished acid secretion)	When pH of gastric secretions fail to decrease below 6.5 after maximal stimulation	Failure of stomach to secrete hydrochloric acid	Pepsin also fails to be secreted, which requires acid medium for activity	
Disorders of small intestine	Pancreatitis	Inflammation of pancreas; comes in form of acute pancreatitis or chronic pancreatitis	Drinking excess alcohol Blockage of the papilla of Vater by a gallstone	With gallstone blockage: accumulation of trypsinogen within pancreas activates trypsin and other proteolytic enzymes, causing rapid digestion and destruction of pancreas	
	Sprue	Inadequate absorption of nutrients from small intestine mucosa	Nontropical sprue: (idiopathic sprue, celiac disease, gluten enteropathy) result of toxic effects of gluten	Destruction of intestinal enterocytes, thus decreasing absorptive surface area	Removal of wheat and rye flour from diet results in cure within weeks
			Tropical sprue: often occurs in tropics	Possibly by inflammation of intestinal mucosa from unidentified infectious agents	Treat with antibacterial agents
Disorders of large intestine	Megacolon (Hirschsprung disease)	Severe constipation	Lack or deficiency of ganglion cells in myenteric plexus in a segment of the sigmoid colon	Tremendous accumulation of fecal matter within colon Failure of defecation reflexes and/or strong peristaltic motility	Requires surgical removal of involved bowel. May present with toxic megacolon
	Diarrhea	Rapid movement of fecal matter through large intestine	Enteritis: inflammation of intestinal tract caused by either virus or bacteria (e.g., cholera)	Increased motility of intestinal wall Increased quantity of fluid	Intravenous fluid to replace fluid and electrolytes as rapidly as lost
			Psychogenic diarrhea: excessive stimulation of the parasympathetic nervous system	Increased motility Excess secretion of mucus in distal colon	
			Ulcerative colitis: extensive areas of walls of large intestine become inflamed and ulcerated; cause is unknown	Repeated diarrheal bowel movements	Ileostomy to heal ulcers or Surgical removal of entire colon
Gastrointestinal tract	Chemoreceptor trigger zone	Initiation of vomiting by drugs or by motion sickness	Nervous signals arising in chemoreceptor trigger zone for vomiting Drugs (amorphine, morphine, some digitalis derivatives) Rapid change of direction or rhythm of motion of body		

Nausea and vomiting are the most common and disturbing postoperative patient complaints, after pain. The neural pathways involved are both peripheral and central. Vagal and sympathetic afferent nerves can activate the chemoreceptor trigger zone and vomiting center, located in the medulla close to the area postrema and fourth ventricle. Neurotransmitters involved include acetylcholine, dopamine, histamine, substance P, and serotonin. The vestibular apparatus, toxic substances in the GI tract, and opioids can also provide a stimulatory effect. Clinical risk factors for postoperative nausea and vomiting include female gender, nonsmoking status, history of motion sickness, perioperative opioid use, and use of inhaled anesthetics (see Chapter 34).

Anesthetic Pharmacology and the Gastrointestinal Tract

Anesthetic drugs that affect the GI tract in clinically significant ways include the depolarizing neuromuscular blocker succinylcholine, anticholinergic drugs, cholinesterase inhibitors, and opioids.

Succinylcholine mimics the effect of acetylcholine at the neuromuscular junction, producing an initial muscle contraction that is clinically evident as fasciculation (see Chapter 22). Fasciculation is associated with increased intragastric pressure, potentially sufficient to overcome the lower esophageal sphincter and result in reflux of gastric contents with possible aspiration. Prevention of fasciculation with the use of a "defasciculating" or subparalytic dose of a nondepolarizing neuromuscular blocking agent might prevent or reduce the increase in intragastric pressure.[59] However, that intervention is not entirely benign as it is associated with partial paralysis, aspiration, and patient complaints of difficulty breathing.[60]

Commonly used anticholinergic drugs include atropine, glycopyrrolate, and scopolamine. Scopolamine is used primarily for its central effects, whereas atropine and glycopyrrolate are more commonly used for their peripheral effects. Some of these uses are as antisialagogues and as antagonists of the muscarinic effects of neuromuscular blocker reversal agents (cholinesterase inhibitors), which include bradycardia, nausea, increased gastric fluid secretion, and increased GI motility (see Chapter 22). Cholinesterase inhibitors also have potentially salutary effects on the GI tract, such as increasing lower esophageal tone or treating ileus.[2]

Opioids are strongly associated with nausea and vomiting as the result of reducing peristaltic activity throughout the small and large intestines and increasing tone in the pyloric sphincter, ileocecal valve, and anal sphincter. Opioid-induced biliary spasm can confound diagnosis of cardiac disease and might also be misinterpreted as a biliary stone or stricture on cholangiogram. Opioids also cause pancreatic duct contraction, releasing pancreatic amylase and lipase and also potentially confounding a diagnosis of pancreatitis; however, the clinical significance of these effects has been challenged.[61]

Opioid-induced bowel dysfunction is a particularly troublesome complication in both surgical and medical patients because of its association with increased postoperative complications, bothersome and therapy-limiting symptoms, and hospital length of stay. Alvimopan, a peripherally acting μ-opioid receptor antagonist that does not cross the blood-brain barrier, has been shown to decrease both symptoms and hospital length of stay without compromising pain relief.[62,63]

Studies have documented the salutary effects of regional anesthesia and analgesia on GI motility compared with general anesthesia for abdominal surgery.[64] It is believed that a contributing factor to postoperative ileus is sympathetic stimulation caused by the surgical stress response and pain. Neuraxial regional anesthesia, which blocks afferent pain signals and efferent sympathetic outflow, can potentially minimize the depressive effects of surgery on postoperative GI motility.

Emerging Developments

Tissue Engineering

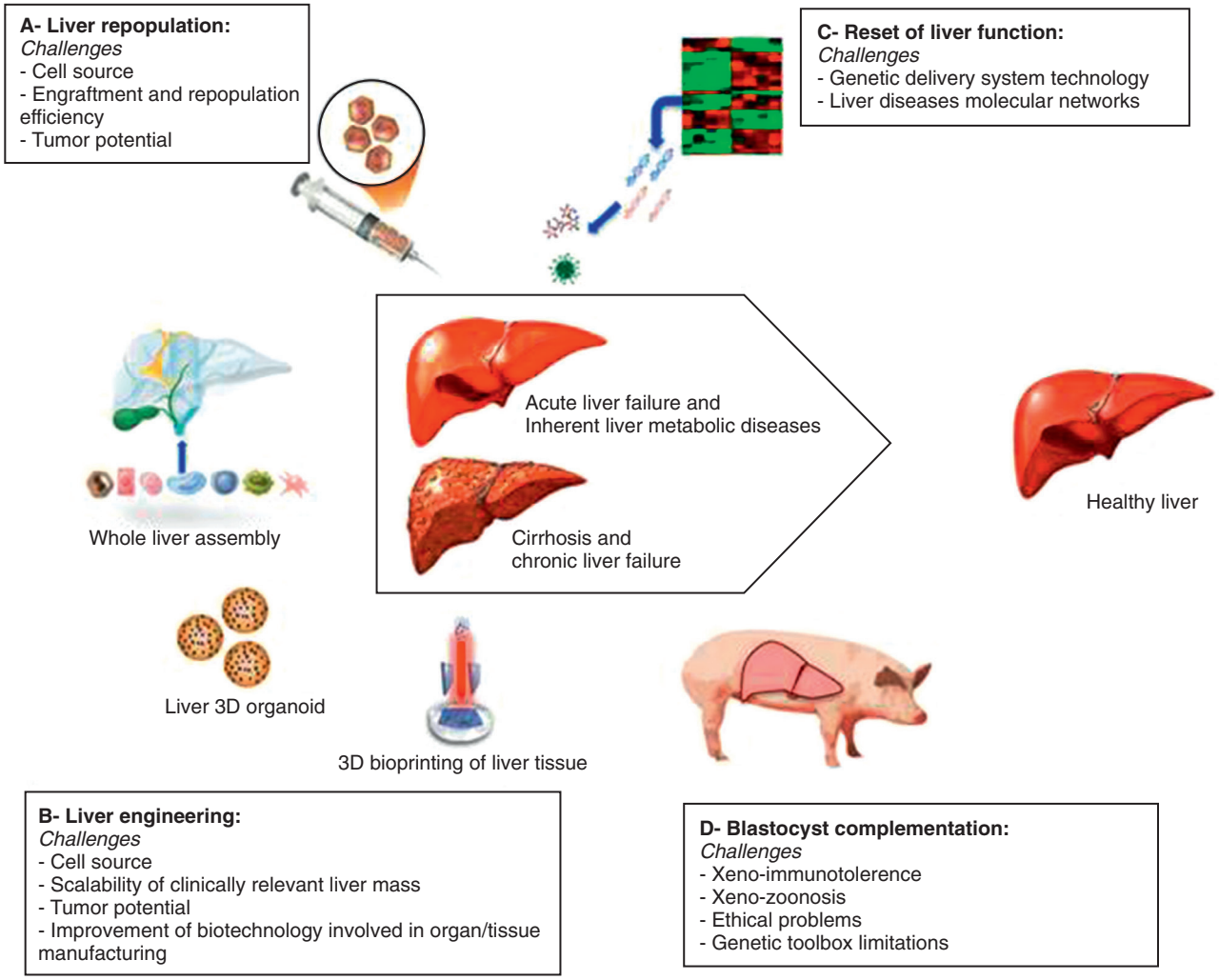
End-stage liver disease from any cause dramatically alters liver physiology and microanatomy. Currently the only curative therapy for end-stage liver disease is orthotopic liver transplantation. Advances in molecular biology, stem cell biology, and tissue bioengineering focused on hepatology have resulted in exciting new possibilities to repair or replace damaged liver tissue and thereby restore normal hepatic physiology. Some of these approaches are summarized in Fig. 31.8.

Stem cells are at the center of this development effort. Induced pluripotent stem cells (IPSCs) are multipotential cells derived from somatic cell populations. The nucleus of a mature cell, such as a fibroblast, can be "reprogrammed" by exposure to certain transcription factors to an undifferentiated state. These IPSCs can then be directed to develop into specific cell types.[65] Hepatocytes developed in this way (theoretically from the patient's own cells) could potentially represent a source of cells for regenerative therapies (e.g., hepatocyte transplantation) or bio-artificial organ development.[66,67]

Most recently, a popular approach aimed toward the construction of an artificial liver involves the "decellularization" of a whole organ followed by "reseeding" with the appropriate cell types. Although in a preliminary stage, these techniques have shown promise in animal models. Similarly, automated engineering platforms emulating standard three-dimensional printer technology can be used to design and develop three-dimensional tissue configurations of various cell types, including cell structures that resemble liver tissue in terms of how the hepatocytes are organized in space relative to other cells types. These "biomanufactured" tissues have exciting potential in the quest to develop artificial "whole" livers for transplantation.[66–69]

Refinements in xenograft approaches are also a significant part of this hepatology research frontier. Blastocyst complementation, wherein IPSCs are used to create a chimeric animal that complements an artificially induced deficit in the recipient, is an exciting example. The result is an organ with specified genetic characteristics within an animal host. The technique has been applied successfully in animal models for the pancreas and kidney. Application to hepatology is the natural next step.[66,67]

Finally, the application of CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats [CRISPR]–CRISPR-associated protein [Cas]9) technology to transplant hepatology has yielded an important advance. A key limitation in creating a potentially unlimited pool of donor organs from genetically modified animals (pigs in the case of liver transplantation) has been the fear of transmitting retroviruses to humans. CRISPR-Cas9 techniques have been used to edit the porcine genome, accurately and precisely inactivating the porcine endogenous retroviruses.[70] This advance eliminates a significant obstacle in development of genetically modified porcine xenotransplants for end-stage liver disease.



• **Fig. 31.8** Schematic representation of novel approaches under investigation in regenerative medicine for liver replacement and regeneration. The cell source for liver repopulation (A) and liver engineering (B) should be facilitated by an unlimited supply of induced pluripotent stem–derived hepatocytes, but the underlying tumor potential would remain to be elucidated. Successful liver repopulation will require optimizing functional hepatic cells to achieve high engraftment and repopulation efficiency. "Resetting" liver functions (C) to normal will require improvement of in vivo genetic delivery systems and better understanding of complex molecular networks associated with liver diseases. Important health and ethical issues associated with blastocyst complementation (D) will need to be addressed. The liver may contain host cells and pathogens that could pose a threat of immunologic rejection and transmission of interspecies diseases. Ethical concerns could be solved once the genetic toolbox makes it possible to restrict differentiation toward particular organs (brain and gonads). *3D,* Three-dimensional. (Adapted from Collin de l'Hortet A, Takeishi K, Guzman-Lepe J, et al. Liver-regenerative transplantation: regrow and reset. *Am J Transplant.* 2016;16:1688–1696.)

Key Points

- The liver has a dual afferent blood supply consisting of systemic blood from the hepatic artery and portal venous blood from the splanchnic circulation.
- The liver plays a key role in provision of energy requirements through the synthesis and metabolism of carbohydrates, proteins, and fats.
- The liver detoxifies and transforms exogenous and endogenous compounds, including anesthetics. Altered liver function can lead to encephalopathy and alter the metabolism, volume of distribution, and protein binding of drugs.
- Bile production by the liver is important in the absorption of fats. Biliary obstruction results in steatorrhea and vitamin K deficiency.
- End-stage liver disease is associated with multisystem organ failure. In addition to encephalopathy, hyperdynamic changes occur in the cardiovascular system; pleural effusions and ascites reflect decreased oncotic pressure and elevated portal pressure; varices and coagulopathy lead to GI bleeding; infections occur as the result of decreased reticuloendothelial function; and renal failure can result from alterations in renal blood flow.
- The GI tract is functionally divided into sections that systematically break down food to its discrete components that are absorbed and presented to the liver for storage or use.
- Surgical trauma affects GI function, particularly if surgery is intraabdominal.
- Anesthetic agents can affect the function of the GI tract.
- Although GI dysfunction might not present a problem in the operating room, it is a contributor to perioperative morbidity in the forms of aspiration, postoperative nausea and vomiting, postoperative ileus, and delayed feeding.
- Considered selection of anesthetic agents and technique can mitigate the untoward effects of anesthesia and surgery on GI function.
- Although still at a preclinical stage, advances in molecular biology, stem cell biology, and tissue bioengineering focused on hepatology have resulted in exciting possibilities to repair or replace damaged liver tissue and thereby restore normal hepatic physiology.

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32

Liver and Gastrointestinal Pharmacology

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CHAPTER OUTLINE

Liver Pharmacology
- Cytochrome P450 Enzymes
- Hepatic Extraction
- Plasma Protein Binding

Anesthetic Drugs and the Liver
- Anesthetic Agents and Hepatic Blood Flow
- Metabolism of Volatile Anesthetics and Hepatotoxicity
- Metabolism of Intravenous Anesthetic Agents
- Hepatobiliary Metabolism and Elimination of Neuromuscular Blockers

Gastrointestinal Pharmacology
- Basic Principles
- Gastric Acid–Suppressing Medications
- Drugs to Reduce Portal Venous Pressure
- Opioids and the Gastrointestinal System
- Sphincter of Oddi Spasm
- Statins
- Other Treatments for Dyslipidemia
- Hepatitis C Treatment

Emerging Developments
- Suppression of Gastric Acid Secretion
- Direct-Acting Antivirals for Hepatitis C Treatment
- PCSK9 Inhibitors for Dyslipidemia
- Obeticholic Acid

One of the main functions of the liver is to protect against toxins. The endoplasmic reticulum of hepatocytes contains families of enzymes that protect the organism against an accumulation of lipid-soluble exogenous and endogenous compounds. This is done by transforming compounds to water-soluble metabolites, which are more readily excreted by the kidneys. Gastrointestinal absorption of orally administered drugs and the pharmacology of the gastrointestinal tract are critical to pharmacotherapy and to perioperative medicine.

Liver Pharmacology

Cytochrome P450 Enzymes

The bulk of liver drug metabolism is carried out by the cytochrome P450 (CYP 450) enzyme system (Tables 32.1 and 32.2) (see Chapter 4). CYP 450 enzymes in the endoplasmic reticulum oxidate lipid-soluble compounds in phase I and phase II reactions.[1] Drug response varies from 25% to 60% among patients because of environmental, genetic, and disease influences.[2] Phase I reactions transform lipophilic molecules into hydrophilic molecules.[3–6] Phase II reactions then conjugate drugs and metabolites to highly polar compounds that are more readily excreted.[7,8]

The CYP1, CYP2 and CYP3 families perform almost 80% of oxidative drug metabolism and 50% of drug elimination. Although the liver is the major site of CYP 450–mediated metabolism, small intestine enterocytes are a secondary site. More than 65 commonly used drugs are metabolized by CYP 2D6. Genetic variability in CYP 2D6 metabolism can thereby lead to subtherapeutic or supratherapeutic drug levels and effects. This variability is usually unanticipated because CYP 450 genotyping is not widely available.[9] Slow metabolism by CYP 2D6 is a major factor in warfarin toxicity, for example.[10] The CYP 3A family also metabolizes a wide variety of drugs.[11] Drug-drug interactions expand variability up to 400-fold. CYP 5 catalyzes the isomerization of prostaglandin endoperoxide to thromboxane A, a reaction that leads to platelet aggregation and potentially thrombosis.[12]

Hepatic Extraction

The fraction of drug presented to the liver that is eliminated during a single pass is called the *hepatic extraction ratio.* The hepatic extraction ratio becomes equal to 1 (unity) when the drug that reaches the liver is completely eliminated. When no drug is eliminated by the liver, the extraction ratio is zero.[13] For oral drugs that are completely absorbed into the portal circulation, bioavailability depends on the extraction ratio. Bioavailability for high–extraction ratio drugs is much less than for low–extraction ratio drugs (Table 32.3).

Hepatic clearance reflects the removal of the drug as it passes through the liver and is the product of hepatic blood flow multiplied by the extraction ratio (Fig. 32.1). If the liver is very efficient in

Abstract

One of the main functions of the liver is to protect the organism against intoxication. The endoplasmic reticulum of liver cells contains enzymes that protect the organism against an accumulation of lipid-soluble exogenous and endogenous compounds. This is done by transforming the compounds to water-soluble metabolites, which are then easily excreted by the kidney. Gastrointestinal absorption of orally administered drugs and pharmacology of the gastrointestinal tract is an equally complex system mediated by neuronal and hormonal influences.

Keywords

liver
gastrointestinal
pharmacology
first pass
hepatic extraction
bioavailability

TABLE 32.1 Human Cytochrome P450 Enzymes Involved in Metabolism of Xenobiotics Located in Extrahepatic Tissues

CYP Enzyme	Tissue
1A1[a]	Lung, kidney, gastrointestinal tract, skin, placenta, lymphocytes, and others
1B1	Skin, kidney, mammary, prostate, uterus, fetus
2A6	Lung, nasal membrane, and possibly others
2B6	Gastrointestinal tract, lung
2C	Gastrointestinal tract (small intestine mucosa), larynx, lung
2D6	Gastrointestinal tract
2E1	Lung, placenta, and others
2F1	Lung, placenta
2J2	Heart
3A	Gastrointestinal tract, placenta, fetus, uterus, kidney, lung
4B1	Lung, placenta
4A11	Kidney

CYP, Cytochrome P450.
[a]After induction.
From Rendic S, Carlo FJ Di. Human cytochrome P450 enzymes: a status report summarizing their reactions, substrates, inducers, and inhibitors. *Drug Metab Rev.* 1997;29:1–2.

TABLE 32.3 Hepatic Extraction Ratios of Important Drugs

Low Ratio (<0.3)	Intermediate Ratio (0.3–0.7)	High Ratio (>0.7)
Carbamazepine	Aspirin	Alprenolol
Diazepam	Quinidine	Cocaine
Indomethacin	Codeine	Desipramine
Naproxen	Nifedipine	Lidocaine
Nitrazepam	Nortriptyline	Meperidine
Phenobarbital		Morphine
Phenytoin		Nicotine
Procainamide		Nitroglycerin
Salicylic acid		Pentazocine
Theophylline		Propoxyphene
Valproic acid		Propranolol
Warfarin		Verapamil

From references 102–105.

TABLE 32.2 Examples of Clinical Substrates, Inhibitors, and Inducers for Cytochrome P450–Mediated Metabolism

CYP Enzyme	Sensitive Substrates	Moderately Sensitive Substrates	Strong Inhibitors	Moderate Inhibitors	Strong Inducers	Moderate Inducers
1A2	Alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, theophylline, tizanidine	Clozapine, pirfenidone, ramosetron	Ciprofloxacin, enoxacin, fluvoxamine, zafirlukast	Methoxsalen, mexiletine, oral contraceptives	—	Phenytoin, rifampin, ritonavir, smoking, teriflunomide
2B6	Bupropion	Efavirenz	—	—	Carbamazepine	Efavirenz, rifampin, ritonavir
2C8	Repaglinide	Montelukast, pioglitazone, rosiglitazone	Clopidogrel, gemfibrozil	Deferasirox, teriflunomide	—	Rifampin
2C9	Celecoxib	Glimepiride, phenytoin, tolbutamide, warfarin	—	Amiodarone, felbamate, fluconazole, miconazole, piperine	—	Aprepitant, carbamazepine, enzalutamide, rifampin, ritonavir
2C19	S-mephenytoin, omeprazole	Diazepam, lansoprazole, rabeprazole, voriconazole	Fluconazole, fluoxetine, fluvoxamine, ticlopidine	—	Rifampin, ritonavir	Efavirenz, enzalutamide, phenytoin
2D6	Atomoxetine, desipramine, dextromethorphan, nebivolol, nortriptyline, perphenazine, tolterodine, venlafaxine	Amitriptyline, encainide, imipramine, metoprolol, propafenone, propranolol, tramadol, trimipramine	Bupropion, fluoxetine, paroxetine, quinidine, terbinafine	Cimetidine, cinacalcet, duloxetine, fluvoxamine, mirabegron		

CYP, Cytochrome P450.
From Isoherranen N, Lutz JD, Chung SP, et al. Importance of multi-P450 inhibition in drug-drug interactions: evaluation of incidence, inhibition magnitude, and prediction from in vitro data. *Chem Res Toxicol.* 2012;25:2285–2300.

removing a drug (extraction ratio ~1) but blood flow is low, clearance will also be low. At the same time, if the liver is extremely inefficient in removing a drug, clearance will be low even if blood flow is high.[14,15]

Plasma Protein Binding

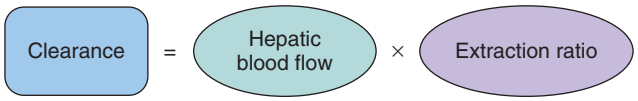
Only unbound drug is able to cross membranes and be eliminated. In patients with low plasma proteins, such as those with end-stage liver disease, the proportion of unbound drug increases. If a drug has a low extraction ratio, an increase in the fraction of unbound drug will proportionally increase clearance. Therefore the unbound drug concentration remains constant and no dose adjustment is required. On the other hand, if a drug has a high extraction ratio, as the fraction of unbound drug increases the clearance remains constant. As the unbound concentration increases, toxicity can ensue.[16]

Anesthetic Drugs and the Liver

Anesthetic Agents and Hepatic Blood Flow

Maintaining hepatic perfusion is important, particularly in patients with compromised hepatic function. The hepatic arterial buffer response, which increases hepatic artery flow when portal vein flow is reduced, is impaired with inhaled anesthetics.[17] Table 32.4 summarizes the effects of various anesthetic agents on hepatic blood flow. Halothane and nitrous oxide decrease hepatic blood flow in a dose-dependent fashion.[18–20] Hepatic blood flow is maintained at 1 minimum alveolar concentration (MAC) of isoflurane and sevoflurane.[17–19] Whereas desflurane decreases hepatic blood flow in animals, a single-center human study showed increased hepatic blood flow at 1 MAC desflurane compared with isoflurane.[21,22]

Intravenous (IV) and neuraxial anesthetic agents also affect hepatic blood flow. Propofol and opioids increase hepatic blood flow[23–26] (Table 32.5). Ketamine does not affect hepatic flow, but oxygen delivery is reduced, possibly owing to increased oxygen consumption by other organs.[20] Etomidate, barbiturates, dexmedetomidine, and benzodiazepines decrease hepatic blood flow.[27–29] Thoracic epidural anesthesia decreases hepatic blood flow, consistent with previous studies of lumbar epidurals.[30,31]



• **Fig. 32.1** Hepatic clearance = hepatic blood flow multiplied by hepatic extraction ratio.

TABLE 32.4 Volatile Anesthetic Effects on Hepatic Blood Flow

Halothane	Isoflurane	Sevoflurane	Desflurane	Nitrous Oxide
Decreased	Maintained	Maintained	Decreased in animals, possibly increased in humans	Decreased

From references 17–19, 21, 22, 25.

Metabolism of Volatile Anesthetics and Hepatotoxicity

Many volatile anesthetics are oxidized to variable extents by CPY 2E1 in the liver (see Chapter 3).[32] Halothane use has fallen out of favor because of concerns about hepatotoxicity, which involves two different mechanisms. The first reaction is a transient benign postoperative transaminase elevation. The second reaction, halothane hepatitis, is a rare autoimmune reaction leading to centrilobular necrosis and acute liver failure with a high mortality rate.[33] Halothane is oxidized, leading to trifluoroacetyl adduct formation, which leads to antibody production in susceptible patients. Repeat exposure to halothane leads to hepatocyte necrosis. Desflurane, isoflurane, and enflurane also undergo oxidation to trifluoroacetyl, with rare reports of autoimmune liver failure. Sevoflurane does not form reactive trifluoroacetyl intermediates and therefore presents a lower concern for immune-mediated hepatitis.[33]

Metabolism of Intravenous Anesthetic Agents

The majority of IV hypnotic agents undergo hepatic metabolism (see Chapter 2). Their pharmacokinetics depend on hepatic blood flow, degree of hepatic extraction, and plasma protein binding. Patients with hepatic dysfunction have greater susceptibility to pharmacologic effects owing to decreased hepatic metabolism, decreased hepatobiliary clearance, and low serum protein and albumin concentrations.[34] The liver oxidizes propofol with a very high extraction ratio; therefore elimination depends largely on hepatic blood flow.

Barbiturates are potent CYP 450 inducers. Patients with deficiencies in heme synthesis pathways receiving barbiturates are at risk of inducing aminolevulinic acid synthase, precipitating an attack of acute intermittent porphyria.[35] The liver is centrally involved in the pathogenesis of this disorder, as aminolevulinic acid synthase induction leads to increased demand for hepatic heme and consumption of hepatic CYP 450 enzymes.[36] Furthermore, liver transplantation has been used for treatment of refractory acute porphyria.

The liver oxidizes midazolam to 1-hydroxymethylmidazolam, an active central nervous system depressant metabolite that can accumulate in patients with hepatic or renal dysfunction.[37] By

TABLE 32.5 Intravenous and Neuraxial Anesthetic Effects on Hepatic Blood Flow

Propofol	Ketamine	Etomidate	Barbiturates	Dexmedetomidine	Benzodiazepines	Opioids
Increased	Maintained	Decreased	Decreased	Decreased	Decreased	Increased

From references 23, 24, 26, 28, 29, 31.

contrast, lorazepam undergoes glucuronidation to inactive metabolites.

Most opioids are metabolized in the liver.[34] Patients with cirrhosis have decreased clearance of opioids, leading to increased accumulation, which can precipitate hepatic encephalopathy. Lower opioid doses and longer intervals between doses are advocated in these patients.[34]

Hepatobiliary Metabolism and Elimination of Neuromuscular Blockers

The hepatobiliary system metabolizes selected neuromuscular blockers. For aminosteroid nondepolarizing agents (rocuronium, vecuronium and pancuronium), prolonged blockade becomes apparent after redosing or continuous infusion, because redistribution is responsible for recovery from a single bolus dose.[38] A higher initial dose of a nondepolarizing neuromuscular blocker may be needed in patients with cirrhosis owing to an increased volume of distribution.[38] Cisatracurium and atracurium undergo chemical degradation independent of the liver and are useful in redosing when rapid recovery is desired.[39] Succinylcholine is metabolized by plasma cholinesterase, a product of the liver; patients with liver disease can have prolonged blockade.[40] Current reversal agents, including suggamadex, do not undergo hepatic metabolism or excretion.[41]

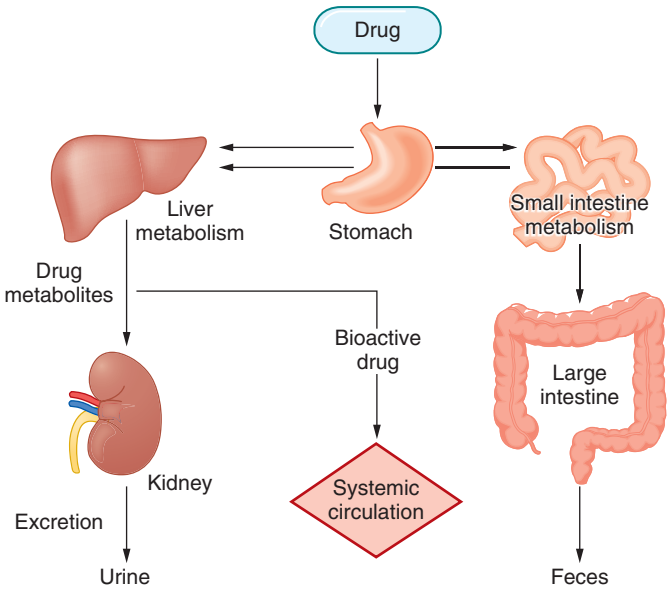
Gastrointestinal Pharmacology

Basic Principles

Gastrointestinal function is controlled by a variety of influences, including extrinsic autonomic innervation, a complicated intrinsic neural system, and multiple hormones such as gastrin, glucagon, and somatostatin. Gastrointestinal motility is a function of nerve inputs, and slow electrical waves generated in the longitudinal layer located in the smooth muscle are required for peristalsis.[42] Drugs targeting the gastrointestinal system tend to focus on decreasing gastric acid secretion, treating nausea and vomiting, and diminishing side effects of slowed motility causing constipation.

Because of convenience, oral drug administration is the preferred route of delivery for many medications, particularly in the outpatient setting. After oral administration of a drug, CYP 450 enzymes can reduce the portion of the dose that reaches the systemic circulation, influencing the drug's effects, which is known as *first-pass metabolism*.[43] Oral administration is highly dependent on drug bioavailability, which is determined by the quantity of drug absorbed from the gastrointestinal tract and hindered by first-pass elimination in the gastrointestinal wall, liver, and lung. Gastrointestinal absorption depends on the stability of the drug in gastrointestinal fluids, absorption time, solubility, and how readily the drug permeates the gastrointestinal epithelium (Fig. 32.2).[44] The primary site of drug absorption is the small intestine, followed by the stomach and colon.[45] For about 40% of commonly used drugs, less than half of the administered oral dose is bioavailable because of limited absorption, first-pass metabolism, or both. Oral bioavailability can be altered by drug interactions that result in either inhibition or induction of the involved enzymes. Drug metabolism differences in the intestine and liver between patients are common and are major contributors to differences in drug response, including adverse effects.[11]

When an orally administered drug undergoes extensive first-pass metabolism, its bioavailability in the setting of CYP 3A inhibition



• **Fig. 32.2** Transit of drug through gastrointestinal tract and drug metabolism leading to bioactive drug in systemic circulation.

can increase severalfold, whereas the rate of elimination can be reduced[43] (Table 32.6). When a drug is administered orally, intestinal CYP 3A enzymes are exposed to higher concentrations of the drug and are inhibited to a greater degree than are unaffected hepatic CYP 3A enzymes. An example of this is an interaction between grapefruit juice and CYP 3A substrates.[46,47] Grapefruit juice is contraindicated in patients receiving drugs that are extensively metabolized by CYP 3A, including calcium channel blockers and statins, as a single glass can cause CYP 3A inhibition for 24 to 48 hours.[11]

There are many recognized potent inhibitors of CYP 3A that result in increased plasma concentrations of drugs even when administered at recommended doses. These situations are sometimes used to therapeutic advantage. CYP 3A inhibition is typically reversible, normally within 2 to 3 days once the interacting drug is discontinued. In some cases, CYP 3A is destroyed and new CYP 3A enzyme must be synthesized, leading to a prolonged drug effect.[48] Treatment with drugs such as the rifamycin and some anticonvulsants predictably results in a major decrease in the plasma concentrations of certain drugs administered concurrently. CYP 3A activity is especially sensitive to such drug interactions involving upregulation of several proteins critical to drug disposition, and CYP 3A substrate metabolism is acutely affected by treatment with these inducing agents.[49] In this situation, drug dosages that were previously effective become ineffective.[50] New protein must be synthesized; thus the consequences of CYP 3A induction are not immediate. Steady-state levels generally are reached in 2 to 3 weeks. Similarly, the induction effect after discontinuing the inducing agent takes several weeks to wash out. Adequate drug therapy is still achievable by creating stepwise increases or decreases in the medication regimen while monitoring plasma levels.[51]

Gastric Acid–Suppressing Medications

The two classes of gastric acid suppressing medications in common use are proton pump inhibitors (PPIs) and H_2-histamine receptor antagonists (H_2RAs). They are used to decrease peptic ulcers, treat

TABLE 32.6 Common Drug Substrates, Inhibitors, and Inducers of CYP 3A According to Drug Class

CYP 3A Substrates	CYP 3A Inhibitors	CYP 3A Inducers
Calcium Channel Blockers	**Calcium Channel Blockers**	**Rifamycins**
Diltiazem	Diltiazem	Rifabutin
Felodipine	Verapamil	Rifampin
Nifedipine		Rifapentine
Verapamil		
Immunosuppressant Agents	**Azole Antifungal Agents**	**Anticonvulsant Agents**
Cyclosporine	Itraconazole	Carbamazepine
Tacrolimus	Ketoconazole	Phenobarbital
		Phenytoin
Benzodiazepines	**Macrolide Antibiotics**	**Anti-HIV Agents**
Alprazolam	Clarithromycin	Efavirenz
Midazolam	Erythromycin	Nevirapine
Triazolam	(Not azithromycin)	
Statins	**Anti-HIV Agents**	**Others**
Atorvastatin	Delavirdine	St. John's wort
Lovastatin	Indinavir	
(Not pravastatin)	Ritonavir	
	Saquinavir	
Macrolide Antibiotics		
Clarithromycin		
Erythromycin		
Anti-HIV Agents		
Indinavir		
Nelfinavir		
Ritonavir		
Saquinavir		
Others		
Losartan		
Sildenafil		

CYP, Cytochrome P450; *HIV,* human immunodeficiency virus.
From Wilkinson GR. Drug metabolism and variability among patients in drug response. *N Engl J Med.* 2005;352:2211–2221.

gastroesophageal reflux, and for stress ulcer prevention. In anesthesia practice, these medications are used to reduce stomach acidity and thereby reduce the risk of lung injury in the event of aspiration of stomach contents into the trachea.

PPIs are benzimidazole derivatives that decrease gastric acid production through inhibition of the parietal cell hydrogen-potassium adenosine triphosphatase (Fig. 32.3). Available PPIs include omeprazole, lansoprazole, pantoprazole, and esomeprazole. Because proton pumps are stimulated by ingested food, oral PPIs should be given 30 to 60 minutes before a meal to ensure high serum concentration when proton pumps are active. A single dose is effective for up to 15 hours, but several days of administration can be necessary to reach maximal efficacy.[52]

Multiple PPIs, including lansoprazole, pantoprazole, and esomeprazole, are available as intravenous (IV) formulations. IV PPIs have the advantage of rapid onset within 1 hour with effects lasting up to 12 hours.[53] Oral and IV pantoprazole have demonstrated similar efficacy in reducing gastric acidity.[54]

Long-term side effects of PPI use include malabsorption of key electrolytes and vitamins, particularly calcium, magnesium, and vitamin B_{12}, and a predisposition toward infections including *Clostridium difficile* and pneumonia.[55,56] Concerns exist for risk of osteoporosis, renal insufficiency, and dementia with long-term PPI use, although randomized controlled trial evidence is limited.[56] Results of observational studies have raised concerns about decreased efficacy of clopidogrel when given with PPIs. However, there was no apparent cardiovascular interaction in a large randomized trial.[57] Observational studies show a consistent association of long-term PPI use with gastric polyps, although there is not a clear clinical association with gastric or colon cancer.[56]

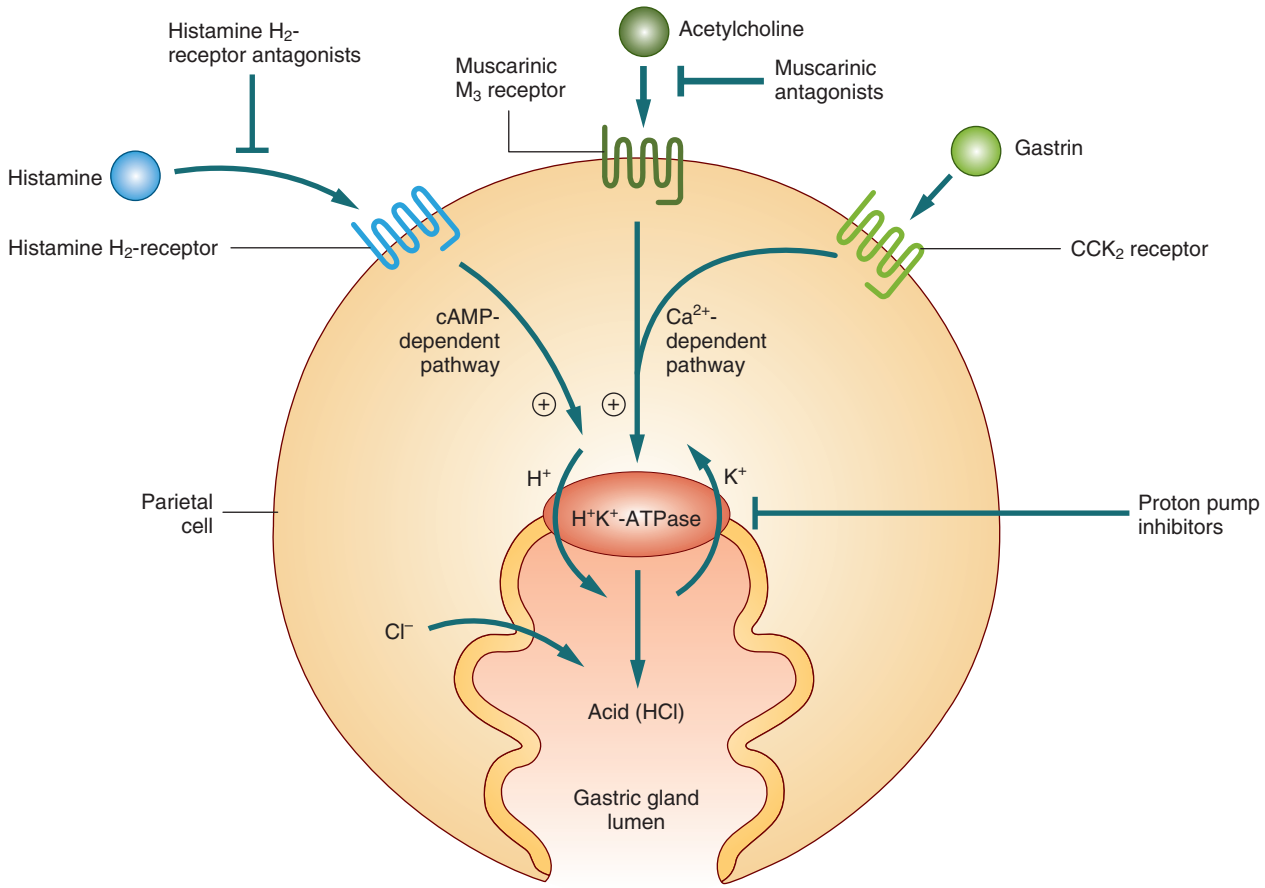
Histamine receptor antagonists, including famotidine, cimetidine, and ranitidine, suppress gastric acid through competitive antagonism of histamine binding on stomach parietal cells (see Fig. 32.3). Famotidine is more potent than cimetidine and ranitidine and has a longer duration of action.[58] Oral H_2RAs have rapid onset with time to peak serum concentration 1 to 3 hours after ingestion, but they undergo extensive first-pass metabolism, with bioavailability of 43% to 60%.[59] IV onset is less than 1 hour.[60] Drug half-life is increased and clearance is reduced in renal failure and advanced and neonatal age; therefore the dose should be reduced in these patients.[59]

The most common side effects reported with H_2RAs are diarrhea, headache, drowsiness, fatigue, and muscular pain. Other possible side effects include gynecomastia, bone marrow suppression, drug-induced hepatitis, increased creatinine levels, and cardiac arrhythmias including bradycardia associated with rapid infusion. Doses should be reduced in elderly patients and those with renal and hepatic dysfunction owing to the risk of altered mental status.[59] Compared with PPIs, H_2RAs are less effective at preventing gastrointestinal bleeding in patients in intensive care units but are associated with a lower risk of pneumonia.[60] H_2RAs can interact with a number of other drugs. Cimetidine interacts with CYP 450, potentially leading to increased plasma levels of warfarin, theophylline or phenytoin. This interaction is also possible with ranitidine, but it binds less avidly to CYP 450.[59]

Several randomized trials have examined the effects of gastric acid–suppressing medications in reducing gastric volumes and pH in perioperative settings. In adults undergoing elective surgery, IV pantoprazole and ranitidine reduced gastric pH and gastric volume within 1 hour.[53,61] Based on the lack of conclusive evidence regarding reduction of pulmonary aspiration, a task force of the American Society of Anesthesiologists recommended against routine perioperative administration of gastric acid–suppressing medications in patients with no apparent increased risk for pulmonary aspiration.[62]

Drugs to Reduce Portal Venous Pressure

Standard therapy for upper variceal bleeding is a combination of a vasoconstrictor, a PPI, and endoscopic therapy to obtain effective acute control of bleeding and prevent early rebleeding.[63] Vasoconstrictors include somatostatin, its analog octreotide, and terlipressin (see Chapter 25). Somatostatin interacts with cells through G-protein–coupled receptors, leading to modulation of intracellular signaling pathways including adenylyl cyclase, phosphotyrosine phosphatase, and mitogen-activated protein kinase.[64] These vasoconstrictors decrease portal venous pressures, although the



• **Fig. 32.3** A cartoon summarizing the mechanisms of selected acid-lowering therapies. Gastric acid is secreted by parietal cells of the stomach in response to stimuli, such as the presence of food in the stomach or intestine, and the taste, smell, sight, or thought of food. Such stimuli result in the activation of histamine, acetylcholine or gastrin receptors (the H_2, M_3 and CCK_2 receptors, respectively) located in the basolateral membrane of the parietal cell, which initiates signal transduction pathways that converge on the activation of the H+,K+-ATPase—the final step of acid secretion. Inhibition of this proton pump has the advantage that it will reduce acid secretion independently of how secretion is stimulated, in contrast to other pharmacologic approaches to the regulation of acid secretion. For example, the inhibition of acid secretion by H_2-receptor antagonists can be overcome by food-induced stimulation of acid secretion via gastrin or acetylcholine receptors. *Ca^{2+},* Calcium ion; *cAMP,* cyclic adenosine monophosphate; *CCK_2,* cholecystokinin 2 receptor; *Cl^-,* chloride ion; *H^+,* hydrogen ion; *H^+,K^+-ATPase,* hydrogen potassium adenosine triphosphatase; *HCl,* hydrochloric acid; *K^+,* potassium ion; *M_3,* muscarinic acetylcholine receptor 3. (Adapted with permission from Olbe L, Carlsson E, Lindberg P. A proton-pump inhibitor expedition: the case histories of omeprazole and esomeprazole. *Nat Rev Drug Discov.* 2003;2:132–139.)

mechanism is uncertain; possible mechanisms are inhibition of glucagon and insulin-like growth factor 1 or reducing hepatic metabolism and portal inflow. It has been hypothesized that octreotide infusions may be able to lower the need for red blood cell transfusion during orthotopic liver transplantation through portal vasoconstriction. In a small underpowered study of 50 patients, red blood cell transfusion was reduced from 20 to 18 units, although there was no statistically significant difference.[65]

Opioids and the Gastrointestinal System

Coordination of peristalsis depends on the central nervous system and enteric nervous system that control smooth muscle contraction, blood flow, and secretions. Opioids interfere with gastrointestinal function, delaying recovery, particularly after abdominal surgery. Opioid-related gastrointestinal effects include decreased gastric motility and enzyme secretion, inhibition of intestinal propulsion, and increased anal sphincter tone mediated primarily through the mu-opioid receptor (see Chapter 17).[66]

New treatments for opioid-induced constipation have been developed based on nonabsorbable opioid receptor antagonists. Methylnaltrexone is a charged molecule resulting from N-methylation of naltrexone, an opioid antagonist. This charged derivative cannot cross the blood-brain barrier and has been shown to conserve analgesic effects of opioids while maintaining normal gastrointestinal function.[67] Alvimopan is a trans-3,4-dimethyl-4-(3-hydroxyphenyl) piperidine peripheral mu-opioid receptor antagonist used to reduce postoperative ileus. Side effects of alvimopan include anemia, dyspepsia, and urinary retention. When studied as a twice-daily dosing regimen for long-term use as a treatment of chronic opioid-induced constipation, a higher incidence of myocardial infarction was seen; alvimopan is only approved by the U.S. Food and Drug

Administration (FDA) for short-term in-hospital use (maximum of 15 doses per patient).[68]

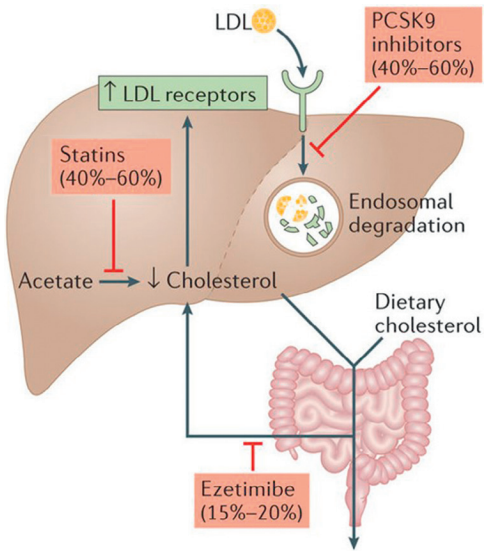
Sphincter of Oddi Spasm

The smooth muscle sphincter of Oddi controls biliary and pancreatic secretions into the duodenum under the influence of cholecystokinin.[69] Spasm can be provoked by opioids, manipulation of the common bile duct, or injection of contrast.[70] Meperidine might be less likely to induce spasm compared with other opioids, notably morphine. Pharmacologic treatments for sphincter of Oddi spasm include somatostatin, glucagon, nitroglycerin, calcium channel blockers, nalbuphine, and naloxone.[71]

Statins

Statins, used to treat dyslipidemia and to prevent and treat coronary artery disease and cerebrovascular disease, lower plasma low-density lipoprotein (LDL) cholesterol by competitively inhibiting HMG-CoA reductase, a precursor of cholesterol (Fig. 32.4). With long- term therapy, upregulation of LDL receptors occurs.[72] Statins have a complex hydrophobic ring structure, and bioavailablity decreases with increasing hydrophobicity.

Chronic statin use is associated with stabilization of atherosclerotic plaques.[73] Adverse drug reactions include myopathy, rhabdomyolysis, and renal failure.[72] Although transient transaminase elevations can occur with initiation of therapy, hepatotoxicity is rare and acute liver failure is extremely rare.[74] Although concern exists for a serious interaction between statins and succinylcholine leading to rhabdomyolysis and hyperkalemia, there is limited evidence from clinical trials and observational studies to support this interaction.[75,76] One study showed patients using statins who were given IV succinylcholine in doses of 1.5 mg/kg had greater myoglobinemia and fasciculations, but the level of myoglobin reached was not sufficient to cause renal toxicity.[76]



• **Fig. 32.4** A diagram summarizing the mechanisms of selected cholesterol-lowering therapies. Statins, exetimibe, and PCSK9 inhibitors all increase the expression of low-density lipoprotein *(LDL)* receptors and reduce LDL cholesterol levels (by percentages shown). Statins inhibit cholesterol synthesis in the liver, ezetimibe blocks cholesterol absorption in the intestine, and proprotein convertase subtilisin-kexin type 9 *(PCSK9)* inhibitors block the PCSK9-mediated degradation of LDL receptors. (Adapted with permission from Grundy SM. Dyslipidaemia in 2015: advances in treatment of dyslipidaemia. *Nat Rev Cardiol.* 2016;13:74–75).

Other Treatments for Dyslipidemia

Bile acid sequestrants (cholestyramine, colesevelam, colestipol) are positively charged molecules that bind negatively charged intestinal bile acids to block cholesterol absorption. They also inhibit bile acid reabsorption, leading to increased bile acid synthesis and competitive inhibition of cholesterol synthesis. Bile acid resins are associated with mild transaminase elevations but no clinically apparent acute liver injury.[77]

Ezetimibe is a synthetic azetidinone that inhibits intestinal cholesterol absorption and is associated with a low rate of transaminase elevations and clinically apparent liver injury.[78]

Fibrates (gemfibrozil, fenofibrate, clofibrate) are fibric acid derivatives that lower plasma lipids and triglyceride levels. Chronic therapy has been associated with mild elevations in transaminases and rare acute liver injury.[79]

Omega-3 fatty acids are essential polyunsaturated fatty acids used for the treatment of hypertriglyceridemia that are well tolerated and have not been implicated in liver injury.[80]

Niacin (nicotinic acid, vitamin B_3) is a water-soluble, essential B vitamin that in high doses lowers LDL cholesterol and raises high-density lipoprotein cholesterol. Niacin can raise transaminases. High doses and certain formulations have been linked to acute liver injury.[78]

Hepatitis C Treatment

Alpha interferons are immune-regulating signaling proteins with antiviral and antiproliferative activity. Treatment with interferon alfa (IFN-α) alone can occasionally completely eradicate hepatitis C infection, but sustained virologic response is seen in less than 20% of patients.[81,82]

Pegylated interferon is a synthetic interferon to which polyethylene glycol has been attached, prolonging duration of action. Treatment with pegylated INF-α leads to increased and sustained virologic response compared with standard IFN-α, especially when combined with the antiviral drug ribavirin.[82]

Ursodeoxycholic acid (ursodiol) is a bile acid that is used in chronic hepatitis C treatment for its immunomodulatory effects and to decrease clinical symptoms of liver disease such as pruritus.[83,84]

Emerging Developments

Suppression of Gastric Acid Secretion

A novel class of potassium-competitive gastric acid blocker, vonoprazan fumarate, has been on the market in Japan since 2015. It is used as an oral medication prescribed once daily for both treatment of gastric ulcers and secondary prevention of gastric acid reflux. Vonoprazan reversibly inhibits hydrogen potassium adenosine triphosphatase (H^+,K^+-ATPase) activity, resulting in a decrease in gastric acid secretion 350 times greater than standard PPIs.[85] In a study of healthy adults, vonoprazan showed inhibition of gastric acid secretion (pH > 6) lasting for almost 24 hours. Other benefits over PPIs include its stability in acidic environments, improved solubility in the stomach, and stronger inhibition of H^+,K^+-ATPase activity overall, leading to more effective lowering

of gastric acid secretion.[86] Additional clinical trials are underway, but vonoprazan has not been approved for use in the United States. If approved, vonoprazan could replace PPI use for treatment of gastroesophageal reflux disease, erosive esophagitis, peptic ulcer disease, prevention of nonsteroidal antiinflammatory drug–associated gastrointestinal events, and, used in combination with antibiotics, for treatment of *Helicobacter pylori* infection.[87]

Direct-Acting Antivirals for Hepatitis C Treatment

Prior treatment of hepatitis C virus (HCV) was based on pegylated IFN-α plus ribavirin therapy, which was associated with a multitude of negative side effects, including anemia, fatigue, and malaise. Since 2011 a new generation of HCV treatments classified as oral direct-acting antivirals has been released, including boceprevir, telaprevir, and simeprevir. The most commonly used is a combination of ledipasvir 90 mg and sofosbuvir 400 mg approved by the FDA in 2014 for genotype 1 HCV infection.[88] In a phase III clinical trial, this combination showed a 97% to 99% sustained virologic response (defined as undetectable HCV ribonucleic acid [RNA] at 12 weeks after treatment) in patients receiving once-daily treatment in combination or without concurrent ribavirin treatment with treatment for either 12 or 24 weeks.[89]

Direct-acting antivirals target the life cycle of the HCV RNA virus to inhibit replication. Ledipasvir targets one of the nonstructural HCV proteins called nonstructural protein 5A (NS5A) used in viral replication and absent in human cells.[90] Common side effects include fatigue, headache, nausea, and diarrhea.[91] Ledipasvir is used in combination with sofosbuvir, an NS5B polymerase inhibitor owing to its high rate of resistance.[90] The ledipasvir-sofosbuvir combination is indicated for use in adults with HCV genotype 1, 4, 5, or 6 without cirrhosis or with compensated cirrhosis. In combination with ribavirin, it can be used in patients with HCV genotype 1 with decompensated cirrhosis or liver transplant recipients without cirrhosis. It is also FDA approved in children older than 12 years or weighing more than 35 kg. The usual course of treatment is 12 weeks but can be extended to 24 weeks in patients who have received previous treatment with compensated cirrhosis.[92]

PCSK9 Inhibitors for Dyslipidemia

Previous standard treatments for hypercholesterolemia relied on diet modification and use of statins. A novel class of medications—monoclonal antibodies that inhibit proprotein convertase subtilisin-kexin type 9 (PCSK9)—includes evolocumab and alirocumab; similar to statins, these agents increase LDL receptor activity in the liver (see Fig. 32.4).[93] In phase II and III clinical trials (Open Label Study of Long Term Evaluation Against LDL-C [OSLER-1 and OSLER-2], respectively) common adverse reactions to evolocumab include injection site reactions, arthralgias, headache, and muscle pain leading to discontinuation of the medication in 2.4% of study patients. When compared with standard therapy, evolocumab decreased LDL cholesterol by 52%, decreased total cholesterol by 36%, and raised high-density lipoprotein cholesterol by 7%.[94]

Although evolocumab was successful at lowering LDL cholesterol, a follow-up study (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Patients with Elevated Risk [FOURIER]) was performed to evaluate effects on reducing cardiovascular endpoints, such as myocardial infarction, stroke, unstable angina, or need for coronary revascularization. The combination of evolocumab plus standard statin therapy significantly reduced the risk of cardiovascular death, myocardial infarction, or stroke by 20%, which correlated with decreases in LDL levels.[95] Evolocumab is currently FDA approved for treatment of hypercholesterolemia in combination with other lipid-lowering medications (e.g., statins, ezetimibe), and is only recommended as single-agent therapy in patients diagnosed with primary hyperlipidemia, which is typically an inherited disease. It is given as a 140-mg subcutaneous injection once every 2 weeks or 420 mg monthly.[96]

Obeticholic Acid

Nonalcoholic steatohepatitis (NASH) is associated with obesity, diabetes mellitus, and insulin resistance. Behind hepatitis and alcoholic cirrhosis, is the third most common indication for liver transplantation in the United States. In 2009, 9.7% of liver transplant recipients were performed for NASH cirrhosis.[97] An emerging treatment for NASH is obeticholic acid, a variant of the naturally produced bile acid chenode oxycholic acid, which activates the farnesoid X nuclear receptor, activation of which promotes insulin sensitivity and decreases hepatic lipid synthesis.[98] In the FLINT (Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis) trial of patients with biopsy-proven NASH, 45% of patients treated with obeticholic acid had histologic improvement (decreased fibrosis, hepatocellular ballooning, and steatosis) on liver biopsy compared with 21% in the placebo group. The obeticholic treatment group also showed elevations in total serum cholesterol and LDL cholesterol, particularly within the first 12 weeks of initiating treatment.[99]

Obeticholic acid was also studied as treatment for primary biliary cholangitis in a randomized phase III clinical trial comparing obeticholic acid in combination with standard of care ursodiol. In the obeticholic acid group, 77% of patients had a reduction of at least 15% in alkaline phosphatase compared with placebo (29%). Other markers, including total bilirubin, conjugated bilirubin, gamma-glutamyl transferase; alanine aminotransferase, and aspartate aminotransferase, also showed decreases in the treatment group. Despite improvement in laboratory values, patient symptoms showed no change on questionnaire.[100]

Key Points

- Hepatic drug metabolism takes place primarily by cytochrome P450 enzymes, where genetic variability in metabolism can affect drug plasma concentrations.
- Volatile anesthetics undergo oxidative metabolism in the liver and have variable effects on hepatic blood flow.
- Individual differences in drug metabolism in the intestine and liver are common and are major contributors to differences in drug response, including adverse effects.
- Proton pump inhibitors and H_2-histamine receptor antagonists are effective in decreasing gastric acid secretion but have

long-term side effects, including vitamin and electrolyte malabsorption, and possible predisposition toward infections, such as *C. difficile* and pneumonia.
- New treatments for opioid-induced constipation include methylnaltrexone and almivopan.
- Statins lower plasma low-density lipoprotein cholesterol and contribute to stabilization of atherosclerotic plaque. Adverse reactions include myopathy, transient transaminase elevations, and rare hepatoxicity, rhabdomyolysis, and renal failure.
- Oral direct-acting antivirals are a new generation of hepatitis C treatments, including ledipasvir-sofosbuvir, boceprevir, telaprevir, and simeprevir.
- Other novel gastrointestinal medications include vonoprazan fumarate, a reversible potassium-competitive gastric acid blocker, PCSK9 inhibitors, which increase low-density lipoprotein receptor activity in the liver, and obeticholic acid, a novel treatment for nonalcoholic steatohepatitis.

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33

Nutritional and Metabolic Therapy

DEREK K. ROGALSKY AND ROBERT G. MARTINDALE

CHAPTER OUTLINE

Fasting in the Perioperative Period

Benefits of Early Enteral Feeding

Timing of Nutrient Delivery

Pharmaconutrition-Immunonutrition

Specific Nutrients

- Glutamine
  - *Clinical Outcome Studies Using Glutamine*
- Arginine
  - *Clinical Outcome Studies Using Arginine*
  - *Recommendations Regarding Delivery of Arginine*
- Omega-3 Fatty Acids
  - *Clinical Outcome Studies Using 20 and 22 Carbon Omega-3 Fatty Acids*
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Timing of Delivery of Nutrients as Pharmacologic Agents

Use of Protocols Enhance Safe Delivery of Nutrients

Emerging Developments

- New Malnutrition Definitions and Other Nutrients
- Probiotics

Conclusion

Macronutrients have traditionally been regarded as a means to satisfy basic energy needs for cellular homeostasis, while amino acids are considered necessary for anabolism and protein synthetic machinery of the cell. Surgical, traumatically injured, and critically ill patients, however, are in a dynamic state between systemic inflammation, immune suppression, and persistent chronic inflammatory states.[1] It often takes weeks or months for the inflammatory states resulting from major surgical intervention or intensive care unit (ICU) admission to resolve. Nutrition plays an integral and ever-changing role in both sustaining life and modifying critical illness. Many factors will influence the duration and severity of the hyperdynamic inflammatory state, including preoperative nutritional optimization of the patients, timing of surgery or injury, the anesthesia and sedation provided, and the provision of appropriate postoperative nutrition to both support a patient's macronutrient needs and modify the inflammatory status.

As a result of a recent elucidation of metabolic pathways from tracer technology, gene regulation, proteomics, and genomics, the basic science and clinical research supporting the benefits of supplemental specific nutrients have increased exponentially.[2–6] Although it has long been realized that preoperative malnutrition is a risk factor for poor wound healing,[7] perioperative complications,[8] and even mortality,[9] the most common anesthetic consideration is fasting status. While gastric volume and pH at the time of induction of anesthesia affect the risk of aspiration of stomach contents, other aspects of a patient's nutritional state will significantly influence the patient's outcome and that patient's ability to tolerate the procedure. Indeed, the paradigm of many hours of preoperative fasting has been challenged in multiple ways, with an aggressive trend to minimize periods of "fasting."

Fasting in the Perioperative Period

Time elapsed from last oral intake is perhaps the most immediate and relevant issue regarding how nutrition affects the delivery of anesthesia to patients. The risk of aspiration on induction presents a severe, potentially modifiable risk to patients, such that the American Society of Anesthesiology promulgates fasting guidelines for patients undergoing elective procedures requiring anesthesia. The most recent 2017 guidelines recommend fasting times for clear liquids of 2 or more hours, 4 or more hours for breast milk, 6 or more hours for a light meal, and eight or more hours for a fatty meal, prior to undergoing general anesthesia, regional anesthesia, or sedation.[10,11]

With the emergence of Enhanced Recovery After Surgery (ERAS) pathways, there has been renewed interest in nutritional optimization in the immediate perioperative period. The thought that major elective surgery is stressful and strenuous has led investigators to question whether preoperative carbohydrate loading might improve outcomes. In a recent meta-analysis, Amer et al. showed that a carbohydrate load of at least 10 g of glucose within 4 hours of surgery conferred a small, but real benefit in hospital length of stay (LOS) when compared to fasting.[12] It appears that "carbo loading" may yield attenuation of the insulin resistance associated with the surgical insult.[13]

If not for the risk of aspiration, might it be optimal to continue nutrition through the surgical period? While it is standard care to continue parenteral nutrition (PN) through surgery, as there is no increased risk for aspiration, best practices for enteral nutrition (EN) are still the subject of debate and research. It is clear that there are certain populations of patients who benefit from EN up to and during surgical interventions. In critically injured burn patients, it has become common practice at many centers to feed through operations with significant improvement in total calories delivered.[14] Feeding up to and through surgery has also been reported in orthopedic procedures and has recently been extended to other

Abstract

The field of surgical and critical care nutrition has evolved beyond the basic provision of macronutrients to sustain metabolism into a discipline that treats and modifies disease states with immunonutrients and timely provision of macronutrients to modulate deranged physiology. Evidence-based, multidisciplinary, and protocol-driven nutritional interventions have proven effective in improving outcomes in surgical and critically ill patients. A mastery or at least understanding of the principles of nutrition therapy are in integral part of the practice of anesthesia, surgery, and critical care medicine.

Keywords

perioperative fasting
enteral feeding
nutrient delivery
immunonutrients
nutrition protocols

surgical groups.[15] There are also data to suggest that continuing postpyloric tube feeding in the critically ill intubated patient presenting for nonabdominal surgery does not increase the incidence of aspiration, suggesting that EN can be safely continued in the perioperative period.[16]

Benefits of Early Enteral Feeding

Early EN in the ICU has myriad reports explaining the diverse mechanisms to support the observed benefits (Table 33.1). The gastrointestinal tract comprises the largest immune organ in the body and is responsible for the production of over 80% of the immunoglobulin transported to extraintestinal sites. The ability of the gut to function appropriately as an immune organ is dependent on the maintenance of both structural and functional integrity. The integrity of the gut, in turn, is greatly dependent on continued exposure to luminal nutrient substrates. Both adaptive and innate immune defenses are active in this process. Innate mechanisms are dependent on epithelial tight junctions and secretory capabilities of the mucosa. Secretory immunoglobulin A (IgA) is an important component of the adaptive immune system, as antigens are tagged and presented to dendritic cells within Peyer patches, which are in highest concentration in the distal small bowel. Gut disuse over a period of as little as 5 days has been shown to dramatically decrease the mass of gut-associated lymphoid tissue (GALT) and the production of secretory intestinal IgA.[4,5,17] These changes are completely reversed with reinstitution of EN therapy.[6] Increases in intestinal permeability have been shown to correlate with the development and severity of multi-organ failure (MOF) syndrome.[3,18] Using EN to modify the severity of the systemic inflammatory responses by attenuating metabolic and oxidative stress is a primary goal of nutritional therapy in the surgical or critically ill patient.[19,20]

Timing of Nutrient Delivery

The optimal time to start nutrition support is influenced by a host of factors, including age, premorbid conditions, route of nutrient delivery, metabolic state, and organ perfusion and function.[21,22] As previously noted, literature evaluating nutritional support for critically ill patients has analyzed heterogeneous populations. Nevertheless, these diverse studies provide a foundation to guide nutritional therapy in a wide range of ICU patient types (e.g., burn, trauma, abdominal surgery, oncologic surgery, and so on).[23,24]

TABLE 33.1 Metabolic Benefits of Early Enteral Feeding

- Attenuates inflammatory response to stress/critical illness
- Prevents mucosal atrophy, loss of gut barrier
- Luminal delivery maintains GALT and MALT
- Supports systemic immune response
- Helps maintain normal gut bacterial flora (microbiome)
- Decreases insulin resistance, better glycemic control
- Maintains vagal-mediated antiinflammatory reflex
- Luminal (portal) nutrient delivery allows for hepatic first-pass metabolic effects
- More balanced nutrient delivery possible when compared to parenteral nutrition

GALT, Gut-associated lymphoid tissue; *MALT,* mucosal-associated lymphoid tissue.

The reported physiologic benefits of early EN are, among others, prevention of adverse structural and functional alterations in the mucosal barrier, augmentation of visceral blood flow, and enhancement of local and systemic immune response.[25,26] The clinical benefits of early EN, defined as within 24 to 48 hours of ICU admission, include reduced infectious morbidity, LOS, and, in some reports, reduced mortality, all with minimal risk of harm to the patient.[27–31] Despite these acknowledged benefits, nutrition delivery remains suboptimal in a significant percentage of critically ill patients.[32,33]

Acknowledging that the early initiation of nutrition support constitutes best practice, a multidisciplinary approach to determining appropriate timing in the individual patient cannot be overemphasized. Enteral feeding should not proceed until appropriate resuscitation has been undertaken (Table 33.2). Early resuscitation remains a cornerstone of ICU therapy. Early and aggressive resuscitation, or "early goal-directed therapy," involves the placement of invasive lines for monitoring, drug delivery, and volume resuscitation, with vasopressors if the patient fails to respond appropriately to volume expansion.[34] While there is no one laboratory or hemodynamic parameter signaling the successful resuscitation of the critically ill patient, trends in hemodynamic parameters—including mean arterial pressures, central venous pressures, and pressor requirements in conjunction with urine output, arterial base deficit, serum lactate, and venous oxygen saturations—are utilized in order to determine the relative success of resuscitation.

Splanchnic circulation can increase by as much as 40% to 60% in the setting of enteral feeding. The specific actions of digestion and absorption increase the metabolic demand and oxygen utilization by the gastrointestinal tract.[35] If supply falls short of demand, rare but devastating complications, such as nonocclusive mesenteric ischemia (NMI), can ensue (Fig. 33.1). Fortunately, nonocclusive mesenteric ischemia is a very rare complication, but since its effects can be devastating, with mortality rates reported as high as 80%,[36] enteral feeding in the hemodynamically unstable patient should be undertaken with extreme caution.[24]

Following adequate resuscitation and assuming that no other absolute contraindication to enteral feeding exists (e.g., bowel obstruction), enteral support should be initiated as soon as possible,

TABLE 33.2 Considerations Before Any Nutritional Intervention, Either Enteral or Parenteral, in Intensive Care Unit Settings

Optimize Timing and Intensity of Resuscitation

Correct volume deficits, electrolytes, acid–base disorders.
Obtain infection source control if it is in question.

Institute Antibiotic Therapy as Indicated

Early, aggressive broad-spectrum antibiotics, then deescalate as cultures become available.

Attempt to Maximize Visceral Perfusion

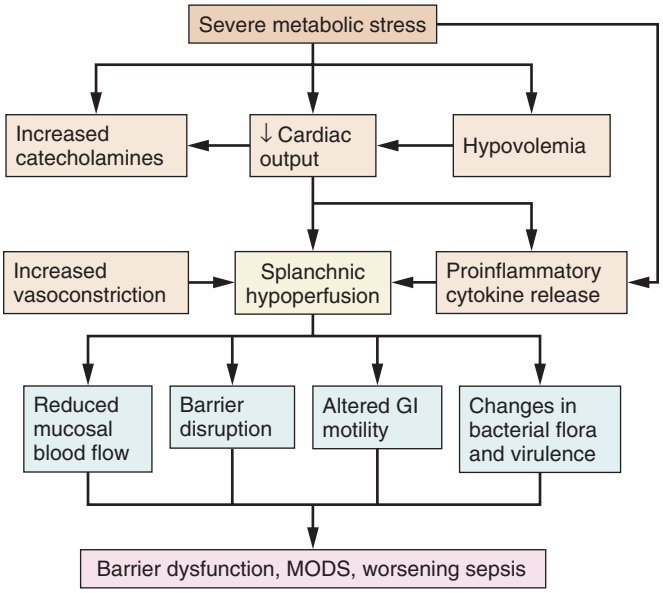
Prevents loss of gut mucosal integrity.

Consider Specific Organ Support as Indicated

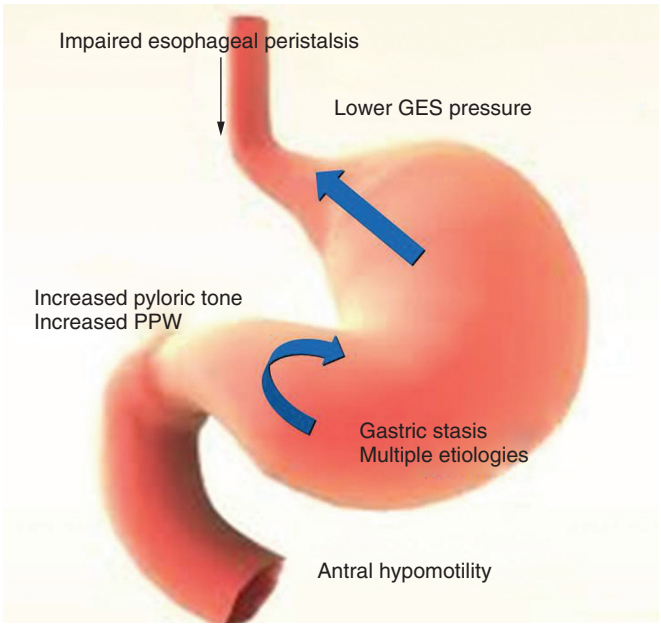
Examples: pulmonary, renal, cardiac, hepatic

Maintain Glycemic Control

Intravenous insulin drips (protocols) to maintain glycemic control in range of 140–80 mg/dL



• **Fig. 33.1** Pathophysiology of splanchnic hypoperfusion often associated with critical illness. *GI,* Gastrointestinal; *MODS,* multiple organ dysfunction syndrome. (Modified from Schmidt H, Martindale R. The gastrointestinal tract in critical illness: nutritional implications. *Curr Opin Clin Nutr Metab Care.* 2003;6:587–591; and Mutlu GM, et al. GI complications in patients receiving mechanical ventilation. *Chest.* 2001;119:1222–1241.)



• **Fig. 33.2** Mechanisms involved in gastric dysmotility in the intensive care unit population. *GES,* Gastroesophageal sphincter; *PPW,* pyloric pressure wave. (Modified from Caddell KA, Martindale R, McClave SA, et al. Can the intestinal dysmotility of critical illness be differentiated from postoperative ileus? *Curr Gastroenterol Rep.* 2011;13:358–367.)

regardless of the status of traditional markers of bowel function (bowel sounds, flatus, passage of stool).

Numerous reports support the concept that the initiation of EN should not be delayed while waiting for evidence of bowel function, though the absence of the clinical markers of bowel function may be predictive of worse patient clinical outcomes and higher rates of EN intolerance.[37] The approach of waiting for these signs leads to unnecessary delays in feeding. In a randomized trial, oral feeding initiated within 48 hours of gastrectomy, without waiting for traditional predictors of feeding tolerance (e.g., passing flatus) demonstrated the safety of the approach.[38] There was no increase in morbidity, and there was a reduction in LOS. A recent meta-analysis, examining 15 studies and 1240 patients with gastrointestinal anastomoses, demonstrated reduced postoperative complications when feeding was initiated within 24 hours of operation.[31] Other meta-analyses, specifically in ICU and trauma patients, report a significant decrease in mortality and infectious complications.[18,39]

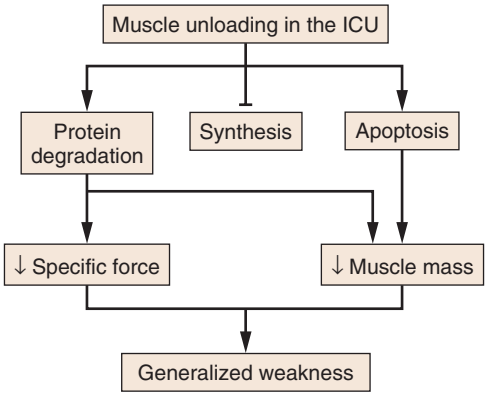
Recent approaches to maximize gut function in the postoperative and critical care settings include maintenance of visceral perfusion; glycemic control; electrolyte correction; early EN; and minimization of medications that alter gastrointestinal function, such as anticholinergic agents, opioids, and high-dose vasopressors.[37] Gastrointestinal intolerance should be continually reassessed, as it can manifest clinically in a variety of forms, including acidosis, abdominal distension, increased gastric residual volumes or nasogastric output, abdominal pain, or diarrhea. The segmental contractility of the gastrointestinal tract should be considered, as dysmotility can be focal (affecting predominantly either the proximal or distal bowel) or diffuse. Impaired gastric and proximal gastrointestinal motility (Fig. 33.2) can be overcome rather efficiently through the placement of postpyloric feeding tubes. Postpyloric tubes can be successfully placed at the bedside in greater than 80% of patients.[40]

Prokinetic agents can be used early and are helpful in some patients. Erythromycin acts on motilin receptors, resulting in increased motility, and can be used on a short-term basis but is limited due to tachyphylaxis. Metoclopramide, a 5-hydroxytryptamine ($5HT_4$) receptor agonist, works via cholinergic stimulation and is primarily efficacious in the proximal gut. When using **metoclopramide** (see Chapter 32), one must also consider the potential for extrapyramidal side effects, especially in patients with altered mental status from traumatic head injury or cerebral vascular events. **Alvimopam** (see Chapters 17 and 18), a peripherally acting μ-antagonist, has demonstrated some success in the setting of dysmotility associated with opioid administration in the postoperative setting.[41] No single prokinetic agent will have uniform success in the ICU, and the factors contributing to gastrointestinal dysmotility in each patient must be considered. Caution should be taken when using prokinetic agents on patients at high risk for bowel necrosis or obstruction.

Early EN is best accomplished in the ICU and postoperative settings, using standardized protocols.[25,42] Protocolizing early enteral feedings in appropriately selected patients can reduce duration of mechanical ventilation, infectious complications, hospital LOS, and mortality.[43]

Pharmaconutrition-Immunonutrition

In 1794, John Hunter described in his book, *A Treatise on Blood, Inflammation and Gunshot Wounds, A Mechanism of Inflammation*, an observation that "many types of injury produce a similar inflammation."[44] Similarly, in 1904, Sir William Osler stated, "except on few occasions the patient appears to die from the body's response to infection rather than from it." These two extremely insightful and prophetic comments were both made over 100 years ago. The current strategy in the ICU of using nutrition therapy to modulate inflammation and immune response in the surgical, traumatically



• **Fig. 33.3** Explanation for muscle loss during unloading of muscle in the intensive care unit. These effects culminate in prolonged, generalized muscle weakness. Weakness lasts for weeks to months; up to 50% of survivors do not return to pre-ICU function at 1 year.

TABLE 33.3 Nutrients/Compounds Reported to Have Immune and/or Metabolic Activity

Arginine*	Ginger	Selenium*
Boswellia	Glucosamine	Shark cartilage
Caffeine	Glutamine*	Taurine
Capsaicin	Glutathione	Threonine
Carnitine	Leucine*	Tumeric
Chamomile	Licorice	Vitamin C*
Creatine	Probiotics	Vitamin E*
Curry paste	Omega-3 FA (EPA/DHA)*	Willow bark
Cysteine	Resveratrol	Zinc*
Echinacea	Saffron	
Garlic		

DHA, Docosahexaenoic acid; *EPA*, eicosapentaenoic acid; *FA*, fatty acid.
These compounds have all been reported to alter metabolic or immune function in human models. The majority of data is with vitamins E and C, trace mineral zinc and selenium, the amino acids, glutamine, arginine, and leucine, in addition to the fish oils (indicated with asterisk).

injured, and critically ill populations is now widely accepted. This strategy of nutrition therapy, sometimes called pharmaconutrition or immunonutrition, uses specific nutrients to attenuate or control the body's metabolic response to stress and trauma rather than allowing systemic inflammatory response syndrome (SIRS) to progress to persistent inflammation, immunosuppression, and catabolism syndrome (PICS). The metabolic response to stress that can ultimately lead to PICS has been well described,[45] which includes a hyperdynamic cardiac and pulmonary state, insulin resistance, hyperglycemia, accelerated protein catabolism from muscle, poor adaptation to starvation, and increased oxidative stress. Unabated, the metabolic response to stress can culminate in immune suppression.[46] During this hyperdynamic phase of critical illness, surgery, or trauma, the loss of lean body mass continues, despite delivery of seemingly adequate enteral or parenteral protein and calories. In effect, administration of standard "calories and protein" to the hyperdynamic patient will not reverse the adverse effects of ongoing loss of lean body tissue. The hyperdynamic induced loss of lean body tissue is made worse by "muscle unloading" (Fig. 33.3). Several reports have now shown that using specific nutrients—such as fish oils, selected amino acids (e.g., arginine, glutamine, leucine), antioxidants, and nucleic acids—in quantities greater than necessary for "normal" metabolism has resulted in multiple outcome benefits, including shortened length of ICU and hospital stays, decreased incidence of infections, and reduced mortality in some cases.[24,47,48]

A wide range of select specific nutrients have been reported to benefit the critically ill patient when delivered at pharmacologic quantities. Many of these compounds are now considered to be therapeutic agents in the management of complex, catabolically stressed patients (Table 33.3). A collaboration between the Society of Critical Care Medicine (SCCM) and the American Society of Parenteral and Enteral Nutrition (ASPEN) resulted in Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient, which has been recently updated. These guidelines summarize the available evidence, and recommend that postoperative surgical ICU patients and patients with traumatic brain injury benefit from EN with immunomodulating formulas.

Several immune and/or metabolic modulating enteral formulas are now available globally. These products contain a variable quantity of nutrients identified and reported as beneficial during critical illness. Well over 100 prospective randomized human trials have been conducted with different combinations of these immune and metabolic modulating nutrients in various ICU, surgical, and medical populations. A wide range of methodologic quality is observed in these studies from relatively small, poorly designed studies to large prospective randomized clinical trials with intention-to-treat analysis. Most of the larger studies have been extensively analyzed and methodologically scrutinized by numerous reviewers. Despite the heterogeneity of the study designs, the majority of these studies report a clear benefit of reduced intensive care and hospital LOS, decreased antibiotic use, and reduced rates of infection.[24,49] In particular, evidence cited in ASPEN/SCCM Guidelines suggests clinical effects of specific pharmaconutrients. These nutrients—including glutamine, fish oils, and arginine—have been credited with a reduction in infections and LOS in surgical patients. They produce a similar favorable impact on these outcomes in other ICU populations, although less dramatic benefit is noted.

Specific Nutrients

For decades, amino acids were believed to modulate intermediary metabolism, but the clinical outcome benefits of specific amino acids have only been reported over the last 15 years. Dietary supplementation with the amino acids glutamine, arginine, and leucine has been the focus of the majority of clinical trials, but other amino acids—specifically, glycine, taurine, citrulline, and glutamate—have received interest recently.[50] This chapter will present only a brief summary of amino acid and Omega-3 fatty acid supplementation.

Glutamine

Since the early 1980s, glutamine has gained popularity in the critical care and surgical arena, following reports of its wide range of metabolic and outcome benefits, from decreasing mortality in critical care and trauma to enhancing mood in psychiatry.[51] Although little controversy exists over the potential benefits of glutamine in the surgical setting, there is still some doubt about the need for routine supplementation in all ICU populations.[52]

Glutamine is a nonessential amino acid that can be synthesized in most tissues of the body.[53] Skeletal muscle, by virtue of its mass,

produces the majority of endogenous glutamine. During major catabolic insults, demand for glutamine outstrips the endogenous supply, resulting in its designation as a conditionally essential amino acid. Glutamine serves as the primary oxidative fuel for rapidly dividing tissues, such as the small bowel mucosa, proliferating lymphocytes, and macrophages.[54] Glutamine has numerous roles in intermediary metabolism, including maintenance of acid–base status, as a precursor of urinary ammonia, and in interorgan nitrogen transfer for the biosynthesis of nucleotides, amino sugars, arginine, glutathione, and glucosamine.[55,56] During periods of stress, glutamine can provide the carbon skeleton for gluconeogenesis and is the primary substrate for renal gluconeogenesis.[55] In addition to the proposed benefits described earlier, glutamine supplementation has recently been shown to be effective in decreasing peripheral insulin resistance in stressed human and other mammalian models.[57–59] In addition, glutamine supports optimal gut growth and repair and decreases sepsis and other infectious conditions. Further, glutamine enhances nitrogen balance and supports endogenous antioxidant functions via nuclear factor kappa B (NFkB) and glutathione.[60]

There is a rapidly growing volume of human data regarding the use of parenteral and enteral glutamine supplementation.[61] There is little dispute that administration by the parenteral route as a dipeptide currently yields a better clinical outcome than the enteral route in the ICU population.[62] The majority of enterally delivered glutamine, estimated at 70% to 80%, is metabolized in the viscera, with only a fraction reaching the systemic circulation. Despite this, outcome benefits have been reported with the delivery of enteral glutamine.[61,63] As a result of the constraints by the US Food and Drug Administration, parenteral glutamine is not readily available in the United States. Intravenous glutamine is widely used by much of the world in the form of glutamine dipeptide.[64]

In animal models and limited human experience, supplemental glutamine has been shown to enhance intestinal adaptation after massive small bowel resection[65] and to attenuate intestinal and pancreatic atrophy.[56] Glutamine appears to maintain gastrointestinal tract mucosal thickness, stabilize DNA and protein content, and reduce bacteremia and mortality after chemotherapy and following sepsis or endotoxemia.[58,61] Glutamine has also been reported to enhance glutathione synthesis, the primary endogenously produced antioxidant in mammalian species.[59]

One additional mechanism grounded in basic science literature explaining some of the benefits observed with glutamine supplementation is the induction of heat shock proteins (HSPs; HSP-70, HSP-32, HSP-27), which are critical to the cell's ability to survive injury and attenuate SIRS during critical illness.[66–69] HSPs are a family of highly conserved cellular cytosolic chaperone proteins involved in cell protection during various metabolic stressors.[70] They assist in cellular recovery following injury and partially protect the cell and involved organ from subsequent failure.[68]

Clinical Outcome Studies Using Glutamine

In humans undergoing surgical stress, glutamine-supplemented PN appears to help maintain nitrogen balance and the intracellular glutamine pool in skeletal muscle tissue.[71] In trauma patients, a reduction in pneumonia by over 50% has been demonstrated with glutamine supplementation when compared to an isonitrogenous, isocaloric control.[63] In critically ill patients, glutamine supplementation has been shown to attenuate villous atrophy and the increased intestinal mucosal permeability associated with parenteral nutrition.[72,73] In a randomized blinded trial of 84 critically ill patients, of which 71% were septic on admission, parenteral glutamine supplementation showed significant improvement in mortality at 6 months.[74] PN supplemented with glutamine has also resulted in fewer infections, improved nitrogen balance, and significantly shorter mean hospital LOSs in bone marrow transplantation patients.[75] Oral glutamine supplementation reduced the severity and decreased the duration of stomatitis that occurred during chemotherapy in bone marrow transplant patients.[76] Glutamine supplementation at the level of 30 g/d in esophageal cancer patients undergoing radiation was associated with preserved lymphocyte response and decreased gut permeability.[77] In a multicenter, prospective, blinded trial involving 114 ICU patients with multiple trauma, complicated surgery, or pancreatitis, total PN supplemented with the dipeptide L-alanyl-L-glutamine was compared to L-alanine + L-proline control. The glutamine supplemented group had significantly fewer infections, decreased incidence of pneumonia, and better glycemic control.[64]

In 2002, a meta-analysis evaluating the use of glutamine in the ICU population concluded that in surgical patients, glutamine supplementation may be associated with a reduction in infectious complication rates and shorter LOS.[78] Large multicenter trials using glutamine have recently been published with mixed results, depending on dosing concentrations, patient heterogeneity, and route of delivery.[62,79]

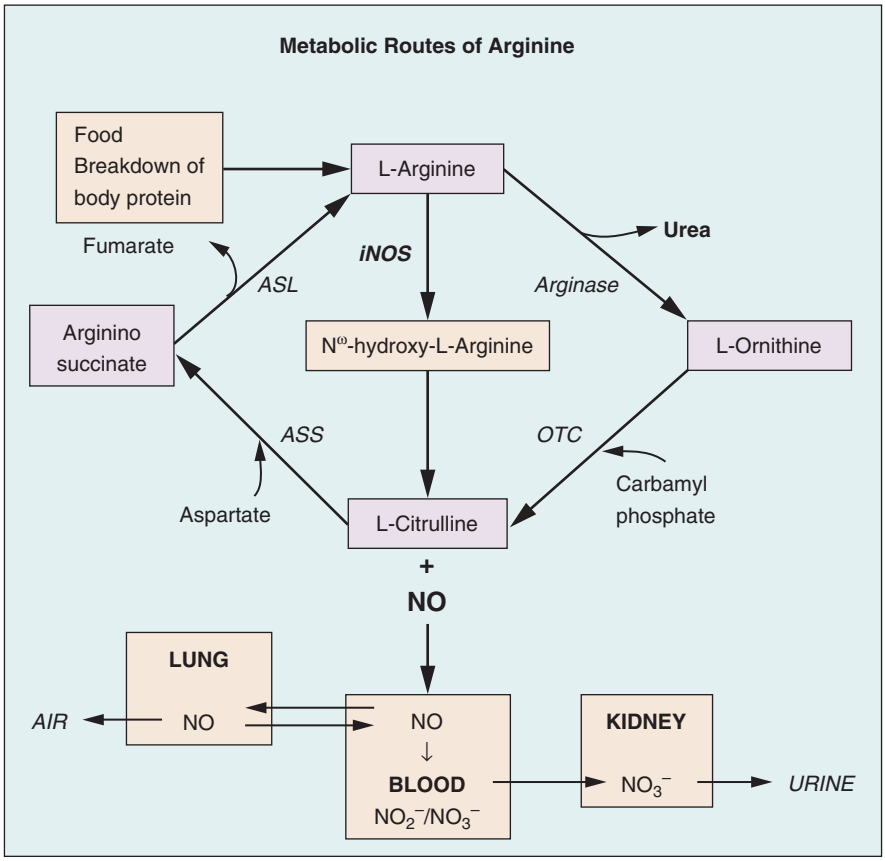
A large multicenter trial in the United Kingdom in which patients received 20 g/d resulted in no benefit in reducing infections, LOS, and modified Sequential Organ Failure Assessment (SOFA) score.[79] In the Scandinavian glutamine trial, in which glutamine dipeptide was delivered at a dose of approximately 0.3 g/kg/d, there was a reduced mortality benefit in those patients who received glutamine for greater than 3 days.[62] Trials in enteral glutamine continue, notably the RE-ENERGIZE Study (RandomizEd Trial of ENtERal Glutamine to minimIZE Thermal Injury), which is ongoing.[80]

Arginine

Arginine is considered a nonessential amino acid under normal physiologic conditions of cell growth and development. Arginine becomes conditionally essential in the stressed mammalian host and plays a significant role in the intermediary metabolism of the critically ill patient.[81] Key contributions of arginine include it being a secretagogue for the release of growth hormone, prolactin, and insulin, as well as stimulation of proliferation and activation of T cells.[82,83] L-Arginine is available to the host from endogenous synthesis as part of the urea cycle (via citrulline conversion in the kidney), from endogenous protein breakdown, and from dietary protein sources (Fig. 33.4). A typical western diet only contributes about 20% to 25% of total arginine.

Arginine is a prominent intermediate in polyamine synthesis (one of the primary regulators of cell growth and proliferation), proline synthesis (wound healing and collagen synthesis), and is the only biosynthetic substrate for nitric oxide (NO) production from the three isoforms of nitric oxide synthase (eNOS, iNOS, nNOS). NO is a potent intracellular signaling molecule influencing virtually every mammalian cell type. Arginine also serves as a potent modulator of immune function via its effects on lymphocyte proliferation and differentiation,[53,82] as well as its benefits in improved bactericidal action via the arginine NO pathway.

The de novo synthesis and dietary intake is reduced in acute surgical and major metabolic insults. Following these insults, immature cells of myeloid origin are present in the circulation and lymph tissue; these cells express high levels of arginase-1,



• **Fig. 33.4** Metabolic pathways for arginine. In critical illness, the exogenous supply of L-arginine is reduced and endogenous demand is increased by increases in arginase and iNOS activity. Reduced levels of L-arginine lead to T-cell dysfunction and impaired immune responses, resulting in infection. *ASL,* Arginosuccinate lyase; *ASS,* arginosuccinate synthase; *NO,* nitric oxide; NO_2^-, nitrate; NO_3^-, nitrate; *iNOS,* inducible nitric oxide synthase; *OTC,* ornithine transcarbamylase.

an enzyme that degrades arginine to ornithine. While exogenous and endogenous supply of arginine is decreased, the host's cellular demand for arginine is increased. This accelerated demand for arginine in the settings of trauma, surgery, sepsis, and critical illness is driven mainly by the upregulation of arginase in several tissue beds (arginase I and arginase II) yielding urea and ornithine and of iNOS yielding NO and citrulline.[53,84] This state of relative arginine deficiency is manifested in the suppression of T-lymphocyte function and proliferation. Other signs of T-cell dysfunction after surgery or trauma include a decrease in the number of circulating CD4 cells, increased production of interleukin-2 and interferon gamma, and the loss of the zeta chain peptide, which is essential in the T-cell receptor complex. These changes in arginase activity result in impaired immune function at multiple levels of the immune response.[85] This defect in immunocompetence can contribute to an increased risk of infection for critically ill patients.

Making generalized statements about amino acid metabolism in critical care is extremely difficult because the ICU population is such a heterogeneous group. Without strong scientific evidence validating the toxicity or benefits of today's most popular dietary supplements, let alone an amino acid with the metabolic complexity of arginine, making global recommendations is naïve. Both animal and human data are available to support arguments for and against the use of supplemental arginine in the ICU populations. These results will strongly depend on dose given, model chosen to study, and duration of therapy. Trends are beginning to show the majority of the literature supporting use of arginine supplementation in both medical and surgical populations.[28,86]

Clinical Outcome Studies Using Arginine

Of all the pharmaconutrients, arginine has prompted the most controversy. The theoretical concept that arginine may pose a threat to the surgical or critically ill patient is mainly based on the perception that postoperative or septic surgical patients are often hemodynamically unstable, with upregulated iNOS enzyme activity. Consequently, by delivering supplemental arginine in metabolic states of upregulated iNOS, an increase in NO will result in vasodilation and hypotension, leading to even greater hemodynamic instability and organ dysfunction.[87] This hypothesis has not held up in clinical practice; a nonselective NOS inhibitor was administered in high doses to counteract vasodilation and hypotension in patients with severe sepsis in septic shock. The 28-day mortality rate was significantly increased when compared to patients receiving placebo (5% dextrose), 59% versus 49%, respectively ($P < 0.001$).[83] In fact, in this study, the highest mortality occurred within 72 hours in the treatment group. An alternate, equally valid hypothesis would be that controlled vasodilation would be beneficial in critical illness and sepsis. Shock, by definition, is inadequate delivery of oxygen and nutrients to maintain normal tissue and cellular function.[87] It is logical to think that the vasodilation resulting from supplemental arginine is a cellular adaptive mechanism attempting to increase delivery of oxygen to the cell. This concept was illustrated

in a study in which investigators attempted to modulate asymmetric-dimethylarginine (ADMA) in septic patients by tight glycemic control but was unsuccessful in altering the course of sepsis. As with other studies, the investigators were left to question whether the effect of an endogenous inhibitor of NOS synthases is preferable to potentially beneficial effects of arginine.[88,89]

ADMA has been shown to increase in states of inflammation in acute infections and other stress models and has been well described.[89] It has been suggested that an imbalance of arginine and ADMA is associated with altered endothelial cell function and cardiac dysfunction. Some investigators reported that elevated arginine and lower ADMA resulted in improved mortality in septic patients.[90] A lower ratio of arginine to ADMA resulted in poor organ perfusion and decreased cardiac output. Until recently, few studies had evaluated supplemental arginine as a single agent in the critically ill and septic patient population. An elaborate series of tracer studies in a clinical trial dealing with citrulline and arginine metabolism in septic patients has shed light on this controversy.[91] The complex metabolic alterations noted in sepsis that contribute to reduced citrulline and arginine availability suggest that supplemental arginine may, in fact, be beneficial in the septic population. In another study using tracer technology, investigators evaluated arginine in sepsis and also concluded that arginine may be deficient in sepsis because of inadequate de novo synthesis.[92]

Arginine is perhaps the most controversial of the immunomodulating nutrients, but it is important to reiterate that investigations examining the physiologic impact of arginine and its related enzymes, the NOSs, have been conducted in different critically ill populations (medical vs. surgical, severely septic vs. nonseptic, and so on) using variable dosing, making generalizations to all ICU populations difficult. Current expert opinion suggests that there may be subgroups of patients whose vascular function is improved by L-arginine supplementation and there may be other subgroups of patients who simply do not benefit from L-arginine dietary supplementation. At this time, the ASPEN/SCCM 2016 guidelines do not recommend routine arginine supplementation for medical ICU patients, but do recommend its routine use in surgical and trauma patients, including those with traumatic brain injury. Arginine dose and patient selection are likely important factors affecting any study outcome.[93]

Arginine is available to the host from numerous sources. "Normal" arginine intake for a western diet is between 5 and 7 g/d, while endogenous production of arginine is estimated at 15 to 20 g. Studies using different doses of arginine, from 5 to 30 g/d in the normal host, have shown varying results. It appears that orally delivered arginine supplementation up to 30 g/d is safe, with few gastrointestinal side effects.[50,83] The current routinely used critical care enteral formulas deliver between 0 to 18.7 g of supplemental arginine per liter of formula. It is estimated that, on average, an ICU patient receiving arginine supplemented enteral feeding at prescribed rates would receive between 15 to 30 g/d of supplemental arginine. Several factors must be considered when deciding if arginine fits into the therapeutic plan of the critically ill patient. One must evaluate organ systems involved, timing of nutrient delivery, and location and route of delivery and, interestingly, coadministration without other "immune" or "metabolically" active agents (e.g., fish oils or nucleic acids). In very different models, several studies have both shown that delivery of an omega-3 fatty acid (FA) with arginine will significantly alter the arginine metabolism via arginase and iNOS, possibly yielding more available arginine.[94,95] Ornithine alpha-ketoglutarate (OKG) and citrulline are other nutrients that have been reported to have potential interaction with arginine. Citrulline is poorly metabolized by the liver, essentially bypassing the first-pass hepatic nutrient metabolism, making it highly bioavailable via oral route. Citrulline is then converted to arginine in the kidney, making citrulline a key component in arginine homeostasis, especially in the critically ill population.[84] Ultimately, it can be difficult to tease out the separate effects, as immunonutrients are often given together with overall good clinical outcomes in both critically ill patients and those who are not critically ill.[27,96]

The appropriate arginine level and supplemental dose of arginine in the critically ill or hypermetabolic patient in which a proinflammatory state exists is difficult to determine and remains to be defined. Arginine is very tightly regulated within the cell by multiple mechanisms—including regulation of arginine membrane transporters, as well as arginase and NOS enzymatic activity—and the colocalization of enzymes in the membrane leads to variable concentration within the intracellular space.[84] Arginine appears safe and beneficial in the levels delivered by commercially available formulations containing supplemental arginine. It is clear that additional research is needed on the influence of arginine in specific populations, specific disease conditions, and the gene–nutrient interactions.

Recommendations Regarding Delivery of Arginine

It appears from review of human data that arginine is safe and beneficial at doses delivered in immune and metabolic modulating formulas for most all hemodynamically stable ICU populations able to tolerate enteral feeding. This would include medical and surgical ICU patients, trauma patients, major surgical patients, and those post-myocardial infarction or with pulmonary hypertension. Elective major surgical patients across multiple surgical specialties can be expected to benefit from a reduction of surgical infections when arginine-containing formulations are applied in the perioperative setting.[49]

Omega-3 Fatty Acids

Although lipids are a mainstay in nutritional therapy for the critically ill and surgical populations and numerous choices exist (Table 33.4). Controversy still exists regarding lipid digestion, absorption, and utilization in hyperdynamic surgical settings.[97,98] The heterogeneous nature of the ICU population makes lipid administration in these groups somewhat challenging. Although uncertainty exists on which lipid formulation to deliver, there is no debate regarding the need to meet the essential FA and cellular oxidation requirements. The use of lipids in this manner replaces malabsorbed lipid nutrients and serves as a daily source of calories shown to be equally nitrogen sparing with glucose when administered continuously for 4 days.[99] The beneficial antiinflammatory effects of n-3 FAs, primarily eicosapentaenoic acid and docosahexaenoic acid (EPA and DHA, respectively), have been well documented in several chronic inflammatory diseases, including rheumatoid arthritis, Crohn disease, ulcerative colitis, lupus, multiple sclerosis, and asthma (see Table 33.4).[59,100–102]

In addition to the use of antiinflammatory lipids in the setting of chronic illness, the use of specific antiinflammatory lipid substrates in the acute hyperdynamic setting to maintain vital organ function and to modulate key processes—such as immunity, inflammation, and antioxidant defenses—has now become routine in many surgical and ICU settings.[103] It has been reported in numerous human randomized clinical trials that appropriate use of omega-3 FAs (EPA/DHA) can partially attenuate the metabolic response,

TABLE 33.4 Lipid Choices in Intensive Care Unit Stress States

Lipid absorption and utilization is very dependent on source, route, and metabolic state of the patient.

Enteral vs. Parenteral Lipids

Enteral superior to parenteral: significantly more lipid options enterally

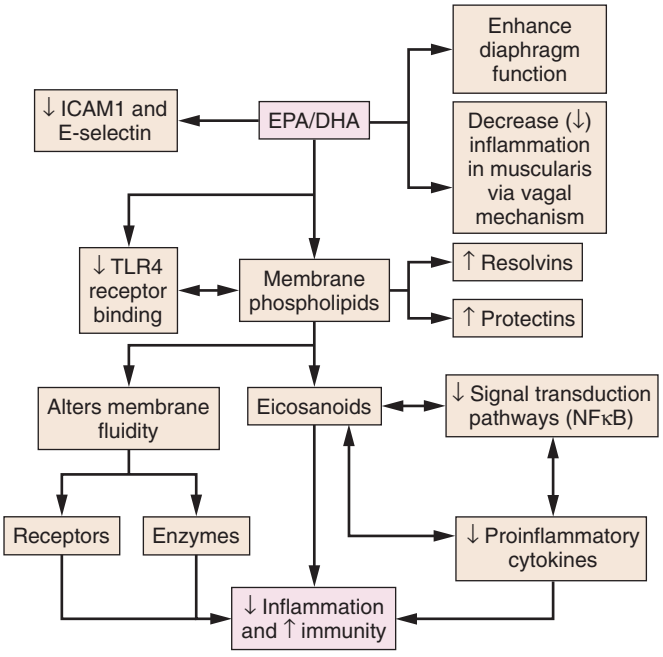
Lipid Substrate

SCFA (requires colonic fermentation of soluble fibers)
- Acetate, butyrate, propionate
- Increase utilization in stress models

MCFA
- 6–12 carbons
- Dual absorption via portal and lymphatics
- No carnitine required to enter inner mitochondria membrane for β oxidation
- Increase utilization

LCFA
- Omega-6
- Omega-3
- Utilization variable depending on carnitine, oxygenation, for example

LCFA, Long-chain fatty acids; *MCFA,* medium-chain fatty acids; *SCFA,* short-chain fatty acids.



• **Fig. 33.5** Multiple beneficial effects of eicosapentanoic acid and docosa hexaenoic acid in the critical care setting. *DHA,* Docosahexaenoic acid; *EPA,* eicosapentaenoic acid; *ICAM-1,* intracellular adhesion molecule-1; *NFκB,* nuclear factor kappa B; *TLR-4,* toll-like receptor-4.

reverse or minimize the loss of lean body tissue, prevent oxidative injury in a variety of tissues, and improve outcome by modulating synthesis of proinflammatory and antiinflammatory mediators.[97,103–105] The mechanisms of these effects are multiple, which include changes in cell membrane phospholipids, alterations in gene expression, and modifications to endothelial expression of intracellular adhesion molecule 1 (ICAM)-1, E-selectin, and other endothelial receptors regulating vascular integrity and function. Additionally, EPA and DHA derivatives—including resolvins, docosatrienes, and neuroprotectins—now commonly called specialized proresolving molecules (SPMs) have been shown to be potent active effectors of the resolution of inflammation.[97,106] SPMs regulate polymorphonuclear neutrophil (PMN) transmigration and decrease neutrophil infiltration, proinflammatory gene signaling, and NFκB binding. These protective mediators are found to be highly conserved among species, from primitive fish to mammals.[107] In fact, some data suggest that EPA can help prevent loss of diaphragm function in sepsis[108] and promote resistance to gram-negative pathogens, such as *pseudomonas*.[109]

Recent evidence supports the concept that EPA and DHA can be thought of as not just *passively* modulating the inflammatory process but as *actively* involved in the resolution of inflammation via these SPM compounds.[110,111] The use of enteral and parenteral formulations containing antiinflammatory lipids, primarily EPA and DHA, can be used as pharmacologic agents to modulate the hyperdynamic response and outcomes in surgical and critically ill patients.

Clinical Outcome Studies Using 20 and 22 Carbon Omega-3 Fatty Acids

When evaluating the literature regarding the use of omega-3 FAs, it is important to take into account the species evaluated and the experimental model, along with the total quantity of macronutrient delivered, carbon structure, and lipid ratios involved. Variable and occasionally even contradictory results can be obtained in cell cultures, animal models, or in human clinical trials depending on these factors. Other significant factors to evaluate are the route of delivery, timing of delivery in relation to the specified event, and the percent of lipid calories delivered. If the omega-3 fat is delivered in the 18 carbon α-linolenic acid form (canola oil or flaxseed oil), it often has little effect in humans.[112] If it is given as EPA or DHA, however, rapid and dramatic effects have been reported.[113] Other issues to evaluate include the amount of antioxidant vitamins and micronutrients being delivered simultaneously. This is especially important for vitamin E, as the amount of polyunsaturated fatty acid (PUFA) delivered can alter vitamin E requirements.[114]

Recommendations Regarding Delivery of Omega-3 Fatty Acids

Similar to the pharmaconutrients previously discussed, the optimal dose, timing, and formulation of omega-3 FAs is unknown. A prominent meta-analysis that aggregated the results of 3 randomized clinical trials (RCTs) conducted in patients with adult respiratory distress syndrome (ARDS) found that an enteral formula enriched with fish oils appears to significantly reduce ICU LOS, ventilator days, and mortality.[115] More recent prospective, randomized trials of fish oils and borage oil in ARDS, however, have shown no benefit.[116,117] Several issues should be resolved before abandoning the use of fish oils in ARDS, such as the method of feeding, background nutrition, and the patient's absorptive capacity with bolus delivery of the pharmacologic agents. Previous studies supplied adequate additional macronutrients as background when giving the antiinflammatory lipid compounds, while the two most recent studies delivered the bolus irrespective of background nutrition. While there is variability in outcome benefit seen in results from clinical trials using omega-3 antiinflammatory therapy in critically ill patients, doses greater than 5 g/d have consistently shown significant benefit in this population, specifically those with acute lung injury (ALI)/ARDS or sepsis/septic shock.[118] Numerous other studies in ICU populations continue to support the use of fish oils Fig. 33.5.[119]

Timing of Delivery of Nutrients as Pharmacologic Agents

The timing for optimal delivery of pharmaconutrients appears to be before the stressful or traumatic event. A now classic study demonstrated that when the nutrients arginine, fish oils, and nucleic acids were given as oral supplements 5 to 7 days before major gastrointestinal surgery, there was a lower infection rate and a lower overall complication rate.[120] Most recently, a meta-analysis of 35 studies concluded that when arginine is given preoperatively, benefits include a significant decrease in infectious complications.[49] This effect was consistent over a wide range of surgical specialties.

To date, we have inadequate supportive literature to yield the optimal time to deliver immune and metabolically active nutrients once a planned metabolic stress has taken place as opposed to that found in the surgical setting. Timing will depend on several factors, such as the route of delivery, dosing, and method of delivery (e.g., bolus as a single agent versus infusion with other nutrients). The conventional wisdom is that early institution of therapy is likely to be optimal. Growing evidence from mammalian models of sepsis and shock suggest that once oxidative stress has damaged cells, changes in energy production potential may be irreversible.[121,122] It would be safe to say that once the patient has been adequately resuscitated and able to receive enteral feeding, these agents would be safe. One study specifically evaluated delivery of glutamine during shock resuscitation in the emergency department and found it to be safe and associated with enhanced intestinal tolerance to subsequent enteral feeding.[123]

No prospective randomized trials have evaluated or compared the enteral versus parenteral route with regard to delivery of metabolically active nutrients. The optimal route of delivery for the majority of active nutrients remains uncertain, although it appears that the parenteral route may be favorable for glutamine.[24] Parenteral EPA and DHA are reported to have beneficial influences within 1 to 24 hours, while enteral delivery may need 12 to 72 hours to demonstrate the beneficial and antiinflammatory effects.[119,124]

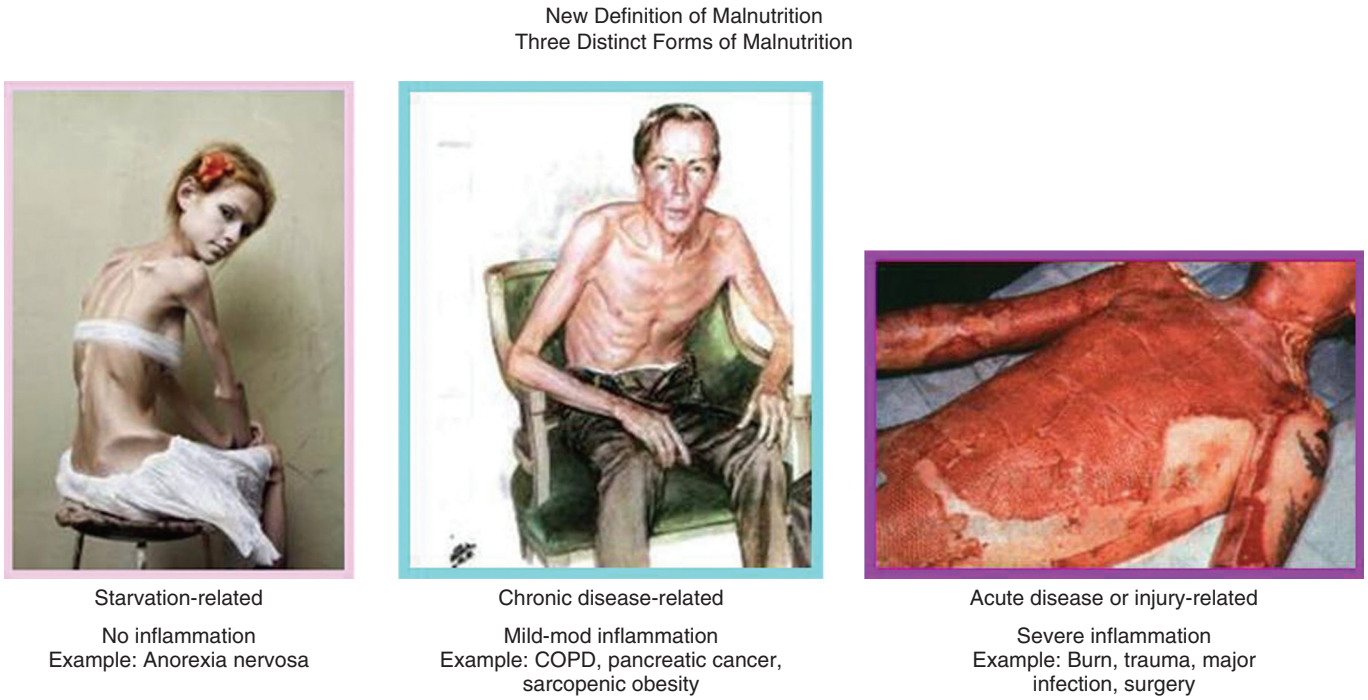
Use of Protocols Enhance Safe Delivery of Nutrients

Protocols to deliver early nutrition effectively and safely either parenterally or enterally have been widely published.[30,42,43,125–128] These protocols have reported advantages in decreasing ventilator days, length of ICU stay, and even mortality.[25,128] The "CAN WE FEED" protocol links resuscitation with clinical assessment and nutrient delivery.[42] This protocol has rapidly gained widespread acceptance in ICUs across the globe, and a protocol-driven approach to initiating EN or PN in critically ill patients is recommended by the ASPEN/SCCM guidelines.

Emerging Developments

New Malnutrition Definitions and Other Nutrients

New definitions for malnutrition have recently been developed[129] (Fig. 33.6). This will aid in the ability to better define the various populations and assess outcomes of interventions.



• **Fig. 33.6** Refined definitions for malnutrition. *COPD,* Chronic obstructive pulmonary disease. (Modified from Jensen GL, Mirtallo J, Compher C, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the international consensus guideline committee. *J Parenter Enteral Nutr.* 2010;34:156–159.)

Several other specific nutrients have been reported to be beneficial in the surgical population. Antioxidants, such as vitamin C and E, and trace minerals, such as selenium and zinc, which function as cofactors for several potent endogenous antioxidants (superoxide dismutase and glutathione peroxidase) have received attention for their ability to improve outcomes in surgical and trauma patients.[130]

Other amino acids—including citrulline, taurine, leucine, and creatine—have also had variable success in improving metabolic outcomes or surrogate markers following major surgery or major trauma.[50] As with glutamine and arginine, these amino acids have been shown to alter gene expression, intracellular protein turnover, and regulate metabolic pathways.[105,131]

Probiotics

The use of probiotics has recently been brought to the forefront, with several studies showing that these "functional foods" can decrease the inflammatory response, stabilize and support the mucosal surface, improve immune function, and decrease infectious complications, including ventilator-associated pneumonia (VAP) and *Clostridium difficile* diarrhea.[132–135]

Probiotics are defined as "live microbial organisms which beneficially affect human health through the prevention of specific disease states."[136] Studies suggest that probiotics may help reduce the incidence of VAP locally by promoting selective colonization and perhaps systematically by immunomodulation.[137]

In a well-executed, prospective, randomized, double-blinded, placebo-controlled trial of 138 mechanically ventilated patients at high risk of developing VAP examined the influence of probiotic therapy.[46] Patients in the treatment arm received 10^9 colony-forming units of *Lactobacillus rhamnosus GG* twice daily, delivered to the gastrointestinal tract via a nasogastric tube. The probiotic group not only decreased VAP infections by about 50% compared to placebo but also reduced the amount of total antibiotics needed when compared to placebo-treated patients. Other groups have used different bacterial species and protocols, including swabbing the mouths of intubated patients with probiotics, and have also found benefit.[138] The clinical science for using probiotics to prevent *Clostridium difficile* diarrhea is even more robust.[134]

General use of probiotics in critically ill patients does not yet have sufficient evidence to be recommended as routine. The majority of studies, however, report trends suggesting a treatment effect of probiotics in terms of reducing the incidence of VAP, *Clostridium difficile*, and antibiotic-associated diarrhea, but controversy remains as to which probiotic to use, optimal timing, duration of therapy, route, and method of delivery.

Conclusion

It is a dynamic and exciting time for the field of nutrition therapy. Of course there are still numerous questions and controversies in the field (Table 33.5). The use of protocols to enhance the safe, early delivery of enteral nutrients is now well established. A large number of new or ongoing randomized controlled trials continue to advance our understanding of the mechanisms that drive the benefits, harms, toxicities, or null effects of pharmaconutrients. Future studies must focus on evidence-based therapies that impact clinically relevant surgical endpoints, such as LOS, infectious morbidity, and mortality, as well as more subtle clues of successful modulation of the stress response, wound healing, time to tracheal extubation, hemodynamic stability, and early mobility. The translation from human trials, mammalian models, and basic science cellular studies has resulted in better understanding of immune and metabolic nutrients. Focused nutrition therapy has now reached a point at which early aggressive enteral feeding via protocols and the use of pharmaconutrients should be incorporated into standard surgical and ICU practice. Novel therapies—such as probiotics and specific amino acid therapy combined with exercise in the ICU setting (even with ongoing mechanical ventilation)—will undoubtedly change practice in the future. The questions of optimal doses, timing, and routes of these nutrients remain to be determined. Despite the variety of controversy in critical care nutrition, most major nutrition societies agree on the majority of issues (see Table 33.6).

TABLE 33.5 Current Issues and Problems With Intensive Care Unit Nutrition

Failure to predict who will need support
Lack of adequate assessment markers
Surrogate markers albumin, prealbumin, CRP, IGF-1 not currently useful
Controversy regarding what is the best formula to feed
Lack of understanding of "neutraceutical" approach
Glutamine, arginine, fish oils (DHA, EPA), carnitine
Overreliance and inappropriate use of parenteral nutrition (PN)
Starting PN for "1 or 2" days
Nonphysiologic lipid and amino acid solutions (in United States)
The morbidly obese critically ill patient
How many calories, IBW, ABW, BMI remain in question
Failure to maximize use of early enteral feeding
Failure to get adequate safe early enteral access
Unfounded indications for stopping and holding enteral feeding
Diagnostic tests, NPO for OR, "road trips," bathing

ABW, Actual body weight; *BMI*, body mass index (formula: weight (kg)/[height(m)]^2; *CRP*, C-reactive protein; *DHA*, docosahexaenoic acid; *EPA*, eicosapentaenoic acid; *IBW*, ideal body weight; *IGF-1*, insulin-like growth factor-1; *NPO*, nothing by mouth; *OR*, operating room.

TABLE 33.6 Critical Care Guidelines

Areas of common agreement: ADA, ASPEN, CPG, ESPEN, SCCM
Early enteral feeding
Enteral superior to parenteral nutrition
Fish oils beneficial (except ADA)
Postpyloric feeding preferable if possible
Supplemental antioxidants
Use of glutamine (except ADA)
Use of arginine in surgery patients
Preop in addition to postop when possible

ADA, American Dietetic Association; *ASPEN*, American Society of Parenteral and Enteral Nutrition; *CPG*, Canadian Clinical Practice Guidelines; *ESPEN*, European Society of Parenteral and Enteral Nutrition; *SCCM*, Society of Critical Care Medicine.

Key Points

- Preoperative malnutrition is a risk factor for poor wound healing, perioperative complications, and mortality.
- The metabolic response to stress includes a hyperdynamic cardiac and pulmonary state, insulin resistance, hyperglycemia, and accelerated protein catabolism from muscle; unabated, this can culminate in PICS, MOF, and death.
- Early enteral feeding in critically ill patients is associated with numerous benefits, including attenuation of the inflammatory response to stress, prevention of loss of gut barrier function, maintenance of GALT, maintenance of normal gut bacteria, and support of the systemic immune response, among others.
- Enteral feeding should not begin until relative hemodynamic stability and other acute resuscitation issues have been accomplished. Institution of premature enteral feeding can result in nonocclusive mesenteric ischemia (NMI), a devastating complication with a high mortality rate.
- Pharmaconutrition or immunonutrition is defined as the provision of key nutrients that may modulate the inflammatory and/or catabolic response associated with critical illness. Pharmaconutrition is distinct from the delivery of balanced macronutrient energy supply to support normal cell metabolism and division.
- Glutamine, arginine, and fish oils are the most prominent pharmaconutrients in contemporary nutritional therapy. The exact dosage and timing of delivery of these pharmaconutrients are not yet well established.
- Nutritional therapy in the ICU is best accomplished on a multidisciplinary basis according to evidence-based protocols and multifaceted assessments (e.g., CAN WE FEED).

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Pharmacology of Postoperative Nausea and Vomiting

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CHAPTER OUTLINE

Historical Perspective

Mechanisms of Nausea and Vomiting

Serotonin Receptor Antagonists
- Ondansetron

Granisetron and Dolasetron
- Palonosetron

Dopamine Receptor Antagonists
- Droperidol
- Haloperidol
- Metoclopramide

Corticosteroids

NK1 Receptor Antagonists
- Aprepitant
- Scopolamine

H_1-Receptor Antagonists
- Dimenhydrinate and Diphenhydramine
- Promethazine

GABA Receptor Agonists
- Propofol
- Benzodiazepines

Opioid Receptor Antagonists
- Naloxone
- Alvimopan

Cannabinoids

Risk-Based Prophylaxis
- Enhanced Recovery After Surgery

Multimodal Therapy

Emerging Developments
- Novel Antiemetic Drugs
- Postdischarge Nausea and Vomiting

Historical Perspective

In the first half of the 20th century, one of the most feared complications of general anesthesia was postoperative vomiting (POV), primarily because aspiration of gastric contents into the lungs could lead to death. Early prophylaxis sometimes consisted of advising patients to consume olive oil before general anesthesia to shield the intestinal wall from emetogenic gases. Prevention of POV was one of the primary motivations for developing local/regional anesthesia blocks, first with cocaine and procaine, then with lidocaine. Postoperative nausea, on the other hand, was considered too minor a complication to measure—until the development in the 1950s and 1960s of anesthetic drugs that could be cleared more rapidly (e.g., halothane, barbiturates, and novel opioids), which meant that patients spent more of the immediate postoperative period awake.[1]

While the antiemetic effect of some drugs, such as anticholinergics, were first described more than a century ago, modern understanding of the specific receptor pathways and intracellular processes involved in postoperative nausea and vomiting (PONV) is relatively recent. It was not until the 1950s that interest in antiemetic drugs took off, with the identification of histamine and dopamine receptors in the nausea and vomiting pathway, and hence the clinical utility of H_1- and D_2-receptor antagonists like cyclizine, chlorpromazine, and promethazine. This surge in research on antiemetics was largely driven by advances in chemotherapy and a focus on chemotherapy-related outcomes. For example, neuro-oncologists first noticed the antiemetic effect of corticosteroids before the same observation was made for PONV in the 1990s.[1]

The development of 5-hydroxytryptamine type 3 ($5\text{-}HT_3$)-receptor antagonists marks the greatest advance in antiemetic drug research. Early $5\text{-}HT_3$-receptor antagonists were not more effective than other available antiemetics, but they were the first to be specifically designed by the pharmaceutical industry to target chemotherapy-induced nausea and vomiting (CINV) and PONV. This led to an increase in large, well-designed PONV studies, marketing of antiemetic agents, and a focus on PONV as a significant postoperative outcome.[1] The first-generation $5\text{-}HT_3$-receptor antagonists are associated with QTc prolongation, but the newest $5\text{-}HT_3$-receptor antagonists, palonosetron, appears to have improved efficacy, duration of action, and side effect profile compared with its predecessors. Neurokinin-1 (NK1)-receptor antagonists, such as aprepitant and rolapitant, are the newest class of antiemetic drugs, and they too benefit from a long duration of action and favorable side effect profile. As the current understanding of the nausea and vomiting pathway, pharmacokinetics and pharmacodynamics, and genetics continues to improve, antiemetic drugs are likely to become safer and easier to tailor to individual patients.

Abstract

Postoperative nausea and vomiting (PONV) are common problems following surgery. This chapter is designed to educate the readers on the spectrum of antiemetic therapy available, and to which populations the modalities may prove most useful. The pharmacology of both traditional and novel drugs is discussed as well as synergies gained from multi-modal combination drug therapy. The use of routine antiemetic prophylaxis is essential for a successful enhanced recovery pathway.

Keywords

Multimodal drug therapy
Risk-based prophylaxis
Antiemetic prophylaxis vs. rescue therapy
Enhanced Recovery after Surgery

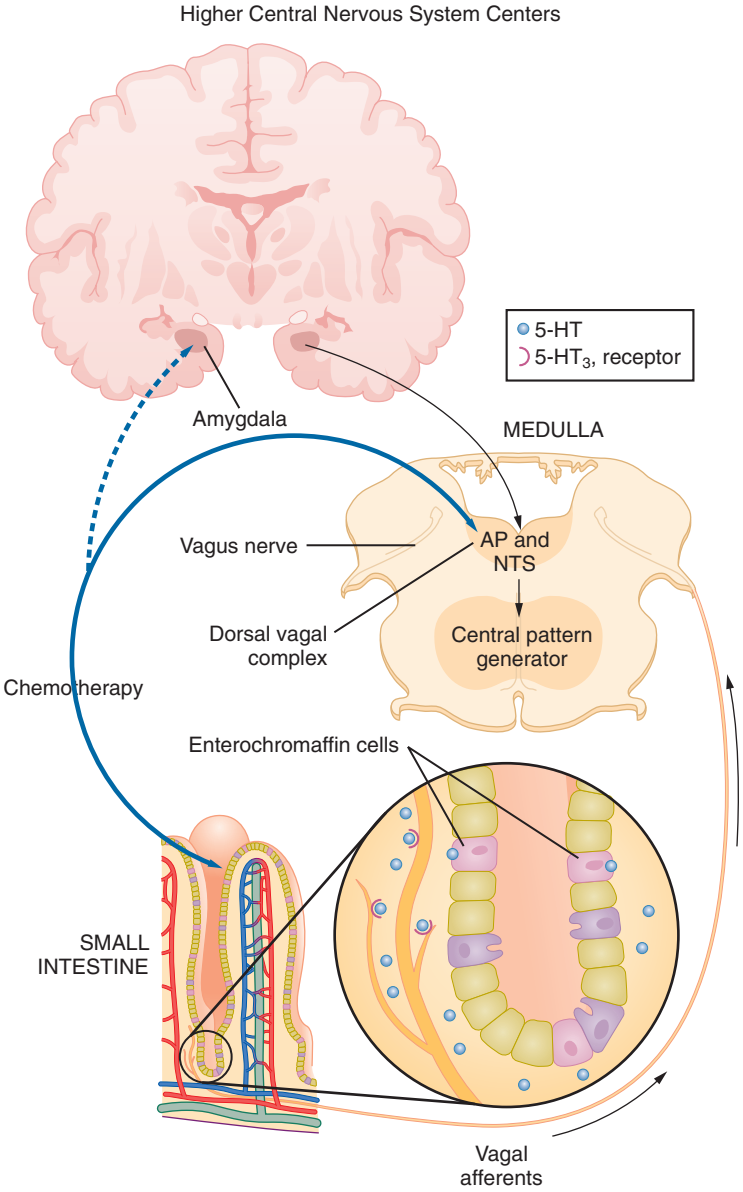
Mechanisms of Nausea and Vomiting

Despite thousands of studies, new insights into target receptor function, and the successful development of novel antiemetic agents, the actual mechanisms of nausea and vomiting remain unclear. Most antiemetic drugs act on one of several putative neurotransmitter pathways. 5-HT_3- receptor antagonists are the most commonly used antiemetic class of drugs (Table 34.1). Other classes include dopamine (D_2), histamine (H_1), NK1, gamma-aminobutyric acid $(GABA)_A$, opioid, and muscarinic cholinergic receptor antagonists.

The receptors on which antiemetics act certainly play a role in nausea and vomiting. However, given that only 20% to 30% of patients respond to any one agent, nausea and vomiting cannot be solely attributed to activity of one—or several—of these receptor classes. It is also likely that individual variability plays a larger role than previously acknowledged. Although it is essential to understand and investigate the drug-receptor relationship, the therapeutic potential of targeting specific receptor classes is limited.

Nausea and vomiting can be triggered by a variety of stimuli, including toxins, anxiety, adverse drug reactions, pregnancy, radiation, chemotherapy, and motion. These stimuli are integrated by the vomiting center in the nucleus tractus solitarius (NTS), located primarily in the medulla as well as in the lower pons. The vomiting center receives input from the adjacent chemoreceptor trigger zone (CTZ), the GI tract, the vestibular system, and the cerebral cortex (Fig. 34.1).

The CTZ is located at the caudal end of the fourth ventricle in the area postrema, a highly vascularized structure that lacks a true blood-brain barrier. Therefore chemosensitive receptors in the CTZ can be directly stimulated by toxins, metabolites, and drugs that circulate in the blood and cerebrospinal fluid. The CTZ communicates with the vomiting center primarily via D_2 receptors as well as 5-HT_3 receptors. Enterochromaffin cells in the GI tract release serotonin, which stimulates vagal afferents that terminate in the CTZ and communicate information regarding intestinal luminal compounds and gastric tone. The vestibular system, located in the bony labyrinth of the temporal lobe, detects changes in



• **Fig. 34.1** Schematic of pathways involved in postoperative nausea and vomiting. *5-HT,* 5-hydroxytryptamine; *5-HT_3,* 5-hydroxytryptamine type 3 receptor; *AP,* area postrema; *NTS,* nucleus tractus solitarius.

equilibrium, which can cause motion sickness. Histamine (H_1 receptor) and acetylcholine (muscarinic acetylcholine receptors) are the neurotransmitters that communicate between the vestibular system and the vomiting center. Anticipatory or anxiety-induced nausea and vomiting probably originates in the cerebral cortex. The cortex has direct input to the vomiting center via several types of neuroreceptors.

Serotonin Receptor Antagonists

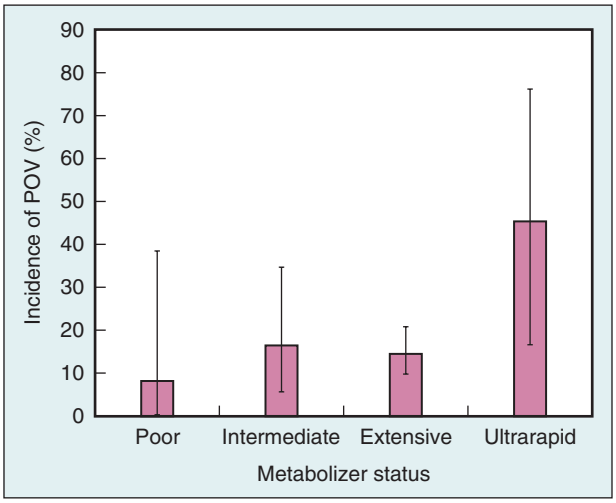
Serotonin (5-HT_3) receptors are ligand-gated sodium ion (Na^+) and potassium ion (K^+) channels found throughout the central and peripheral nervous systems, notably in the CTZ and afferent fibers of the vagus nerve in both the gut and central nervous system (CNS; see Fig. 34.1). Serotonin activation of the CTZ and vagal afferents can both trigger the vomiting reflex. Serotonin plays an important role in anesthesia-, chemotherapy-, and radiation-induced nausea and vomiting. Serotonin receptor antagonists can be used as antiemetic treatment because they inhibit both central and peripheral stimulation of 5-HT_3 receptors, and they are effective, nonsedative, and generally well tolerated. Thus 5-HT_3-receptor antagonists are currently the most commonly used antiemetic agents for PONV, CINV, and rescue treatment.

Ondansetron

Ondansetron was the first 5-HT_3-receptor antagonist approved by the U.S. Food and Drug Administration (FDA), and at the time of its development, was the safest and most effective treatment for early CINV.[2] Its reputation for superior CINV prophylaxis carried over to PONV, but a factorial trial in more than 5000 patients showed that 4 mg ondansetron was only as effective as 4 mg dexamethasone and 1.25 mg droperidol for PONV.[3] Contrary to the common clinical impression that ondansetron is less effective against nausea than against vomiting, the relative risk reduction (RRR, risk ratio) of ondansetron is the same for nausea and for vomiting.[4] However, ondansetron's plasma half-life is only about 4 hours, which is probably why several studies found it to be more efficacious when administered toward the end rather than at the beginning of anesthesia.[5] Like other 5-HT_3-receptor antagonists, ondansetron's side effects are generally mild to moderate and include constipation and headache, the latter of which is increased by about 3%.[6] First-generation 5-HT_3-receptor antagonists like ondansetron have also been associated with QTc prolongation, which potentially increases the risk of cardiac arrhythmia and cardiac arrest.[7] The QTc prolongation associated with ondansetron use is similar to that caused by droperidol.[8]

Even though 5-HT_3-receptor antagonists are among the most effective antiemetic treatments for CINV, 20% to 30% of patients do not respond to 5-HT_3-receptor antagonism in the early phase of CINV.[9] Furthermore, 50% to 60% of high-risk patients do not respond to these drugs in the late phase of CINV.[10,11] Several studies have shown that responsiveness to ondansetron appears to be modulated by variations in cytochrome P450 enzyme 2D6 (CYP 2D6) activity and the *ABCB1* gene. The ability to predict patient responsiveness to 5-HT_3-receptor antagonists based on genetic testing for known polymorphisms could prove to be an important breakthrough in individualizing antiemetic therapy.

Ondansetron is partially metabolized by hepatic CYP 2D6. There are numerous CYP 2D6 polymorphisms, each associated with one of four metabolic phenotypes: poor (no functional alleles), intermediate (less activity than one functional allele), extensive (two functional alleles, and the most common phenotype), and ultrarapid (three functional alleles). Ultrarapid metabolizers can degrade ondansetron more quickly and are therefore less likely to benefit from prophylaxis with the drug. In fact, several studies have shown that patients with three CYP 2D6 alleles, especially those with three functional alleles, are significantly more likely to experience PONV after prophylaxis with ondansetron than patients with fewer alleles (Fig. 34.2).[9,12] Ultrarapid metabolism by CYP 2D6 is believed to be partially responsible for prophylactic ondansetron failures in individuals with an ultrarapid metabolic genotype, whereas other enzymes that metabolize ondansetron—namely, CYP 3A4, CYP 2E1, and CYP 1A2—are thought to play a larger role in drug clearance in individuals with poor, intermediate, and extensive metabolism genotypes.[12]



• **Fig. 34.2** Patients with a genotype associated with ultrarapid metabolism (i.e., three functional copies of CYP 2D6) are at increased risk for postoperative vomiting *(POV)* after prophylaxis with ondansetron in the first 24 postoperative hours. (Adapted from Candiotti KA, Birnbach DJ, Lubarsky DA, et al. The impact of pharmacogenomics on postoperative nausea and vomiting: do CYP2D6 allele copy number and polymorphisms affect the success or failure of ondansetron prophylaxis? *Anesthesiology*. 2005;102:543–549.)

Ondansetron pharmacokinetics also appear to be modulated by polymorphisms of the gene that codes for the drug efflux transporter adenosine triphosphate–binding cassette subfamily B member 1 *(ABCB1)*. The *ABCB1* pump transports at least three 5-HT_3-receptor antagonists, including ondansetron, across the blood-brain barrier, thereby limiting accumulation of these drugs in the CNS.[13] Polymorphisms of *ABCB1* that reduce its activity increase the concentration of 5-HT_3-receptor antagonists in the brain, which enhances efficacy. Indeed, cancer patients with a 3435C>T genetic polymorphism were less likely to experience chemotherapy-induced vomiting (CIV) in the first 24 hours after prophylaxis with ondansetron.[13] Similarly, 3435C>T and/or 2677G>T/A polymorphisms are associated with a lower incidence of PONV in surgery patients, but only within the first 2 postoperative hours.[14]

Granisetron and Dolasetron

Other first-generation 5-HT_3-receptor antagonists include granisetron and dolasetron. Both drugs have a plasma half-life about

TABLE 34.1 Properties of Individual Antiemetic Drugs

	Chemical Name	Empirical Formula	Administration	Daily Dosage (mg) PONV	CINV	C_{max} (ng/mL)
5-HT_3 Receptor Antagonists						
Ondansetron (Zofran)	1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate	$C_{18}H_{19}N_3O$	IV	4	32 (0.15 mg/kg × 3)	
			IM	4	8	
			Oral	16	8 × 2	
			Sup	16	16	
Granisetron (Kytril)	endo-N-(9-methyl-9-azabicyclo [3.3.1] non-3-yl)-1-methyl-1H-indazole-3-carboxamide hydrochloride	$C_{18}H_{24}N_4O$	IV	1	10 μg/kg	64
			Oral	1	2	
			TD	3.1	3.1	
Dolasetron (Anzemet)	(2α,6α,8α,9αβ)-octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl-lH-indole-3-carboxylate monomethanesulfonate, monohydrate	$C_{19}H_{20}N_2O_3$	IV	12.5		
			Oral	100	100	
Tropisetron (Navoban)	1αH,5αH-Tropan-3α-yl indole-3-carboxylate	$C_{17}H_{20}N_2O_2$	IV	2	5	15.1
			Oral	5	5	3.46
Palonosetron (Aloxi)	(3aS)-2-[(S)-1-Azabicyclo [2.2.2] oct-3-yl]-2,3,3α,4,5,6-hexahydro-1-oxo-1*H* benz[*de*]isoquinoline hydrochloride	$C_{19}H_{24}N_2O$	IV	0.075	0.25	5.6
			Oral	0.075	0.5	
D_2 Receptor Antagonists						
Droperidol	1-[1-[3-(p-Fluorobenzoyl) propyl]-1,2,3,6-tetrahydro-4-pyridyl]-2-benzimidazolinone	$C_{22}H_{22}FN_3O_2$	IV	0.625–1.25 × 6–8	25	3.2
			IM	0.625–1.25 × 6–8		
Haloperidol (Haldol)	4-[4-(p-chloro-phenyl)-4-hydroxypiperidino]-4′—fluorobutyrophenone	$C_{21}H_{23}ClFNO_2$	IV	1–2		
			IM			
			Oral			
Metoclopramide (Reglan)	4-amino-5-chloro-N-[2-(diethylamino) ethyl]-2-methoxybenzamide monohydrochloride monohydrate	$C_{14}H_{22}ClN_3O_2$	IV	25–50	100 (1–2 mg/kg) × 8–12	
			IM	25–50		
			Oral			
Corticosteroids						
Dexamethasone	9-fluoro-11β, 17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione	$C_{22}H_{29}FO_5$	IV	4	4 × 4	
			IM		4 × 4	
			SC			
			Oral		4 × 4	
NK1 Receptor Antagonists						
Aprepitant (Emend)	5-([(2*R*,3*S*)-2-((*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy)-3-(4-fluorophenyl)morpholino] methyl)-1*H*-1,2,4-triazol-3(2*H*)-one	$C_{23}H_{21}F_7N_4O_3$	Oral	40	125 D1/80 D2-3	0.7 (40 mg); 1.6 (125 mg); 1.4 (80 mg)
Anticholinergics						
Transdermal scopolamine (Transderm Scop)	α-(hydroxymethyl) benzeneacetic acid 9-methyl-3-oxa-9-azatricyclo [3.3.1.$0^{2,4}$] non-7-yl ester	$C_{17}H_{21}NO_4$	TD	0.5		

AUC (ng•hr/mL)	T_{max} (hr)	Bioavailability (%)	V_d (L/kg)	Protein Bound (%)	Metabolism	Plasma Half-Life (hr)	Adverse Effects	Other
							Constipation, headache, QTc prolongation	No sedation
	0.4 0.7 1.5–2.2	56		70–76	CYP 3A4, CYP 1A2, CYP 2D6	4		
		60	3	65	CYP 3A	3–14		
527	48 0.6 1	75	5.8	69–77	CYP 2D6, CYP 3A, flavin monooxygenase	8		HPB black box warning (Canada)
20.7 32.9 35.8	 2.6 	60–80 97	 8.3	71 62	CYP 3A4, CYP 1A2, CYP 2D6 CYP 2D6, CYP 3A, CYP 1A2	6–8 40		 No QTc prolongation
							EPS, QTc prolongation	
69	17.8		1.5	>90		2–3		FDA black box warning
	 0.2–0.3 3–6 1–2	50–60 80	18 3.5	92 30		12–36 5–6	 Cumulative CINV doses associated with significant EPS	 10 mg PONV dose insufficient EPS <1% at 25–50 mg
		80–90		70	CYP 3A4	36–54[a]	Hyperglycemia	Most dose response studies suggest that 4 mg is sufficient
								No sedation
7.8 (40 mg); 19.6 (125 mg); 21.2 (80 mg)	3 (40 mg); 4 (80–125 mg)	60–65 (80–125 mg)		>95	CYP 3A4, CYP 1A2, CYP 2C19	9–13		
	<24	10–50				72[a]		

Continued

TABLE 34.1 Properties of Individual Antiemetic Drugs—cont'd

	Chemical Name	Empirical Formula	Administration	Daily Dosage (mg) PONV	CINV	C_{max} (ng/mL)
Opioid Receptor Antagonists						
Alvimopan (Entereg)	[[2(S)-[[4(R)-(3-hydroxyphenyl)-3(R),4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid dihydrate	$C_{25}H_{32}N_2O_4$	Oral			
GABA Agonists						
Diazepam (Diastat, Valium)	7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one	$C_{16}H_{13}ClN_2O$	IV IM Oral Sup			
Lorazepam (Ativan)	7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one	$C_{15}H_{10}Cl_2N_2O_2$	IV IM Oral TD		1.5 mg/m^2 2.5 × 2	20
Midazolam	8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo [1,5-a][1,4] benzodiazepine hydrochloride	$C_{18}H_{13}ClFN_3$	IV IM Oral			90
H_1 Receptor Antagonists						
Dimenhydrinate (Dramamine)	2- (diphenylmethoxy)-N,N -dimethylethylamine hydrochloride	$C_{17}H_{21}NO$	IV IM Oral Sup	50–100 × 4–6 50–100 × 4–6 50–100 × 4–6		80–110
Promethazine (Phenergan)	10-[2- (Dimethylamino)propyl] phenothiazine monohydrochloride	$C_{17}H_{20}N_2S$	IV IM Oral Sup	12.5–25 × 4–6 12.5–25 × 4–6 25 × 2 25 × 2		

AUC, Area under the curve; *CINV,* chemotherapy-induced nausea and vomiting; C_{max}, maximum plasma concentration; *CYP,* cytochrome 450; *D,* day; D_2, dopamine 2; *EPS,* extrapyramidal symptoms; *5-HT$_3$,* 5-hydroxytryptamine type 3 (serotonin); *GABA,* gamma-aminobutyric acid-A; H_1, histamine 1; *HPB,* Health Protection Branch (Canada); *IM,* intramuscular; *IV,* intravenous; *NK1,* neurokinin-1; *PONV,* postoperative nausea and vomiting; *QTc,* heart-rate corrected QT interval; *SC,* subcutaneous; *Sup,* suppository; *TD,* transdermal;; T_{max}, time to maximum plasma concentration; V_d, volume of distribution.
[a]Indicates duration of action.

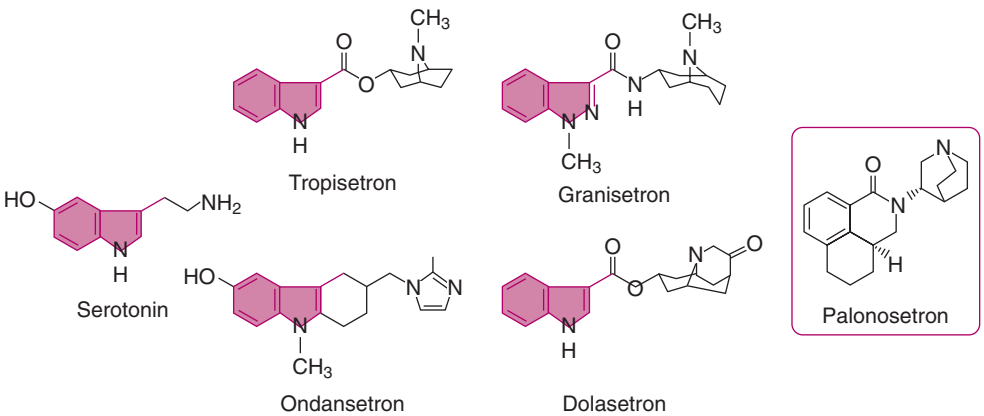
twice as long as ondansetron. In general, 5-HT$_3$-receptor antagonists are considered equally effective at equipotent doses. Compared with 4 mg ondansetron, 12.5 mg dolasetron and 1 mg granisetron appear to be the minimal effective dose for the prevention of PONV.[15] Both drugs are associated with side effects similar to those of ondansetron, including QTc prolongation. CYP 2D6, the enzyme responsible for partial metabolism of ondansetron, is the primary enzyme for dolasetron metabolism.[12] In contrast, granisetron is primarily metabolized by CYP 3A4 and not at all by CYP 2D6.[12] Therefore the efficacy of dolasetron might be modulated by the CYP 2D6 polymorphisms mentioned earlier, whereas *ABCB1* polymorphisms might play a larger role in enhancing the efficacy of granisetron.

Palonosetron

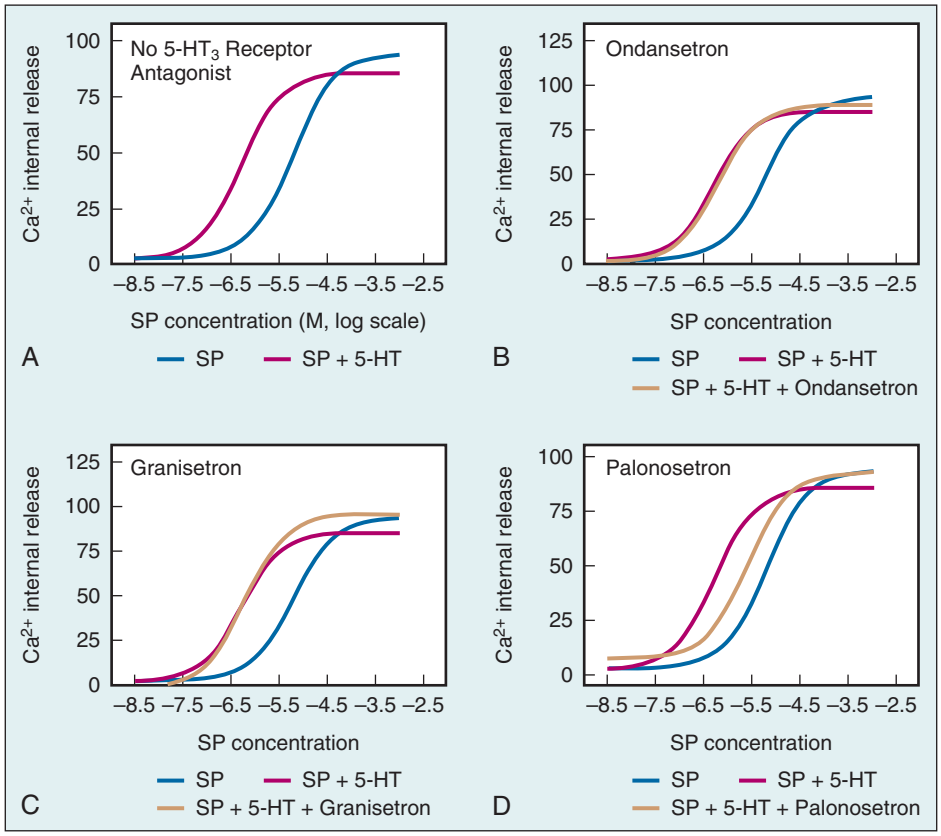
Palonosetron is the newest and most effective 5-HT$_3$-receptor antagonist for preventing acute and delayed emesis associated with chemotherapy and for reducing nausea severity (Fig. 34.3).[16,17] Palonosetron is characterized by 2500-fold greater affinity than serotonin and 100-fold greater affinity than other 5-HT$_3$-receptor antagonists.[18] Palonosetron also has a long half-life of 40 hours. However, palonosetron's high binding affinity and long half-life cannot explain its superiority to other 5-HT$_3$-receptor antagonists. High binding affinity does not account for palonosetron's superiority against higher doses of dolasetron or ondansetron (i.e., higher doses of less potent drugs do not overcome the potency difference). Similarly, a long half-life cannot account for palonosetron's superiority against more frequent redosing of ondansetron.[17]

Instead, recent research suggests that palonosetron's high efficacy can be attributed to the manner in which it binds to 5-HT$_3$ receptors.[17] Whereas other 5-HT$_3$-receptor antagonists bind only to the agonist binding site, palonosetron also binds at an allosteric site that increases receptor affinity for the receptor antagonist at the agonist binding site.[16] Given that granisetron and ondansetron induce little to no receptor internalization, this allosteric binding might also be responsible for palonosetron's relatively high rate (50%–60%) of receptor internalization and low receptor exocytosis. Internalized receptor-antagonist complexes are less likely to be dissociated, and, in turn, bound receptors are less likely to be exocytosed and subsequently reactivated by agonists at the cell surface. The low receptor density at the cell surface owing to palonosetron results in prolonged inhibition of receptor function—that is, protection against delayed emesis. Indeed, studies have

AUC (ng•hr/mL)	T_{max} (hr)	Bioavailability (%)	V_d (L/kg)	Protein Bound (%)	Metabolism	Plasma Half-Life (hr)	Adverse Effects	Other
	2	6		80–90	Intestinal flora		Sedation	Limited evidence
	0.5–2 1–1.5	90–100	0.8–1.0	95–98	CYP 2C19, CYP 3A4	20		
	2	90		85		9–16		
	0.5	>90	1–3.1	97	CYP 3A4	2–6		
		61		78	CYP 2D6	2–9		
	2–3							
		25		93		16–19	Necrosis that may require amputation	FDA black box warning



• **Fig. 34.3** Palonosetron and other 5-hydroxytryptamine type 3 receptor antagonists. The structure of the serotonin is shown on the left.



• **Fig. 34.4** The effect of 5-hydroxytryptamine type 3 receptor antagonists on serotonin enhancement of substance P *(SP)*-induced intracellular calcium ion *(Ca^{2+})* release. NG108-15 neuroblastoma cells were incubated with SP and subsequently exposed to serotonin. A, Serotonin *(5-HT)* enhancement of the SP response. Ondansetron (B), granisetron (C), and palonosetron (D) were preincubated with NG108-15 cells for 2 hours, then removed, after which serotonin was added and the SP response was measured. Unlike ondansetron and granisetron, palonosetron can partially reduce serotonin enhancement of SP activity. (From Rojas C, Li Y, Zhang J, et al. The antiemetic 5-HT_3 receptor antagonist palonosetron inhibits substance P-mediated responses in vitro and in vivo. *J Pharmacol Exp Ther*. 2010;335:362–368.)

shown that prophylaxis with palonosetron decreases CIV in a significant proportion of patients in the 5 days following chemotherapy treatment.[19]

Another mechanism that contributes to palonosetron's high efficacy is its inhibition of cross talk between 5-HT_3 and NK1 receptor signaling pathways.[20] Palonosetron and the NK1 agonist substance P (SP) cannot bind to each other's respective target receptors. However, serotonin and SP enhance each other's potency, and 5-HT_3-receptor antagonists and NK1-receptor antagonists block activation of vagal afferents by the other agonist.[20] Palonosetron is associated with a sixfold reduction in serotonin enhancement of SP potency in vitro (Fig. 34.4). Granisetron and ondansetron, on the other hand, had no effect on SP potency in vitro. In an in vivo study in rat nodose ganglia, palonosetron reduced cisplatin-induced SP activation for hours after cisplatin administration.[20] Palonosetron thus appears to have a prolonged downstream effect on SP function in vitro and in vivo that might be due to palonosetron's ability to cause 5-HT_3 receptor internalization and reduce receptor density at the cell surface.

Studies have shown that 0.25 mg and 0.075 mg palonosetron are effective doses for preventing CINV and PONV, respectively, and with a half-life of 40 hours, palonosetron provides therapeutic effect for a 72-hour period.[19,21] Unlike other 5-HT_3-receptor antagonists, palonosetron is not associated with QTc prolongation. Palonosetron's long half-life makes it a potentially important treatment for postdischarge nausea and vomiting (PDNV), although its relative efficacy in this setting has yet to be demonstrated.

Dopamine Receptor Antagonists

Droperidol

Low-dose (0.625–1.25 mg intravenously [IV]) droperidol is an effective antiemetic for treatment of PONV and opioid-induced nausea and vomiting (OINV), with similar efficacy against nausea (RR [relative risk] = 0.65) and vomiting (RR = 0.65).[3,22] Droperidol has a short half-life of 3 hours and, if used for the prevention of PONV, should be administered toward the end of anesthesia. At low doses, droperidol is an α-adrenergic receptor blocker that causes increased sedation (RR = 1.32).[23] Therefore for PONV prophylaxis, droperidol should be administered at the minimum effective dose of 0.625 mg IV to reduce the risk of adverse effects. For OINV prophylaxis, although 50 μg of droperidol is the most effective dose to add to a morphine or piritramide patient-controlled analgesia (PCA) infusion pump, 25 μg of droperidol is the safer, recommended dose.[24]

In 2001, reports of arrhythmia and death associated with use of droperidol led the FDA to attach a black box warning to the drug's label, after which droperidol use decreased 10-fold in the United States. According to the new label, droperidol is contraindicated in patients with known or suspected QT prolongation. Therefore absence of QT prolongation must be confirmed by electrocardiogram before droperidol administration, and electrocardiogram monitoring must be continued for 2 to 3 hours after drug administration. Many hospitals have removed droperidol from their formularies or placed restrictions on its use, in addition to drug shortages, so that droperidol usage is less than 2% of cases in the United States, even though more than 90% of anesthesiologists believe that the FDA black box warning is unwarranted.[25]

Those who argue against the black box warning question the clinical relevance of droperidol-induced QT prolongation, particularly because QT prolongation is associated with general anesthesia itself, as well as other drugs commonly administered during surgery (e.g., antibiotics). QTc prolongation after placebo, 0.625 mg droperidol, and 1.25 mg droperidol were 12, 15, and 22 msec, respectively.[26] Similarly, 0.75 mg droperidol and 4 mg ondansetron were associated with 17- and 20-msec QT prolongation, respectively.[8] It is possible, however, that these studies were inadequately powered to include patients with a rare but clinically significant predisposition to QT prolongation.[8,26] Of note, there are polymorphisms in the *ether-à-go-go* related gene (hERG) receptor that occur in about 0.5% to 2% of the population, and it is possible that these are the patients who are at high risk when exposed to droperidol. Thus it is not possible to exclude the possibility that adding droperidol to other QT-prolonging interventions, including general anesthesia, can trigger QT prolongations that lead to cardiac arrhythmia.[27]

Haloperidol

As a result of the black box warning for droperidol, there is a renewed interest in haloperidol, an older butyrophenone. Haloperidol is an effective treatment for psychiatric disorders at high doses and is an effective antiemetic at low doses. Haloperidol has a longer plasma half-life of 10 to 20 hours after intravenous administration. Like other D_2-receptor antagonists, haloperidol is associated with extrapyramidal effects, including acute dystonia, pseudoparkinsonism, and akathisia.[28] Haloperidol is metabolized in the liver, where 23% of haloperidol is reduced by a carbonyl reductase into a functional metabolite with high binding affinity to σ-opioid and D_2 and D_3 receptors.[28] However, there is significant interindividual variation in haloperidol pharmacokinetics.[28]

Plasma concentrations of haloperidol correlate with dosage, drug efficacy, and incidence of adverse effects.[28] Although CYP 3A4 is the primary enzyme responsible for haloperidol metabolism, with CYP 2D6 appearing to play only a minor role, several studies have shown that certain CYP 2D6 genotypes are associated with poor metabolism and are correlated with higher haloperidol plasma concentrations and lower drug clearance than genotypes associated with extensive metabolism (Fig. 34.5A and B). Specifically, individuals with 0, 1, 2, and more than 2 active CYP 2D6 alleles are considered poor, intermediate, extensive (most common), and ultrafast metabolizers, respectively. Thus poor metabolizers are at higher risk for adverse effects than are intermediate and extensive metabolizers.[28]

Reports of QT prolongation, torsades de pointes, and sudden death associated with use of haloperidol similar to those associated with droperidol led the FDA to issue an FDA alert for haloperidol in 2007. It has not received a black box label because these severe adverse effects occurred in patients who had received off-label intravenous administration of haloperidol at doses greater than 35 mg/day, whereas only intramuscular administration has been approved by the FDA.

Metoclopramide

Metoclopramide, a procainamide derivative and a benzamide prokinetic agent, is the most commonly used D_2-receptor antagonist for antiemetic prophylaxis, primarily for PONV and chemotherapy associated with low emetogenic risk. It is assumed that both the central D_2-receptor antagonist activity at the CTZ and vomiting center and peripheral activity in the GI tract contribute to the antiemetic effect. Metoclopramide acts on peripheral D_2, muscarinic, and 5-HT_4 receptors to induce prokinetic activity. Opioids can cause delayed gastric emptying, but metoclopramide enhances gastric motility and increases intestinal peristalsis, which reduces reflux of stomach contents and the urge to vomit. Because of its short half-life of 5 to 6 hours, metoclopramide is likely to have greatest efficacy if administered at the end of surgery.

Metoclopramide was first prescribed for CINV in high doses (e.g., 200 mg every 4–6 hours), which cause extrapyramidal symptoms in more than 10% of patients.[29] To reduce the incidence of adverse effects, metoclopramide is available in vials of just 10 mg. However, extensive studies and a meta-analysis have demonstrated that 10 mg metoclopramide has no clinically relevant antiemetic effect.[30] In fact, a large and well-designed dose-response study in more than 3000 patients demonstrated that doses of 25 and 50 mg metoclopramide are effective in reducing PONV by about 37% (RR = 0.63, a similar efficacy as other commonly used antiemetics), whereas the rate for extrapyramidal symptoms was less than 1% (see Fig. 34.5C).[31]

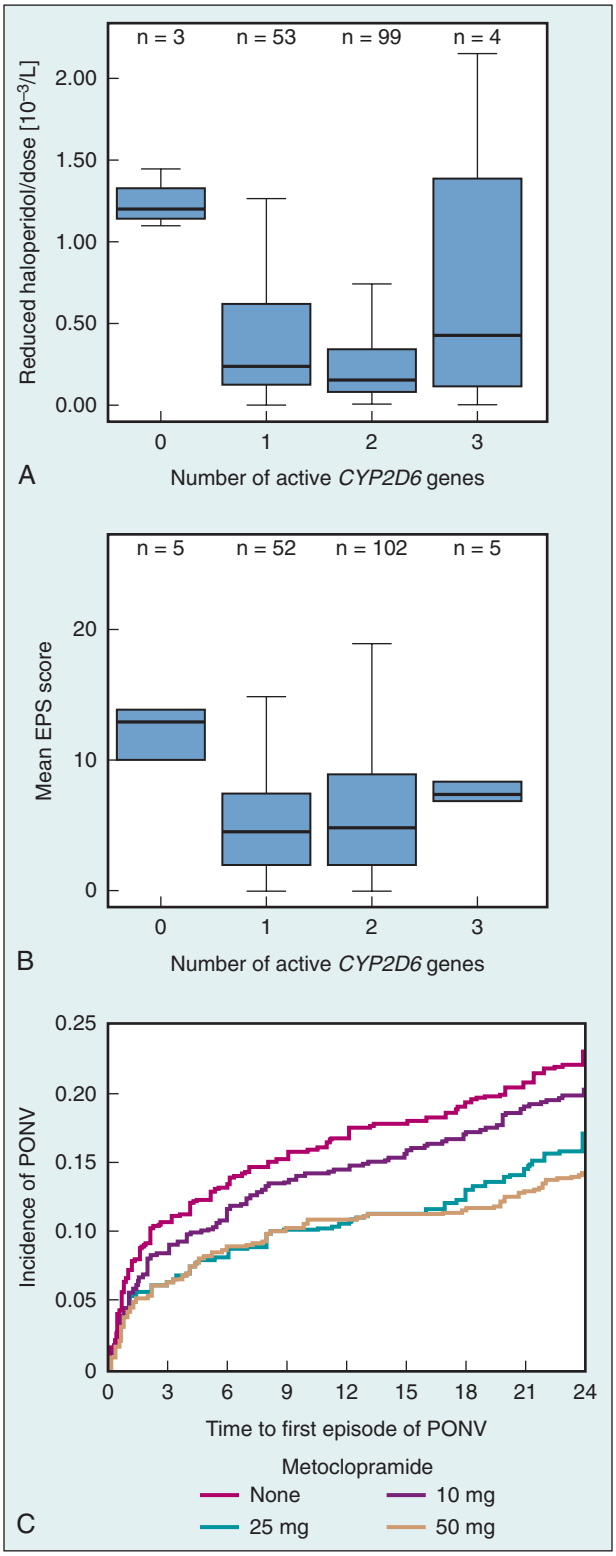
Like haloperidol, metoclopramide is metabolized primarily by CYP 2D6. Although several studies have shown CYP 2D6 polymorphisms that result in reduced CYP 2D6 activity are associated with a higher incidence of metoclopramide adverse effects, no studies have investigated yet whether CYP 2D6 polymorphisms influence the antiemetic efficacy of the drug. Given that nearly 25% of metoclopramide is excreted unchanged, however, the effect of CYP 2D6 polymorphisms might be relatively small, at least in patients with normal renal function.

Like other D_2-receptor antagonists, metoclopramide is associated with severe cardiac adverse effects.[32] High doses are associated with a high incidence of extrapyramidal symptoms, but lower doses (25–50 mg) are associated with a less than 1% incidence of dyskinetic and/or extrapyramidal symptoms.[31] It is important to note that the FDA issued a black box warning for metoclopramide, given the high risk of developing tardive dyskinesia if metoclopramide use extends beyond 12 weeks. However, this concern likely does not apply to a short-term course of metoclopramide in the perioperative setting.

Other D_2-receptor antagonists such as alizapride, perphenazine, and prochlorperazine might be as effective as other commonly used antiemetics, but they are rarely used, and their side effect profiles are unclear compared with that of other antiemetics.[22]

Corticosteroids

Dexamethasone is a synthetic glucocorticoid with antiinflammatory and immunosuppressant properties. With 20 to 30 times the binding affinity for glucocorticoid receptors of endogenous cortisol,



• **Fig. 34.5** Dependence of reduced haloperidol serum trough levels (A) and extrapyramidal symptoms *(EPS)* (B) on CYP 2D6 genotype after haloperidol doses of 2 to 24 mg. On the *x*-axis, 0 = no active alleles; 1 = 1 active allele; 2 = 2 active alleles; and 3 = 1 active and 1 or 2 duplication alleles. *Black lines* show medians, *blue boxes* show interquartile ranges, and *error bars* show the ranges of measured data. C, Cumulative incidence of postoperative nausea and vomiting *(PONV)* in treatment groups receiving placebo or 10, 25, and 50 mg metoclopramide. (A and B, From Brockmoller J, Kirchheiner J, Schmider J, et al. The impact of the CYP2D6 polymorphism on haloperidol pharmacokinetics and on the outcome of haloperidol treatment. *Clin Pharmacol Ther.* 2002;72:438–552; *C,* From Wallenborn J, Gelbrich G, Bulst D, et al. Prevention of postoperative nausea and vomiting by metoclopramide combined with dexamethasone: randomised double blind multicentre trial. *BMJ*. 2006;333:324.)

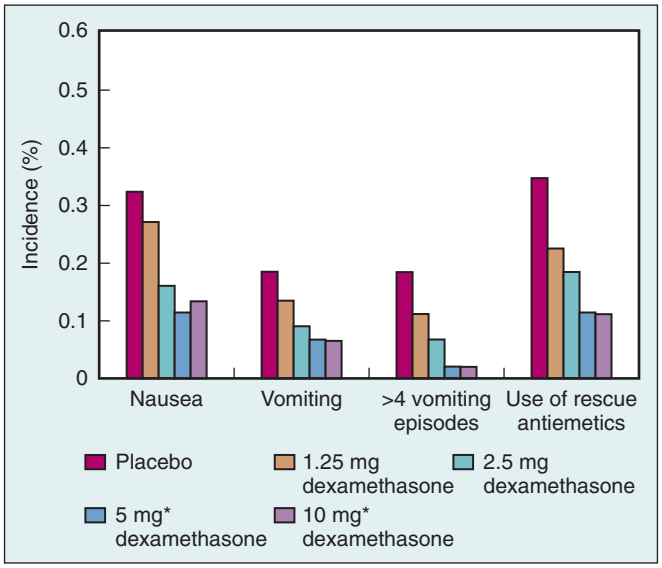
dexamethasone is a potent treatment for PONV and CINV. Even though dexamethasone is one of the most commonly used antiemetics, its mechanism of action remains unclear. Studies in animal models suggest that dexamethasone acts on the glucocorticoid receptor–rich bilateral NTS (i.e., the vomiting center), but not the area postrema.[33]

Although 8 mg is the most commonly used dose for prevention of PONV, dose-response studies suggest that 5 mg is the minimum effective dose for PONV prophylaxis (Fig. 34.6).[34] Furthermore, a large factorial trial in more than 5000 patients found that 4 mg dexamethasone has similar efficacy to 4 mg ondansetron or 1.25 mg droperidol.[35] Thus ambulatory surgery guidelines recommend 4 to 5 mg dexamethasone.[36] Dexamethasone is more effective when given at the beginning rather at the end of surgery, which suggests that there is a delay in onset of action by about 2 hours.[37] Furthermore, a single intraoperative dose of dexamethasone has not been associated with adverse effects.[36] However, like other intravenous drugs containing phosphate esters, dexamethasone has been associated with perineal burning and itching when injected in awake patients.[38] In addition, doses of 12 to 20 mg can be given for CINV.[39]

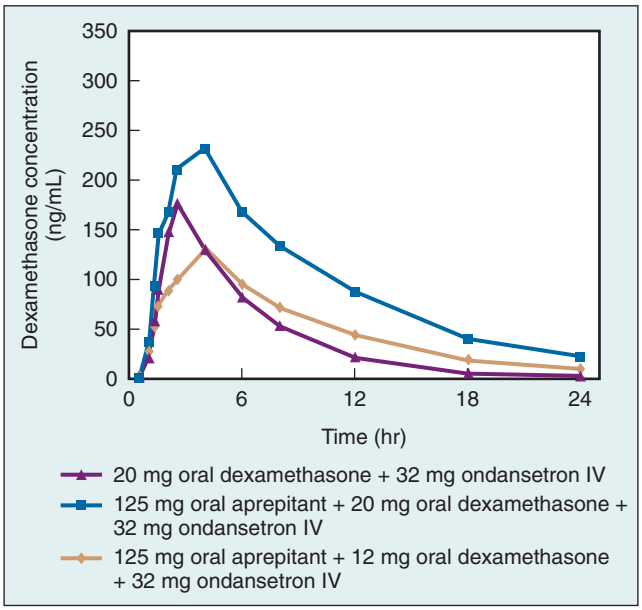
Dexamethasone is an effective and well-tolerated component of antiemetic combination therapy.[35] Adding aprepitant to the typical treatment regimen for CINV—a 5-HT_3-receptor antagonist (ondansetron) and a corticosteroid (dexamethasone)—further reduces the incidence of CINV. The doses of aprepitant recommended for CINV (125 mg on day 1, 80 mg on days 2 and 3) moderately inhibits CYP 3A4, the enzyme responsible for dexamethasone metabolism. In fact, aprepitant's inhibition of CYP 3A4 activity approximately doubles the plasma concentration of dexamethasone (Fig. 34.7). Given that dexamethasone has high (80%) oral bioavailability, and that aprepitant also increases the peak plasma concentration and half-life of dexamethasone, aprepitant's inhibition of CYP 3A4 activity probably plays a larger role in systemic rather than first-pass clearance of dexamethasone.[40] Therefore doses of dexamethasone that are coadministered with aprepitant should be reduced by half to maintain dexamethasone plasma concentrations that are similar to regimens without aprepitant. The pharmacokinetics of ondansetron, which is partially metabolized by CYP 3A4, are not affected by aprepitant.[40]

NK1 Receptor Antagonists

NK1 receptors are G-protein–coupled receptors found in both the central and peripheral nervous systems. NK1 receptors are

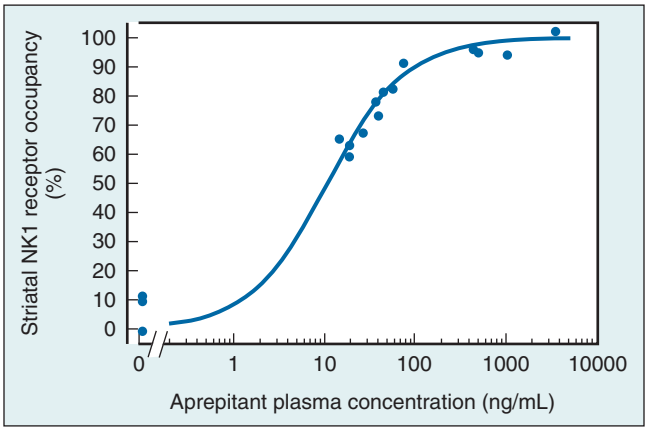


• **Fig. 34.6** Incidence of nausea, vomiting, severe vomiting, and need for rescue antiemetics 0 to 24 hours after dexamethasone prophylaxis in a dose-ranging study. *$P < 0.05$ compared to placebo. (From Wang JJ, Ho ST, Lee SC, et al. The use of dexamethasone for preventing postoperative nausea and vomiting in females undergoing thyroidectomy: a dose-ranging study. *Anesth Analg*. 2000;91:1404–1407.)



• **Fig. 34.7** Mean plasma concentration profiles of dexamethasone when combined with other antiemetics. Aprepitant markedly increased the plasma concentration of dexamethasone. *IV,* Intravenous. (From McCrea JB, Majumdar AK, Goldberg MR, et al. Effects of the NK1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. *Clin Pharmacol Ther*. 2003;74:17–24.)

found in the GI tract and in high concentrations in regions responsible for regulating the vomiting reflex, including the brainstem nuclei, the NTS, and the area postrema. SP, a member of the tachykinin family of neuropeptides, is the dominant ligand of NK1 receptors. In animal models, SP activation of NK1 receptors in the area postrema induces retching, and NK1 receptor antagonists



• **Fig. 34.8** High correlation between aprepitant plasma concentration and NK1 receptor occupancy (0.97 [$P < 0.001$; 95% confidence interval = 0.94-1.00]). (From Bergstrom M, Hargreaves RJ, Burns HD, et al. Human positron emission tomography studies of brain neurokinin 1 receptor occupancy by aprepitant. *Biol Psychiatry*. 2004;55:1007–1012.)

reduce emesis associated with a range of stimuli, including cisplatin, cyclophosphamide, irradiation, ipecacuanha, copper sulfate, opioids, and motion.[41] NK1 receptor antagonists competitively inhibit SP binding to central NK1 receptors, effectively preventing neurotransmission within the central pattern generator for vomiting.[42] Because cisplatin increases plasma levels of SP, NK1 receptor antagonists are particularly important for the prevention and treatment of CINV.[43]

Aprepitant

Currently aprepitant is the only FDA-approved NK1 receptor antagonist. Aprepitant has greater efficacy for preventing vomiting than any other single intervention, with RR reductions of more than 50%.[41,44] Furthermore, aprepitant has greater efficacy against both acute and delayed POV and CIV.[43,45,46] Aprepitant is available as an oral capsule that is easy to coadminister with other surgical premedication for PONV prophylaxis. Whereas aprepitant is highly effective on its own, it reaches its optimal efficacy against early emesis when combined with other antiemetics, such as 5-HT_3-receptor antagonists and/or dexamethasone.[43,45,46] Its efficacy against nausea, however, appears to be comparable to other treatment options.[41] Like 5-HT_3-receptor antagonists, aprepitant is nonsedative; it has a long half-life of 9 to 13 hours. Furthermore, aprepitant is not associated with QTc prolongation.[41] Aprepitant is primarily metabolized by CYP 3A4; CYP 1A2 and CYP 2C19 also contribute to its metabolism.

Positron emission tomography studies have shown that aprepitant can penetrate the blood-brain barrier to bind to NK1 receptors in the area postrema.[47] The FDA-approved dose of aprepitant for PONV prophylaxis is 40 mg, which is associated with only 75% receptor occupancy (Fig. 34.8). Doses of 100 mg or more, such as the FDA-approved 125 mg for CINV prophylaxis, are sufficient to achieve greater than 90% NK1 receptor occupancy. Patients with cancer typically receive 125 mg aprepitant the day of chemotherapy, followed by 2 days of 80 mg aprepitant.[48] Aprepitant doses as high as 375 mg are associated with the same level of receptor occupancy as 125 mg and thus have no clinical advantage.

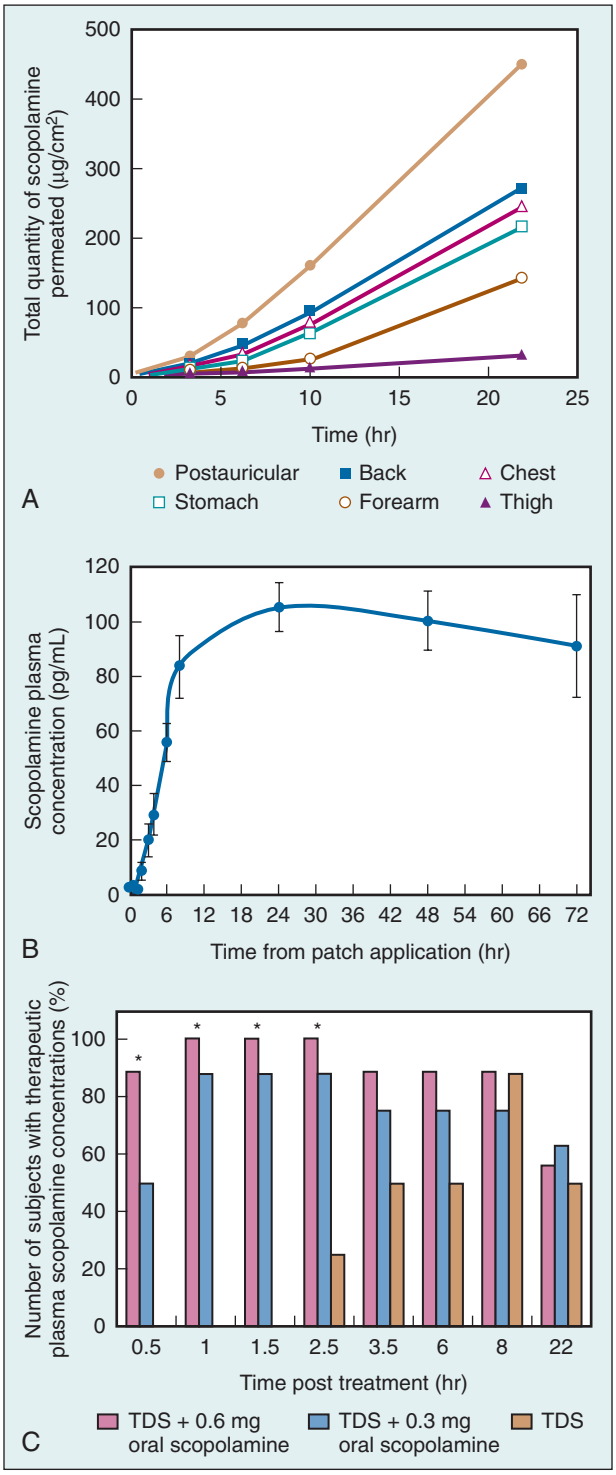
The neurotransmitter acetylcholine acts on cholinergic receptors in the CTZ, vestibular system, and cerebellum. According to the current model of motion sickness, an orientation disparity comparator in the cerebellum compares expected sensory input from memory with actual sensory input, and any significant discrepancy between the two triggers symptoms of motion sickness. Acetylcholine might be involved in integrating sensory stimuli in the vestibular nuclei, as well as transmitting information regarding expected sensory input to the cerebellum. Therefore anticholinergic agents like scopolamine might facilitate habituation to motion by preventing acetylcholine from relaying signals to the comparator and instead allowing a new sensory pattern to develop that reflects the actual environment.[49] Acetylcholine released from the gut wall also appears to increase gut motility and secretion. Anticholinergic agents thus play an important role in the prevention of motion sickness and PONV.

Scopolamine

Scopolamine is a competitive antagonist of acetylcholine at muscarinic receptors, and the most effective single agent for preventing motion sickness.[49] Scopolamine is available in oral, parenteral, and transdermal formulations. The 0.3- to 0.6-mg oral and 0.2-mg parenteral doses are associated with a short duration of action of 5 to 6 hours and some adverse effects, most commonly dry mouth, drowsiness, and blurred vision.[50] Redosing with oral or parenteral doses can result in variable drug plasma concentrations, which if too high are associated with severe autonomic and CNS effects and if too low are associated with inadequate antiemetic efficacy.

A transdermal formulation of scopolamine was developed to overcome the limited half-life and clinical efficacy of the oral and parenteral formulations. A transdermal delivery system is also an advantage when oral doses are intolerable. Transdermal scopolamine (TDS) is available in a thin (0.2-mm) patch made up of four layers: an outer membrane, a drug reservoir mixed with mineral oil and polyisobutylene, a rate-limiting microporous membrane, and an adhesive layer closest to the skin. In vitro studies using human cadavers show wide variation in skin permeability between both application sites and individuals. Therefore the patch is recommended for use at the postauricular site, a highly permeable area, and the rate-limiting microporous membrane has been designed to deliver scopolamine at a slower rate than that achieved in the least porous postauricular skin sample tested.[49] In addition, the adhesive layer contains a 140-µg priming dose of scopolamine to overcome the skin as the primary compartment before a more constant scopolamine delivery leads to steady-state plasma concentrations.

The drug reservoir contains 1.5 mg scopolamine that is released at a constant rate of about 5 µg/hr for 3 days. The controlled drug delivery decreases the incidence of adverse side effects compared with oral and parenteral formulations.[51,52] This delivery rate maintains therapeutic plasma concentrations, estimated to be greater than 50 pg/mL. Plasma concentrations greater than 50 pg/mL and antiemetic efficacy are both observed 6 hours after patch application (Fig. 34.9A).[53,54] Drug efficacy peaks at plasma concentrations greater than 100 pg/mL, observed 8 to 12 hours after application. Therefore TDS should be administered ideally 4 to 6 hours before an antiemetic effect is required. However, supplementing TDS with 0.3 to 0.6 mg oral scopolamine results in therapeutic plasma concentrations after only 1 hour (see Fig. 34.9B and C).[55]



• **Fig. 34.9** A, In vitro permeation of scopolamine at 30°C from various patch locations. B, Transdermal scopolamine *(TDS)* effects on plasma concentrations. Plasma concentrations of scopolamine persist up to 72 hours after TDS application (n = 15). C, Percentage of subjects with plasma scopolamine concentration greater than 50 pg/mL, 0 to 22 hours after treatment in three experimental groups. *$P < 0.05$ (Fisher's exact test) when TDS + 0.6 mg and TDS + 0.3 mg are compared with TDS only group. (From Nachum Z, Shupak A, Gordon CR. Transdermal scopolamine for prevention of motion sickness: clinical pharmacokinetics and therapeutic applications. *Clin Pharmacokinet*. 2006;45:543–566.)

TDS is an effective antiemetic intervention, associated with a risk reduction of 0.56 and 0.54 for PON and POV, respectively, if applied the night before surgery, and with a risk reduction of 0.61 and 0.74 for PON and POV, respectively, if applied the day of surgery.[56] Interestingly, despite wide variation between individual plasma concentrations, correlation of plasma concentrations 8 hours after TDS application in the same individual on different occasions is still 0.52 ($P < 0.05$).[57]

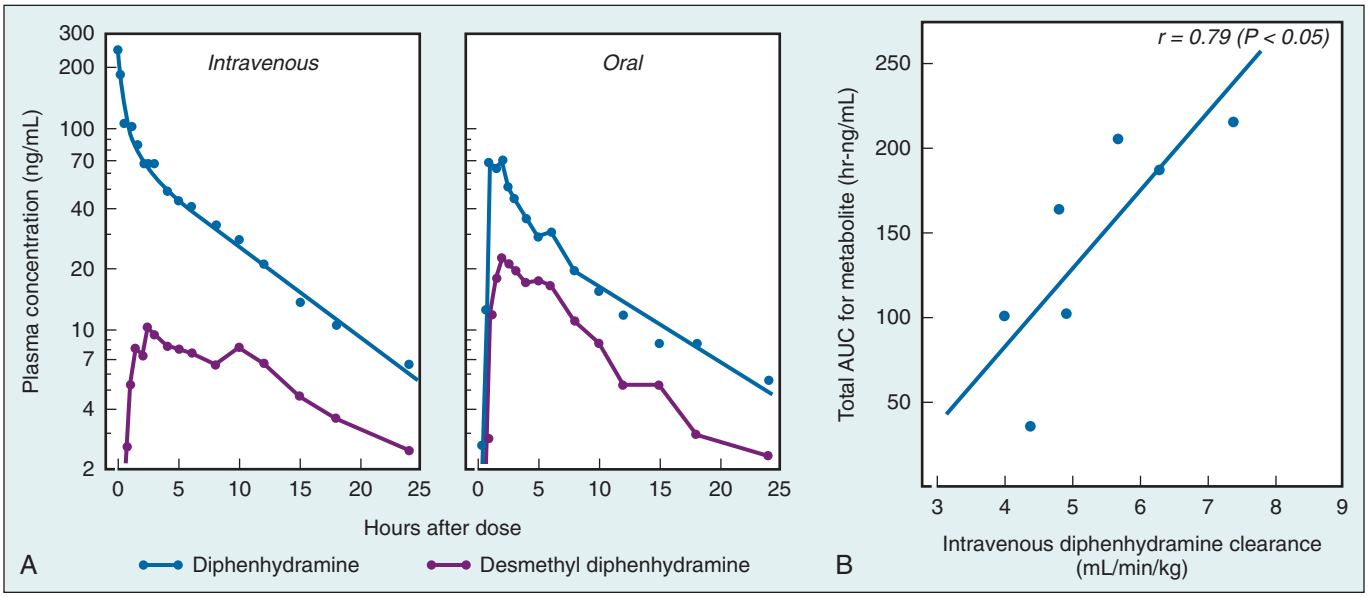
TDS is generally well tolerated; adverse effects are similar to those associated with oral and parenteral scopolamine. The most common adverse effects are dry mouth, allergic contact dermatitis, and drowsiness. The drowsiness appears to be associated with PONV more than motion sickness.[49] Scopolamine is not recommended for pediatric patients and should be used with caution in older patients because of the sedative effects and the risk of delirium.

H_1-Receptor Antagonists

H_1-receptor antagonists can be used for management of motion sickness, PONV, and OINV. Agents like diphenhydramine, promethazine, and cyclizine are reversible competitive H_1-receptor antagonists with moderate anticholinergic (antimuscarinic) and weak antidopaminergic activity. Although the mechanism of their antiemetic efficacy is not fully understood, H_1-receptor antagonists likely act on receptors in the vestibular system and vomiting center.[23] Side effects include drowsiness, dry mouth, blurred vision, urinary retention, and extrapyramidal symptoms.[22,58] Although H_1-receptor antagonists are generally well tolerated, cost-effective, and have been used in clinical practice for several decades, they have not been as well studied as other more recently developed antiemetics.[59] Dose-response relationships, side effect profiles, and the benefit of repeat dosing remain unclear.[58,60] Their efficacy against motion sickness might give H_1-receptor antagonists an important role in antiemetic prophylaxis for ambulatory patients.[61]

Dimenhydrinate and Diphenhydramine

Dimenhydrinate is a theoclate salt composed of diphenhydramine, an ethanolamine derivative, and 8-chlorotheophylline, a chlorinated theophylline derivative, in a 1:1 ratio. Dimenhydrinate must be metabolized into its active ingredient diphenhydramine to attain antiemetic efficacy. Therefore dimenhydrinate has a slower onset of action and is administered as a 60-mg dose to match the potency of 30 mg diphenhydramine.[59] Diphenhydramine itself undergoes N-demethylation to its principal metabolite monodesmethyldiphenhydramine (DMDP) in the liver.[62] Oral diphenhydramine bioavailability ranges from 43% to 72%, probably owing to first-pass metabolism, with peak plasma concentrations of approximately 64 ng/mL after approximately 2.5 hours.[62,63] Plasma concentration of diphenhydramine covaries with that of DMDP (Fig. 34.10A). The observed plasma half-life of oral dimenhydrinate is 3 to 9.3 hours, and the elimination half-lives after intravenous and oral administration are 8.4 and 9.2 hours, respectively, for diphenhydramine and 9.3 and 7.3 hours, respectively, for DMDP (see Fig. 34.10B).[64] The observed metabolite area under the curve (AUC) after oral administration (218 hr.ng/mL) is significantly larger than after intravenous administration (145 hr-ng/mL).[64] Sedative and performance-impairing side effects are typically associated with diphenhydramine doses greater than or equal to 50 mg and differ from placebo only within the first 3 hours.[62,65] Although there is a positive correlation between plasma concentration and sedative effects, there is also wide variation among individuals in the severity and persistence of these effects.[65]



• **Fig. 34.10** A, Plasma concentrations of diphenhydramine and its metabolite desmethyl diphenhydramine following intravenous and oral administration of diphenhydramine. B, Relation of clearance of intravenous diphenhydramine to total area under the plasma concentration-time curve *(AUC)* for the metabolite desmethyl diphenhydramine, as determined by linear regression analysis. Appearance of the metabolite thus mirrors the disappearance of diphenhydramine. (From Blyden GT, Greenblatt DJ, Scavone JM, et al. Pharmacokinetics of diphenhydramine and a demethylated metabolite following intravenous and oral administration. *J Clin Pharmacol*. 1986;26:529–533.)

A systematic review incorporating 18 clinical trials and 3045 patients demonstrated that diphenhydramine is associated with decreased POV and PONV, although its impact on PON was not significant.[58] In addition, 50 mg IV dimenhydrinate is similarly effective as 4 mg IV ondansetron for the prevention of PONV in patients undergoing elective laparoscopic cholecystectomy.[66] For management of motion sickness, 100 mg oral dimenhydrinate is superior to TDS, whereas 50 mg is similarly effective as TDS.[49]

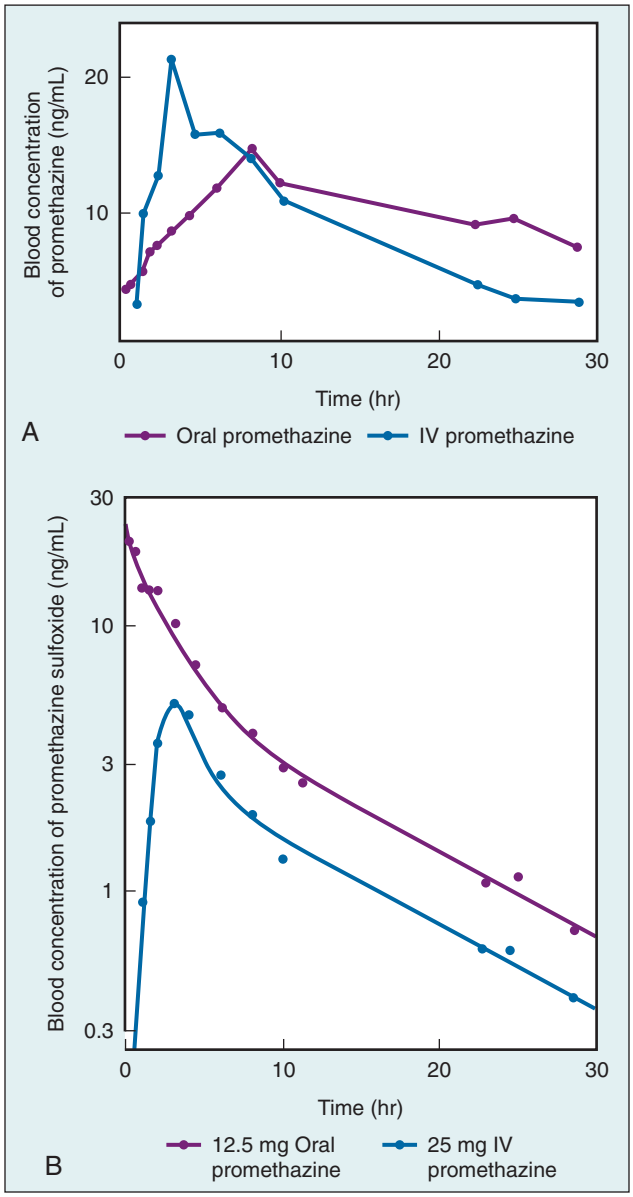
For OINV management, diphenhydramine can be safely and effectively coadministered with morphine via a PCA pump, especially given the similar pharmacokinetic profiles of the two drugs. Administering 30 mg diphenhydramine at induction, followed by a 4.8:1 diphenhydramine-morphine solution via a PCA pump, reduced emesis without morphine-sparing or sedative effects.[59] The initial intraoperative dose serves to establish a therapeutic plasma concentration before the infusion, thereby minimizing the risk of sedative side effects associated with larger diphenhydramine doses during the postoperative period.

Promethazine

Promethazine is a phenothiazine derivative and a potent antihistamine with moderate antimuscarinic activity. Although more than 80% is absorbed, promethazine undergoes extensive first-pass hepatic glucuronidation and sulfoxidation, resulting in low absolute bioavailability of approximately 25%.[67] Peak plasma concentrations of promethazine (2.4–18.0 ng/mL) are observed between 1.5 and 3 hours after administration (Fig. 34.11A). Like other drugs that undergo extensive hepatic first-pass metabolism, plasma concentrations of its metabolite, promethazine sulfoxide (PMZSO), peak earlier and higher following oral administration compared with intravenous administration (see Fig. 34.11B).[67] Overall, however, PMZSO plasma AUCs are not significantly different following oral or intravenous administration. Time to effect after intravenous and intramuscular injection is 5 and 20 minutes, respectively.[68] With a plasma half-life after intravenous and intramuscular injection of 9 to 16 hours and 6 to 13 hours, respectively, promethazine's duration of effect is typically 4 to 6 hours, up to 12 hours.[68]

Promethazine is also effective for rescue treatment of established PONV and has been combined with 5-HT_3-receptor antagonists and TDS to reduce both the frequency and severity of PONV.[69–72] For PONV management, 12.5 to 25 mg is administered toward the end of surgery and every 4 hours, as needed, with doses of coadministered analgesics and/or barbiturates reduced accordingly.[68] Studies investigating a 6.25-mg promethazine dose to reduce the incidence of sedative side effects have produced conflicting results on antiemetic efficacy.[71] Because H_1 receptors are involved in the development of inflammatory pain and hyperalgesia, administering antihistamines like promethazine can also reduce pain levels in addition to the incidence of emesis. In one study, preoperative administration of 0.1 mg/kg IV promethazine reduced postoperative morphine consumption by approximately 30% in the first 24 postoperative hours.[73]

Promethazine received a black box warning from the FDA in 2004 indicating that the drug should not be used in children younger than 2 years of age because of potential fatal respiratory depression. The warning label also recommends that promethazine should be administered with caution and at the lowest effective dose in children 2 years of age and older. The promethazine hydrochloride injection also received a black box warning from the FDA in 2009 indicating that severe tissue injuries, including gangrene, can rarely be associated with intravenous administration of promethazine. In anesthesia practice it is important to inject promethazine only through a well-established and secure IV line or infuse the drug diluted in saline solution.



• **Fig. 34.11** Blood concentration-time profiles of promethazine (A) and promethazine sulfoxide (B) in a human volunteer following administration of 12.5 mg intravenous (*IV, purple*) or 25 mg oral *(blue)* promethazine. (From Taylor G, Houston JB, Shaffer J, et al. Pharmacokinetics of promethazine and its sulphoxide metabolite after intravenous and oral administration to man. *Br J Clin Pharmacol*. 1983;15:287–293.)

GABA Receptor Agonists

Propofol

Propofol has several mechanisms of action, including potentiation of $GABA_A$ receptors. Administration of propofol-based total intravenous anesthesia (TIVA) instead of volatile anesthetics can reduce the incidence of PONV by about 20%.[35] That propofol

has antiemetic effects is supported by the finding that repeat doses of 20 mg propofol via a patient-controlled delivery device in the postanesthesia care unit (PACU) significantly reduced PONV.[74] However, this effect could not be reproduced in a similar study, and another study found that both propofol and midazolam had antiemetic properties only under clinical sedation.[75,76] Therefore it is likely that the reduced incidence of PONV after TIVA with propofol compared with general anesthesia with inhaled gas is at least in part a result of not administering volatile anesthetics rather than the potential antiemetic effects of propofol.

Some patients experience anticipatory nausea and vomiting before chemotherapy begins or earlier in the treatment regimen than expected. As a learned response to chemotherapy, anticipatory nausea and vomiting can affect up to 25% of patients by the fourth treatment cycle.[77,78] However, much about its pathogenesis and management remains unclear.

Benzodiazepines

Benzodiazepines are currently the most commonly used anxiolytics. These agents act as positive modulators of $GABA_A$ receptors. Increased $GABA_A$ receptor activity results in varying levels of CNS depression, including sedative, hypnotic, anxiolytic, anticonvulsant, muscle relaxant, and amnesic effects. In addition to decreased anxiety, the mechanism of action of benzodiazepines is believed to involve $GABA_A$ receptor-mediated reduction of dopamine and $5\text{-}HT_3$ receptor activity in the CTZ.[79] Another specific pathway that has been suggested is that benzodiazepines decrease adenosine reuptake, thereby leading to decreased synthesis, release, and postsynaptic activity of dopamine in the CTZ.[80,81]

$GABA_A$-receptor activation is also associated with reduced opioid analgesia.[82] Opioids are believed to produce an analgesic effect by inhibiting GABA-receptor pain modulation in the periaqueductal gray matter and the rostral ventral medulla. In one study, 0.75 mg IV flumazenil, a benzodiazepine antagonist, enhanced postoperative morphine analgesia in patients who received intravenous diazepam preoperatively compared with patients who did not receive flumazenil.[82] Therefore opioid analgesia can be improved by using benzodiazepines of short duration of action and/or by coadministering flumazenil with morphine in the immediate postoperative period.

Diazepam is typically administered as a 5- to 10-mg dose 2 hours before surgery. The agent appears to be effective against both nausea (RR = 0.50, 95% confidence interval [CI] 0.25–0.99) and vomiting (RR = 0.85, 95% CI 0.58–1.24).[22] Because of a long half-life of more than 24 hours, other benzodiazepines with shorter durations of action, such as lorazepam and midazolam, can be used instead.

Lorazepam is the preferred agent for anticipatory nausea and vomiting. It can also be used for the prophylaxis and treatment of PONV and CINV.[83] Like diazepam, lorazepam appears to have a greater effect on nausea (RR = 0.55, 95% CI 0.33–0.93) than vomiting (RR = 0.61, 95% CI 0.33–1.13) compared with placebo.[22] For PONV prophylaxis, patients receive 0.05 mg/kg (up to 4 mg maximum) 1 to 2 hours before surgery. For anticipatory nausea and vomiting, guidelines recommend 0.5 to 2 mg lorazepam on the night before and morning of surgery, and for CINV management, 0.5 to 2 mg every 4 to 6 hours on days 1 to 4 posttreatment.[84] Lorazepam might be insufficient as an antiemetic on its own, but it can be safely combined with other antiemetic agents to manage CINV.[85] A randomized controlled trial found lorazepam effective in managing anticipatory, acute, and delayed CINV, especially when coadministered with 2 mg/kg metoclopramide IV.[86] Mild sedation (lethargy but arousable without any disorientation) and amnesia (no memory of chemotherapy treatment) were more common in patients treated with lorazepam.

Lorazepam is readily absorbed into the bloodstream with an absolute bioavailability of 90%. Peak plasma concentrations of 20 ng/mL after a 2-mg dose are reached approximately 2 hours after administration. The plasma half-life of lorazepam is approximately 12 hours and 18 hours for its primary metabolite, lorazepam glucuronide.

Intravenous midazolam is the most commonly used premedication in ambulatory surgery for induction of general anesthesia and preoperative sedation owing to its rapid onset of action, relatively short half-life, low cost, and low incidence of side effects.[87] For PONV prophylaxis, a 2-mg dose of midazolam can be given before or after induction or postoperatively as a continuous infusion. Ahn and colleagues examined previous randomized controlled trials of midazolam and PONV via a database search. The investigation revealed a reduction in PONV (RR 0.45, number needed to treat 3) with similar findings for PON and POV in isolation.[88]

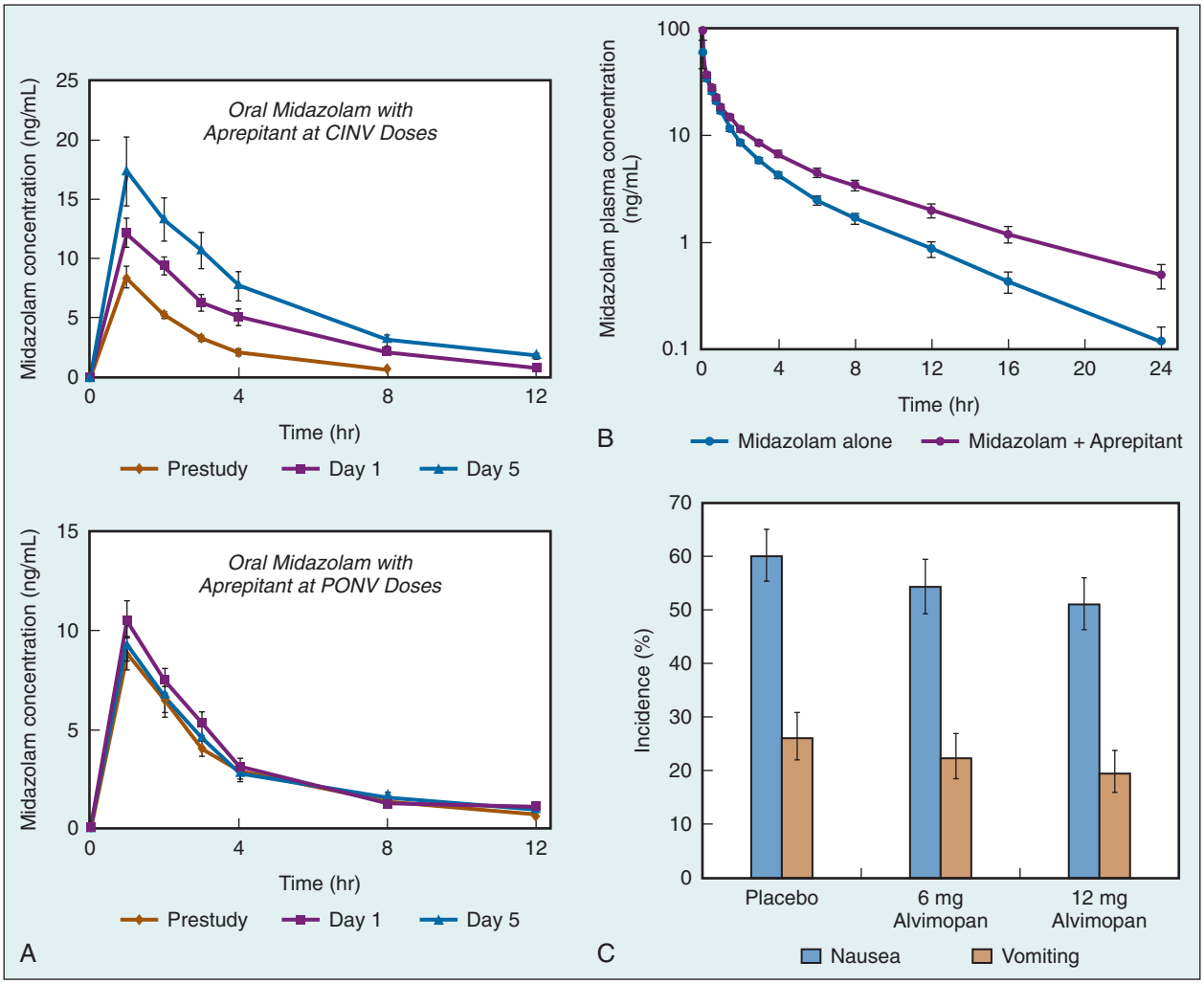
Midazolam is rapidly metabolized to 1′-hydroxymidazolam by both hepatic and intestinal CYP 3A4. Therefore drugs like aprepitant that inhibit CYP 3A4 activity could lead to prolonged sedation owing to increased exposure to midazolam. In a study in which healthy volunteers received a 2-mg dose of oral midazolam during the week preceding the study, a second dose on day 1, and a third on day 5, participants were randomly assigned to receive an aprepitant dosing regimen similar to CINV (125 mg on day 1 and 80 mg on days 2–5) or PONV prophylaxis (40 mg on day 1 and 25 mg on days 2–5).[89] CINV doses of aprepitant led to a 2.3-fold increase in midazolam plasma AUC on day 1 and a 3.3-fold increase on day 5 (Fig. 34.12A, upper panel), as well as increased maximum observed plasma concentrations and half-life of midazolam. The latter can be explained by inhibition of both first-pass metabolism and systemic clearance of midazolam by aprepitant. PONV doses of aprepitant had no significant effect on oral midazolam metabolism (see Fig. 34.12A, lower panel). Because aprepitant cannot inhibit first-pass metabolism of CYP 3A4 substrates when they are given intravenously, it is not surprising that both CINV and PONV doses of aprepitant have no significant effect on intravenous midazolam metabolism (see Fig. 34.12B).[90–92]

Opioid Receptor Antagonists

Although the FDA has not specifically approved the use of $5\text{-}HT_3$- and D_2-receptor antagonists for OINV, these agents significantly reduce the incidence of nausea and vomiting after opioid administration.[93–97] Antiemetic agents that specifically target opioid receptors might also have efficacy against OINV, which has the advantage of simultaneously targeting multiple other opioid-induced adverse effects, such as postoperative ileus.[98]

Naloxone

Other techniques to reduce PONV can come from novel uses of preexisting medications. One such technique is using a low-dose naloxone infusion to reduce the side effects of opioid administration. In one study the authors randomly assigned 60 patients receiving morphine PCA to a continuous infusion of naloxone 0.25 μg/kg per hour, 1 μg/kg per hours, or placebo. They found a reduced rate of adverse side effects, including nausea and vomiting, in both naloxone groups compared with the placebo group. Interestingly,



• **Fig. 34.12** Interaction between midazolam and aprepitant. A, Plasma concentration-time profiles of 2 mg oral midazolam before the study, on day 1, and on day 5 when coadministered with 125 mg aprepitant on day 1 and 80 mg on days 2 to 5 in 8 healthy male subjects *(upper panel)*. Plasma concentration-time profiles of 2 mg oral midazolam before the study, on day 1, and on day 5 when coadministered with 40 mg aprepitant day 1 and 25 mg days 2 to 5 *(lower panel)*. B, Plasma concentrations of midazolam when administered intravenously, alone, and with 125 mg oral aprepitant in 12 healthy subjects. C, Incidence of opioid-induced nausea and vomiting after prophylaxis with 6 and 12 mg alvimopan. *CINV,* Chemotherapy-induced nausea and vomiting; *PONV,* postoperative nausea and vomiting. (A, From Majumdar AK, McCrea JB, Panebianco DL, et al. Effects of aprepitant on cytochrome P450 3A4 activity using midazolam as a probe. *Clin Pharmacol Ther*. 2003;74:150–156; B, From Majumdar AK, Yan KX, Selverian DV, et al. Effect of aprepitant on the pharmacokinetics of intravenous midazolam. *J Clin Pharmacol*. 2007;47:744–750; *C,* From Adolor Corporation. Advisory Panel briefing document. Entereg (alvimopan) Capsules for postoperative ileus. 2007. Available at: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4336b1-02-Adolor.pdf.)

there appeared to be an opioid-sparing effect in the low-dose naloxone group as this cohort used less morphine in the study period compared with placebo.[99]

Alvimopan

Alvimopan, a trans-3,4-dimethyl-4-(3-hydroxyphenyl) piperidine, is approved by the FDA to reverse postoperative ileus after colectomy. Although opioids do have some peripherally mediated analgesic effects, opioid analgesia primarily involves central μ, κ, and δ receptors in the rostral anterior cingulate cortex, the brainstem, and the dorsal horn of the spinal cord.[100] Opioid agonist activity at peripheral receptors in the gut, on the other hand, inhibits the release of acetylcholine from the mesenteric plexus and stimulates μ receptors, thereby reducing muscle tone and peristaltic activity. The resulting delayed gastric emptying and gastric distention stimulate visceral mechanoreceptors and chemoreceptors, which trigger nausea and vomiting via a serotonergic signaling pathway. Alvimopan's high polarity and large zwitterionic structure prevent penetration of the blood-brain barrier, such that potency at binding peripheral μ receptors is 200 times that of central μ receptors.[98,101] By selectively targeting peripheral μ receptors, alvimopan prevents peripheral opioid emetogenic effects without affecting their central analgesic effects.[102,103]

Because of its high binding affinity (K_i = 0.4 nM) and low dissociation rate (half-life = 30-44 min), alvimopan has low bioavailability (6%).[104] Alvimopan is quickly absorbed, with a time to maximum plasma concentration of 2 hours after administration. Alvimopan also has a long half-life of 10 to 17 hours.[104] Plasma clearance averages at 400 mL/min and is primarily mediated by biliary secretion. Alvimopan is metabolized by intestinal flora, with an active but clinically irrelevant amide hydrolysis metabolite (ADL 08-0011) that has lower binding affinity than alvimopan itself.

Alvimopan is only available as a 12-mg oral capsule. Patients can be given 12 mg 30 minutes to 5 hours before surgery, followed by 12 mg twice a day for up to 7 days after surgery (maximum of 15 doses).[104] Furthermore, 12-mg alvimopan has been shown to reduce OINV and to be well tolerated by ambulatory patients in the postdischarge period (Fig. 34.12C).[103]

Cannabinoids

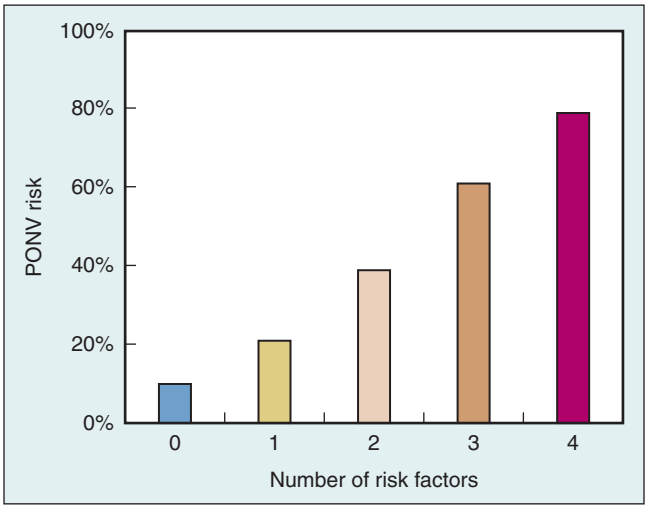
Cannabinoids have demonstrated some success in the prevention of CINV but have never been shown to prevent PONV. Kleine-Brueggeney et al. administered 0.125 mg/kg IV tetrahydrocannabinol or placebo to 40 patients at high risk for PONV. The endpoints examined included PONV during the first 24 hours and side effects including sedation and psychotropic alterations. They found the tetrahydrocannabinol group had a 12% reduction in overall PONV compared with placebo. The authors postulated that this is a less significant effect than standard therapies, which produce a 25% reduction in PONV; this combined with an unacceptable side effect profile provoked the investigators to terminate the study before completion. Thus with the current evidence, cannabinoids cannot be recommended for prevention of PONV in high-risk patients.[105]

Risk-Based Prophylaxis

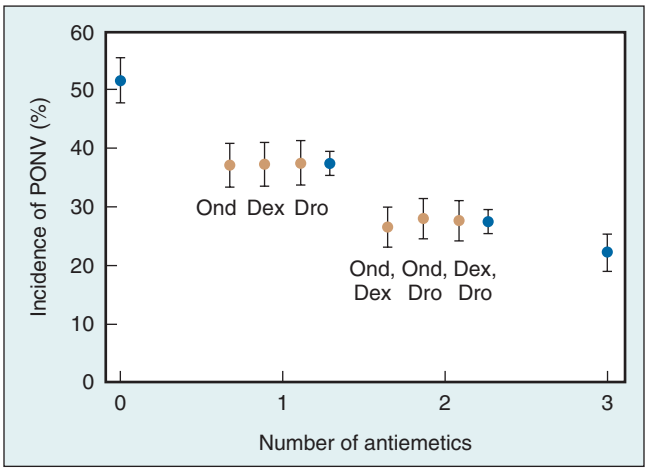
Although all FDA-approved antiemetics have been proven to be safe in multiple clinical trials, no agent is without side effects. Therefore only patients at moderate to high risk for PONV should receive prophylaxis. A simplified risk score, such as the Apfel score (Fig. 34.13), can be useful for predicting PONV in adult patients undergoing inhalational anesthesia and thus for identifying which patients should be targeted for prophylaxis. The positive predictors included in the Apfel score are female gender, history of motion sickness or PONV, nonsmoking, and use of postoperative opioids.[106] The incidence of PONV associated with 1, 2, 3, and 4 risk factors is 10%, 21%, 39%, 61%, and 79%, respectively (Fig. 34.14). An easy-to-remember guideline is that one antiemetic intervention is recommended for each risk factor present. It is also important to note that multimodal therapy should include drugs of different receptor classes, because repeat dosing of drugs of the same receptor class do not improve protection against PONV.[107]

Enhanced Recovery After Surgery

A risk-based assessment of PONV and antiemetic prophylaxis should be part of an enhanced recovery pathway. Patients can be stratified based on established risk factor scoring systems. With increasing risk of PONV, multimodal prophylactic antiemetics should be implemented. Patients with 1 or 2 risk factors should be supplied with 2 prophylactic agents, whereas those with 3 or 4 risk factors should receive 3 prophylactic agents with consideration of adding TIVA. In addition to prophylactic antiemetics, the choice of anesthetics, reduction in preoperative fasting, and adequate hydration may all contribute to the reduction of PONV in this patient population. An overall strategy of minimizing opioids in favor of regional anesthesia and adjuvant nonopioid medications also reduces the likelihood the patient will experience bowel dysfunction, nausea, and vomiting postoperatively.[108]



• **Fig. 34.13** The Apfel simplified risk score for postoperative nausea and vomiting *(PONV)* based on the number of risk factors (female gender, history of motion sickness and/or PONV, nonsmoking, use of postoperative opioids).



• **Fig. 34.14** Results of the IMPACT trial showing the effect of multimodal prophylactic antiemetic therapy on postoperative nausea and vomiting *(PONV).* N = 5161 patients. *Blue dots* show the average value for each number of prophylactic antiemetics. *Orange dots* show the incidence for each antiemetic or combination of antiemetics. *Ond,* Ondansetron; *Dex,* dexamethasone; *Dro,* droperidol. (From Apfel CC, Korttila K, Abdalla M, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med*. 2004;350:2441–2451.)

Multimodal Therapy

No antiemetic agent can completely eliminate the incidence of PONV. A Cochrane review found the overall RR for antiemetics

to be 0.60 to 0.80, that is, an RRR of 20% to 40%.[22] However, the treatment effect might be slightly optimistic given that there is evidence of publication bias toward small studies with more positive results.

The International Multicenter Protocol to quantify the relative impact of single and combined Antiemetics in a randomized Controlled Trial of factorial design (IMPACT) found that the RRs for 4 mg ondansetron, 4 mg dexamethasone, and 1.25 mg droperidol all equal approximately 0.75 (i.e., an RRR of 25% for each intervention; see Fig. 34.14).[35] The study also demonstrated that each antiemetic intervention acted independently, which means that the efficacy of combination therapy can be estimated by multiplying the RR associated with each intervention. This independence of action implies that each additional antiemetic intervention is associated with less effectiveness than the previous one owing to an already decreased baseline risk of PONV. Using new classes of antiemetics synergy with mainstay drugs has reduced the incidence of PONV compared with conventional treatment.

Numerous studies have demonstrated improved outcomes when multiple classes of antiemetics are used together as prophylaxis. One example is a study of chemotherapy-naive patients who were pretreated with antiemetic therapy comprising palonosetron (0.75 mg IV), dexamethasone (9.9 mg IV), and aprepitant (125 mg orally) The primary endpoint was the proportion of patients who did not experience vomiting and did not require rescue medication. Prevalence of the primary endpoint during the acute phase, delayed phase, and overall was 100%, 91.9%, and 91.9%.[109]

A prospective, double-blinded, randomized study compared aprepitant 40 mg orally with dexamethasone versus ondansetron 4 mg IV with dexamethasone in patients undergoing elective craniotomy. The aprepitant dexamethasone group significantly decreased POV up to 48 hours postoperatively (16% vs. 38%). There was no difference in the incidence of nausea or need for rescue medication between the study groups.[110]

A new combination drug available is NEPA, an oral fixed-dose combination of 300 mg netupitant and 0.5 mg palonosetron. In a study of 1455 chemotherapy patients who received dexamethasone plus either single-dose NEPA or palonosetron alone were evaluated for no emesis and no rescue therapy for 25 to 120 hours. Complete response was significantly higher in the NEPA versus the palonosetron group (76.9% vs. 69.5%, $P = 0.001$). The side effect profiles for both drugs were similar. This fixed-dose antiemetic combination offers improved prophylaxis from single-dose treatment.[111]

Acupuncture has been extensively studied as a nonpharmacologic method for the prevention of PONV. Although there are more than 300 acupuncture points, one point that has been shown to be efficacious is the P6 point (the sixth point along the pericardial meridian). It can be located at 2 inches proximal to the palmar aspect of the wrist, between the flexor carpi radialis and palmaris longus tendons. Stimulation of the P6 acupuncture point has shown efficacy for prevention and treatment of nausea and vomiting in the perioperative period. A Cochrane review summarizing 59 trials with 7667 participants drew the following conclusions. P6 acupoint stimulation significantly reduced postoperative nausea (RR = 0.60), vomiting (RR = 0.68), and the need for rescue antiemetics (RR = 0.64) compared with placebo or sham. There is no difference between P6 acupoint stimulation and established antiemetic pharmacotherapy for prevention of PONV. Lastly, there is insufficient evidence to suggest combination therapy is beneficial over acupressure or drug prophylaxis as a sole treatment.[112]

However, some studies have demonstrated mixed results. A study of 94 patients undergoing cesarean section with spinal anesthesia were randomly assigned to receive transcutaneous accupoint electrical stimulation at the P6 point versus a sham location in hope of relieving both intraoperative and postoperative nausea and vomiting. No difference was found between the groups for either endpoint. The authors mentioned the study might have been underpowered.[113]

In general, direct acupuncture needle stimulation and electroacupuncture are associated with greater efficacy compared with acupressure. However, the optimal duration of stimulation and the amount of current is not known.

Emerging Developments

Novel Antiemetic Drugs

With the success of novel antiemetics like aprepitant and palonosetron, there is great promise for other new agents currently under investigation. These include newer NK1 receptor antagonists like the intravenous prodrug of aprepitant known as fosaprepitant, as well as the phase III–ready rolapitant (rolapitant hydrochloride, Schering-Plough SCH619734), both developed for CINV prevention. Upon injection, fosaprepitant is rapidly converted to aprepitant and therefore has the same mechanism of action as aprepitant. For CINV prevention, patients can receive fosaprepitant 150 mg as an IV infusion over 20 to 30 minutes before chemotherapy on the day of chemotherapy, followed by 2 to 3 days of treatment with other antiemetic agents like dexamethasone and ondansetron. Rolapitant appears to have several advantages over aprepitant, including a long half-life of 180 hours. It is more rapidly absorbed and does not inhibit CYP 2C9, 2C19, 2D6, and 3A4 or P-glycoprotein in vitro, suggesting that rolapitant has a low risk of interacting with concomitant medications.[114] Oral doses of rolapitant appear to be rapidly absorbed and well tolerated without significant side effects. A dose-response study reported that rolapitant reduced POV up to 120 hours after surgery in high-risk patients, and that 70 mg and 200 mg were the most effective doses in terms of complete response.[114] However, the optimal rolapitant dose has yet to be determined. In addition, rolapitant is currently available only in an oral formulation and therefore must be administered preoperatively. Amisulpride, a dopamine D2/D3 antagonist, is currently in phase III trials. It is being examined for its efficacy in the prevention of PONV in the adult surgical population.

A multicenter study of adult inpatients undergoing elective surgery with general anesthesia randomly assigned participants to amisulpride 5 mg IV on induction or placebo. The primary endpoint was no retching or vomiting in the 24-hr postoperative period and no use of rescue antiemetics. The incidence of nausea was a secondary endpoint. In the U.S. component of the study, 46.9% of patients achieved the primary endpoint in the amisulpride group while 33.8% achieved in the placebo group ($P = 0.026$). Nausea occurred less in the study group. There was no clinically significant difference in the safety profile of the study drug compared with the placebo. Specific concerns examined were QT prolongation, extrapyramidal side effects, and sedation that were problematic for this group of antiemetics in the past.[115]

Postdischarge Nausea and Vomiting

As the number of surgeries performed on an outpatient basis continues to grow, there is increasing interest in using antiemetic agents to prevent and treat postdischarge nausea and vomiting

(PDNV). Because outpatient procedures are typically less invasive and shorter in duration than inpatient procedures, the relatively lower exposure to emetogenic inhalational anesthetics and opioids predicts a relatively lower incidence of PONV in the postanesthesia care unit. However, a study in 2170 ambulatory patients in the United States found that the incidence of nausea and vomiting after discharge from the hospital was 37%, even after intraoperative prophylaxis with ondansetron or dexamethasone.[116] PDNV is particularly a concern because it occurs when patients no longer have access to fast-acting intravenous rescue treatment, and PDNV limits their ability to tolerate oral antiemetics. Ideal antiemetics for PDNV should have a long duration of action with a safe side effect profile, such as dexamethasone, palonosetron, TDS, and aprepitant. However, further studies are required to investigate the absolute and relative value of these and other antiemetics in the postdischarge setting.

Key Points

- Despite new insights into relevant target receptor function and the successful development of novel antiemetic agents, the actual mechanisms of PONV remain unknown.
- Ondansetron is the most commonly used serotonin type 3 (5-HT_3)-receptor antagonist for prevention and treatment of PONV and CINV, probably because it is not associated with sedation that might slow recovery from anesthesia.
- Low-dose droperidol (0.625–1.25 mg), a dopamine type 2 (D_2) receptor antagonist, used to be the most commonly used antiemetic for the prevention of PONV; however, potential for torsades de pointes and cardiac arrest led to an FDA black box warning that has significantly reduced its usage in the United States.
- Metoclopramide is an alternative D_2 receptor blocker; 25 mg is the minimally effective dose for preventing PONV. Extrapyramidal symptoms associated with the 25-mg dose affect less than 1% of patients, but like other D_2 antagonists, arrhythmias have been described.
- The antiemetic effect of glucocorticoids such as dexamethasone is well established although poorly understood. Most dose-response studies suggest that 4 mg is the minimally effective dose with equal efficacy as 4 mg ondansetron and 1.25 mg droperidol.
- Aprepitant is the first FDA-approved NK1 receptor antagonist. An oral dose of 40 mg aprepitant reduces nausea by about 30% and vomiting by more than 50%. It is thus particularly useful for surgeries in which postoperative vomiting might affect the success of the surgery.
- TDS is the only approved anticholinergic for prevention of PONV. RRR is comparable to other antiemetics; its long duration of action makes TDS a suitable antiemetic for preventing PDNV in ambulatory patients.
- H_1 antagonists such as dimenhydrinate, cyclizine, and promethazine are less popular, mainly because of their sedative and psychotropic side effects and the potential for vein irritation and tissue damage.
- Alvimopan is a peripheral opioid receptor antagonist indicated for the prevention of ileus after colectomies. Secondary data analyses suggest that it might reduce OINV.
- The effectiveness of antiemetics when given prophylactically is critically dependent on the patient's risk for PONV. This can be easily assessed using a simplified risk score for PONV consisting of four risk factors: female sex, history of motion sickness and/or PONV, nonsmoking status, and anticipated use of postoperative opioids.

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Carlisle J, Stevenson C. Drugs for preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev*. 2006;(3):CD004125, A systematic review of more than 730 trials that assessed the efficacy of all antiemetic agents as well as their associated side effects. The individual relative risk versus placebo for all effective antiemetics ranged between 0.60 and 0.80. (Ref. 22).

Cubeddu LX, Hoffmann IS, Fuenmayor NT, et al. Efficacy of ondansetron (GR 38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. *N Engl J Med*. 1990;322:810–816. One of the first papers to show that ondansetron safely and effectively reduced the incidence of CINV in cancer patients undergoing chemotherapy. The results also suggested that cisplatin treatment triggered enterochromaffin cells to release serotonin and that ondansetron worked by blocking 5-HT3 receptors. (Ref. 2).

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35

Endocrine Physiology

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CHAPTER OUTLINE

Pituitary Physiology
- Anterior Pituitary
  - *Hyperpituitarism and Anterior Lobe Tumors*
- Posterior Pituitary
  - *Diabetes Insipidus and Syndrome of Inappropriate Antidiuretic Hormone*

Parathyroid Physiology
- Primary Hyperparathyroidism
- Multiple Endocrine Neoplasia
- Secondary Hyperparathyroidism
- Hypoparathyroidism

Thyroid Physiology
- Hypothyroidism
- Hyperthyroidism
  - *Thyroiditis*

Adrenal Gland Physiology
- Adrenal Cortex Physiology
  - *Cushing Syndrome*
  - *Glucocorticoid Deficiency*
  - *Hyperaldosteronism*
  - *Hypoaldosteronism*

Adrenal Medulla Physiology
- Pheochromocytoma

Pancreas Physiology
- Diabetes Mellitus

Emerging Developments

Endocrine physiology encompasses processes that range from master regulation by the pituitary gland to the much larger pancreas, which controls energy utilization processes of the body. This chapter reviews normal endocrine physiology and pathophysiology, as well as the basic anesthetic implications associated with the 5 major endocrine organs relevant to anesthesiologists: the pituitary gland, parathyroid glands, thyroid gland, adrenal glands, and the pancreas.

Pituitary Physiology

The pituitary gland controls the function of many other endocrine glands, often being referred to as the "master gland." Despite its central role in the endocrine system, the pituitary is extremely small—about the size of a pea—and weighs only about 0.5 g. It is attached to the hypothalamus by the pituitary stalk (or infundibulum) and rests in the sella turcica, a small, bony cavity in the sphenoid bone at the base of the brain. The pituitary secretes at least 8 hormones that regulate organ function and are critical to survival.

Both functionally and anatomically, the pituitary can be divided into the anterior lobe (or adenohypophysis) and the posterior lobe (or neurohypophysis). The lobes are different enough from one another that they can be considered as entirely different glands. In fact, consistent with their distinct structure and function, the embryonic origin of each lobe is entirely different: the anterior pituitary arises from the oral ectoderm whereas the posterior pituitary arises from the neuroectoderm.

Anterior Pituitary

The anterior pituitary is a glandular secretory organ. The most important hormones produced by the anterior pituitary include adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), growth hormone (GH), prolactin (PRL), and the two gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Melanocyte-stimulating hormone (MSH) is also produced by the anterior pituitary but is not required for homeostasis.

The anterior pituitary is composed of 3 cell types, as identified with traditional aniline dye stains: acidophils, basophils (often collectively referred to as *chromophils*), and chromophobes. The chromophils are the principal secretory cell types whereas the chromophobes are not thought to have secretory function. Today, 5 cell types producing the 6 major hormones are best differentiated using immunohistochemical staining, as follows:

- Somatotrophs, which produce GH (acidophilic)
- Mammotrophs, which produce PRL (acidophilic)
- Corticotrophs, which produce ACTH, MSH, and various endorphins (basophilic)
- Thyrotrophs, which produce TSH (basophilic)
- Gonadotrophs, which produce FSH and LH (basophilic)

In general, the balance of releasing factors secreted by the hypothalamus and inhibiting factors secreted by each hormone's target organ control the secretion of each hormone produced by the anterior pituitary. For example, TSH stimulates the thyroid to produce triiodothyronine (T_3) and tetraiodothyronine (T_4). The secretion of TSH by the anterior pituitary is stimulated by the secretion of thyrotropin-releasing hormone by the hypothalamus, but inhibited by both thyroid hormones (T_3 and T_4), creating a

Abstract

This chapter reviews the normal physiology of the five major endocrine organs relevant to anesthesiology: the pituitary gland, parathyroid glands, thyroid gland, adrenal glands, and pancreas. Disturbances in endocrine hormone production from these glands lead to various endocrine disorders (such as thyroiditis, Cushing syndrome, and diabetes mellitus). The pathophysiology of the most common endocrine disorders and considerations for anesthetic management of patients with these disorders are discussed.

Keywords

pituitary disease
hyperthyroidism
hypothyroidism
diabetes
hyperparathyroidism

TABLE 35.1 Major Hormones of the Anterior Pituitary

Hormone	Acronym	Protein Structure	Releasing Factor (From Hypothalamus)	Inhibiting Factors	Anatomic Target	Effects
Adrenocorticotropic hormone	ACTH	Polypeptide	Corticotropin-releasing hormone	Glucocorticoids	Adrenal gland	Secretion of glucocorticoids
Thyroid-stimulating hormone	TSH	Glycoprotein	Thyrotropin-releasing hormone	T_3 and T_4	Thyroid gland	Secretion of thyroid hormones
Growth hormone	GH	Polypeptide	Growth hormone-releasing hormone	Growth hormone, insulin-like growth factor 1 (IGF-1), somatostatin	Liver, adipose tissue	Growth, anabolic, promotes lipid and carbohydrate metabolism
Prolactin	PRL	Polypeptide	See text	Dopamine	Ovaries, mammary glands	Milk production, lipid and carbohydrate metabolism
Luteinizing hormone	LH	Glycoprotein	Gonadotropin-releasing hormone	Estrogen, testosterone	Gonads	Sex hormone production
Follicle-stimulating hormone	FSH	Glycoprotein	Gonadotropin-releasing hormone	Estrogen, testosterone	Gonads	Sex hormone production

feedback loop. The releasing and inhibiting factors for each hormone are summarized in Table 35.1. The exception to this principle is prolactin, which is under tonic-inhibition by dopamine secreted by the hypothalamus.

The action of releasing factors secreted by the hypothalamus is facilitated by the presence of a portal blood supply to the anterior pituitary. The hypothalamus secretes releasing factors into a primary capillary plexus from which they travel to a secondary capillary plexus in the anterior pituitary.

Hyperpituitarism and Anterior Lobe Tumors

Essentially all cases of hyperpituitarism occur secondary to pituitary adenoma. These tumors are commonly encountered in clinical practice. They represent only 10% of diagnosed brain neoplasms; however, as many as 20% of people have a pituitary tumor on postmortem examination, suggesting that many pituitary adenomas are asymptomatic.[1]

Although the majority of pituitary adenomas are asymptomatic, most tumors present in 3 discrete ways: (1) hormonal hypersecretion, (2) local mass effects (including pituitary hypofunction due to compression of the normal gland), or (3) incidental discovery during cranial imaging for an unrelated condition. Approximately 75% of pituitary tumors are "functioning" and produce a single predominant hormone; these patients typically present with the signs and symptoms of hormone excess. For example, patients with a TSH-secreting adenoma have pituitary hyperthyroidism and present with the signs and symptoms of hyperthyroidism. Patients with Cushing disease (secondary to an ACTH-secreting adenoma) and acromegaly (secondary to a growth hormone-secreting adenoma) merit special attention and are discussed later. The perioperative management of patients with pituitary tumors undergoing surgery has been extensively reviewed.[2] Pituitary adenomas are often classified based on their size at the time of discovery. Tumors larger than 10 mm in any dimension are classified as *macroadenomas*; tumors smaller than 10 mm are classified as *microadenomas*.

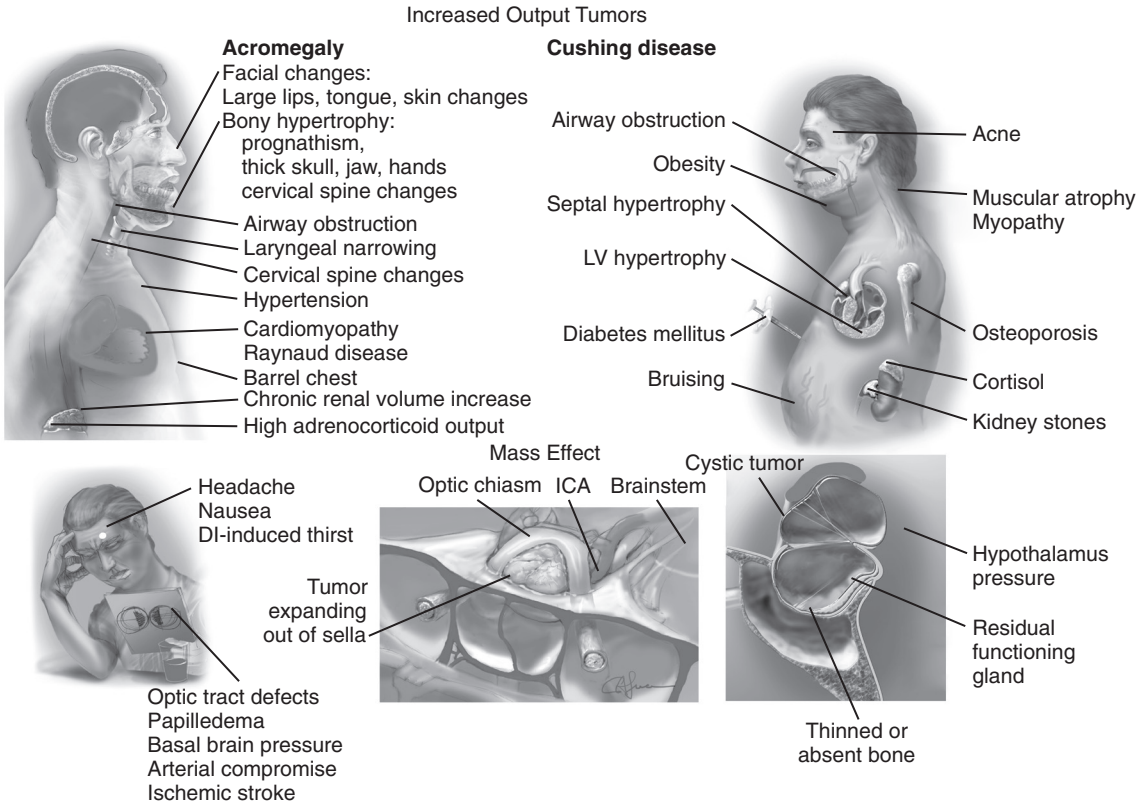
The mass effects produced by pituitary tumors can be extensive and problematic given the location of the pituitary gland within the brain. Patients can present with varying degrees of hypopituitarism secondary to compression of normal anterior pituitary tissue by the expanding intrasellar mass. Seventy percent to 90% of patients with nonfunctioning pituitary macroadenomas exhibit deficiencies in at least one pituitary hormone with formal testing.[3] Thus, while it is easy to focus on the signs and symptoms of glucocorticoid excess in a patient with Cushing disease, for example, the patient with Cushing disease might also suffer from pituitary hypothyroidism. Furthermore, PRL is frequently elevated in patients with all varieties of pituitary tumors secondary to disruption in normal inhibitory tone from the hypothalamus. Regardless, posterior pituitary dysfunction is unusual, even among patients with very large tumors.

Gigantism and Acromegaly

The unregulated hypersecretion of growth hormone by the anterior pituitary leads to increased production of insulin-like growth factor 1 (IGF-1) by the liver. Children in whom the epiphyses have not closed experience gigantism. In contrast, acromegaly develops in adults. Cardiac disease, hypertension, and ventricular hypertrophy are the most important causes of morbidity and mortality in acromegalic patients. Patients with acromegaly have a characteristic facies as the soft tissues of the nose, mouth, tongue, and lips become thicker and contribute to the acromegalic appearance. Airway obstruction and obstructive sleep apnea (OSA) can affect up to 70% of acromegalic patients.[4] A high risk of perioperative airway compromise has been well documented in acromegalic patients.[5] Other manifestations of acromegaly are summarized in Fig. 35.1.

Cushing Disease

Cushing disease specifically results from the unregulated hypersecretion of ACTH by a pituitary adenoma and consequent hypercortisolism. Systemic hypertension is among the most common manifestations.[2] Increased endogenous corticosteroids have been shown to cause systemic hypertension by a variety of mechanisms. Secondary to hypertension, a high prevalence of left ventricular hypertrophy and concentric remodeling has been reported. Glucose



• **Fig. 35.1** Manifestations of acromegaly. *DI,* Diabetes insipidus; *ICA,* internal carotid artery; *LV,* left ventricular. From: Nemergut EC, Dumont AS, Barry UT, Laws ER. Perioperative management of patients undergoing transsphenoidal pituitary surgery. *Anesthesia & Analgesia*. 2005;101(4):1170–1181.

intolerance occurs in at least 60% of patients, with overt diabetes mellitus (DM) present in up to one-third of all patients. Patients are typically obese, with characteristic "moon facies." Although not as common as in acromegaly, patients frequently have OSA. Despite the association with OSA, endotracheal intubation is not usually more difficult.[5] Other manifestations of Cushing disease are summarized in Fig. 35.1. Cushing syndrome is also frequently encountered in clinical practice but, unlike Cushing disease, results from iatrogenic corticosteroid medications (e.g., for asthma, inflammatory conditions, and so forth) and not from a pituitary adenoma. The unique aspects of Cushing syndrome are discussed in detail later.

Prolactinomas

Prolactinomas are the most frequently observed type of hyperfunctioning pituitary adenoma, representing 20% to 30% of all clinically recognized pituitary tumors and half of all functioning tumors. Despite their frequency, prolactinoma is not associated with significant mortality. In women, hyperprolactinemia causes amenorrhea, galactorrhea, loss of libido, and infertility. In men, symptoms of hyperprolactinemia are relatively nonspecific and include decreased libido, impotence, premature ejaculation, erectile dysfunction, and oligospermia.

Posterior Pituitary

Unlike the anterior pituitary, the posterior pituitary gland (neurohypophysis) is not a secretory gland but rather a collection of axon terminals arising from the supraoptic and paraventricular nuclei of the hypothalamus. The posterior pituitary is principally responsible for the secretion of oxytocin and vasopressin, also known as antidiuretic hormone (ADH).

ADH is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus. After initial synthesis, the precursor hormone is transported down the pituitary stalk into the posterior lobe of the pituitary where ADH undergoes final maturation to active hormone and is stored in vesicles for future release. Plasma osmolarity is the primary stimulus for ADH secretion; however, other factors—such as left atrial distention, circulating blood volume, exercise, and certain emotional states—can also alter ADH release. ADH is considerably more sensitive to small changes in osmolarity than to similar changes in blood volume. A 1% to 2% increase in osmolarity is sufficient to increase ADH secretion. ADH binds to vasopressin 2 (V_2) receptors on the renal collecting ducts, which increases their permeability to water. This results in a significant increase in water reabsorption. Additionally, ADH increases blood pressure by increasing systemic vascular resistance through interaction with V_{1a} receptors on blood vessels. The effect of ADH on blood pressure is mild in the healthy state, but becomes much more important in hypovolemic shock. It is used therapeutically as a vasopressor (see Chapter 25).

Diabetes Insipidus and Syndrome of Inappropriate Antidiuretic Hormone

The absence of ADH secretion results in pituitary diabetes insipidus (DI), whereas oversecretion or "inappropriately high" levels of ADH (or ADH-like hormones) results in the syndrome of inappropriate ADH (SIADH). DI is most commonly associated with pituitary surgery and is most often transient. Whereas 18% of 881 patients undergoing transsphenoidal surgery experienced early

TABLE 35.2 Syndrome of Inappropriate Antidiuretic Hormone and Diabetes Insipidus

	SIADH	DI
Associated conditions	1. Neurologic disease (SAH, TBI) 2. Neoplasia (especially non–small cell lung cancer) 3. Nonneoplastic lung disease 4. Drugs (carbamazepine)	1. Pituitary surgery 2. TBI 3. SAH (especially secondary to anterior communicating artery aneurysm)
Presentation	Hyponatremia	Polyuria
Plasma volume (awake patients)	Euvolemic (or slightly hypervolemic)	Euvolemic (practically speaking) Hypovolemic if not allowed access to fluids or unconscious
Serum osmolarity	Hypotonic (< 275 mOsm/L)	Hypertonic (> 310 mOsm/L)
Serum Na^+	Falling (< 135 mEq/L)	Rising (> 145 mEq/L)
Urine volume	Low (but not normally absent)	Voluminous (4–18 L/day)
Urine osmolarity	Relatively high (> 100 mOsm/L)	Relatively low (< 200 mOsm/L)
Urinary Na^+	> 30 mEq/L	Normal (or variable)
Treatment	Fluid restriction If Na^+ < 120 mEq/L consider hypertonic saline to correct sodium (but no faster than 1 mEq/L/h) Intravenous urea Demeclocycline Lithium (rarely used)	Supportive DDAVP

DDAVP, Desmopressin (1-desamino-8-D-arginine vasopressin); *DI,* diabetes insipidus; *SAH,* subarachnoid hemorrhage; *SIADH,* syndrome of inappropriate diuretic hormone; *TBI,* traumatic brain injury.

postoperative DI, only 2% had persistent DI 1 week after surgery.[6] Its onset is heralded by the abrupt onset of polyuria, accompanied by thirst and polydipsia. SIADH is most commonly associated with central nervous system injury or trauma and certain cancers, especially lung cancer. Unlike DI, which typically presents with polyuria, SIADH typically presents with the signs and symptoms of hyponatremia. Characteristics of DI and SIADH are summarized in Table 35.2.

Like ADH, oxytocin is also synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and transported down the pituitary stalk into the posterior pituitary for release. The principal physiologic functions of oxytocin are to stimulate cervical dilation and uterine contraction during labor and to allow milk to be let down into the subareolar sinuses during lactation. Oxytocin is one of the few hormones involved in a positive feedback loop. For example, uterine contractions stimulate oxytocin release from the posterior pituitary, which, in turn, increases uterine contractions.

Parathyroid Physiology

The parathyroid glands generally consist of 4 pea-sized glands located posterior to the thyroid gland in the neck; however, many variations in location, and even number, of the glands exist. The glands possess a rich vascular supply via the inferior thyroid artery and consist mainly of chief cells primarily responsible for secreting parathyroid hormone (PTH) in response to hypocalcemia.

PTH plays a chief role in bone remodeling and Ca^{2+} homeostasis. PTH stimulates bone resorption and consequently release of Ca^{2+} into the bloodstream. In addition, PTH causes renal Ca^{2+} reabsorption in the distal tubule and phosphate excretion in the proximal tubule.[7,8] Note that while the majority of renal Ca^{2+} reabsorption occurs in the proximal tubule, reabsorption at this site is not under hormonal control.[7] PTH facilitates vitamin D conversion to its activated form such that it facilitates intestinal and renal absorption of Ca^{2+}. Activated vitamin D also acts on bone to increase resorption, thus leading to further Ca^{2+} release into the bloodstream. Primary control of the release of PTH comes via negative feedback inhibition once elevated vitamin D and plasma Ca^{2+} levels are detected by a parathyroid Ca^{2+}-sensing receptor.[7] Other mechanisms also affect the release of PTH: (1) increased phosphate levels lead to increases in production and release of PTH; (2) hypomagnesemia, like hypocalcemia, causes release of PTH; and (3) adrenergic agonists, such as epinephrine, increase PTH release through β-adrenergic receptors on parathyroid cells.[8] Indeed, this effect of adrenergic agonists is more pronounced at lower Ca^{2+} levels while it is transient and very mild in the setting of hypercalcemia.[8] In addition, β-adrenergic antagonists, such as propranolol, decrease PTH in normal patients but are less likely to cause secondary hyperparathyroidism.[8] Calcitonin counteracts the effects of PTH, as it inhibits bone resorption and increases excretion of Ca^{2+} through the kidneys.

The net result of the interactions of PTH, Ca^{2+}, vitamin D, and calcitonin is maintenance of normal plasma Ca^{2+} concentration, which, in turn, helps maintain normal cellular function, nerve transmission, membrane stability, bone integrity, coagulation, and intracellular signaling. Normal plasma Ca^{2+} levels are 8.5 to 10.5 mg/dL (2.1–2.6 mM). The majority of Ca^{2+} is stored in the bones and teeth. Only 1% is found in plasma in one of the following forms: ionized or unbound Ca^{2+} (50%; normally 1.0–1.2 mM), protein-bound Ca^{2+} (40%), and Ca^{2+} bound to citrate and phosphate (10%). The ionized, or unbound, Ca^{2+} is the form sensed by the Ca^{2+} receptors in the parathyroid gland. Protein-bound Ca^{2+} is

primarily bound to albumin with implications for changes in blood pH. Acidosis causes a decrease in protein binding, thus leading to higher ionized Ca^{2+}, whereas alkalosis results in higher protein binding, thus reducing the free Ca^{2+} fraction in blood.[9]

Primary Hyperparathyroidism

Primary hyperparathyroidism is excess PTH production and release most often due to parathyroid gland hyperplasia or tumor. The elevated PTH increases bone resorption and extracellular Ca^{2+}. It occurs most commonly in patients aged 30 to 50 years and is more common in women than men.[10] Clinically, patients exhibit increased intact PTH levels, hypercalcemia, hypercalciuria, hypophosphatemia, nephrolithiasis, osteoporosis, and neuromuscular changes, such as fatigue, weakness, and difficulties with cognition. Nausea, vomiting, constipation, and anorexia are common symptoms of hypercalcemia and patients may also complain of depression, confusion, and psychosis. Despite these manifestations, primary hyperparathyroidism is most often asymptomatic and detected incidentally on routine laboratory analysis as isolated hypercalcemia. Treatment of primary hyperparathyroidism centers on surgical excision of the parathyroid glands or tumor because there is increased risk of morbidity and cardiovascular mortality with long-standing hypercalcemia and untreated hyperparathyroidism.[8]

Multiple Endocrine Neoplasia

Hyperparathyroidism may also present in concert with one of the multiple endocrine neoplasia (MEN) familial syndromes. MEN1 is a rare, autosomal-dominant syndrome in which tumors develop in the parathyroid glands, pancreas, and anterior pituitary gland of affected individuals. Most patients with MEN1 present with hyperparathyroidism. MEN2 is also an autosomal-dominant syndrome but has incomplete penetrance and variable expression. MEN2A is associated with medullary thyroid carcinoma (develops in essentially 100% of these patients), pheochromocytoma (50% incidence), and hyperparathyroidism (10%–30% incidence). Hyperparathyroidism is not a component of MEN2B.[8,11,12] MEN4 is a rare familial endocrine syndrome associated with hyperparathyroidism and pituitary adenoma, which has only recently been described.[13]

Secondary Hyperparathyroidism

Secondary hyperparathyroidism is a complication most commonly due to chronic renal failure but can result from any disease that causes chronic hypocalcemia. Early in the course of renal failure, decreased vitamin D and ionized Ca^{2+} levels cause increased production and release of PTH. The kidneys are also unable to excrete the phosphate load, which contributes to low serum Ca^{2+}. Over time, the parathyroid glands become more resistant to the negative feedback mechanism of vitamin D and Ca^{2+} on PTH release, such that an increase in Ca^{2+} results in less efficient inhibition of PTH release. Hyperphosphatemia also further results in uremia-induced parathyroid gland hyperplasia, and PTH production and release. Goals of treatment of secondary hyperparathyroidism include maintaining Ca^{2+} and phosphate levels close to normal, reducing PTH secretion, and treating preexisting bone disease. These treatments focus on dietary phosphate restriction, maintaining daily Ca^{2+} intake greater than or equal to 1500 mg, administration of phosphate binder agents, and vitamin D replacement.

Anesthetic considerations for patients with hyperparathyroidism (whether primary or secondary) focus on the effects of hypercalcemia. Preoperative evaluation should focus on eliciting the cause of the hyperparathyroidism and the degree of hypercalcemia. If hypercalcemia is mild to moderate and patients are without severe cardiovascular or renal complications, most surgery can proceed without further evaluation. Patients can have polydipsia and polyuria, and may present for surgery to remove renal calculi, as nephrolithiasis is common. Commonly observed electrocardiographic (ECG) changes in hypercalcemia include shortened PR interval, shortened QT interval, and cardiac arrhythmias.[8] Patients with hyperparathyroidism can be hypertensive, and severe hypercalcemia can cause significant hypovolemia such that volume resuscitation is required. Severe hypercalcemia should be treated preoperatively. Aggressive volume resuscitation with subsequent diuretic administration can be used to acutely lower serum Ca^{2+} levels. Loop diuretics, such as furosemide, decrease the reabsorption of Ca^{2+} from the proximal tubules. For patients with renal dysfunction or failure, hemodialysis is immediately effective to reduce Ca^{2+} levels. Medications such as mithramycin and calcitonin can also be used but have significant side-effect profiles and should be administered with caution.

Induction and maintenance of anesthesia should proceed carefully but there are no specific requirements as to choice of agent. Most anesthetic concerns for parathyroid surgery focus on emergence and postoperative care. After surgery of the thyroid and parathyroid glands, recurrent laryngeal nerve damage, airway swelling, and hematoma formation are serious potential complications with severe implications. The recurrent laryngeal nerves innervate all muscles of the larynx with the exception of the cricothyroid, which is supplied by the external laryngeal nerve. If the recurrent laryngeal nerve is completely paralyzed, the vocal cord will be abducted, resulting in stridor and hoarseness.[8] If the recurrent laryngeal nerve is partially paralyzed, the vocal cord will be adducted. Thus, a partial lesion is more concerning for airway obstruction and a complete lesion more concerning for possible aspiration risk.[8] Hypocalcemia can occur quickly after parathyroid removal; therefore, patients should be monitored with serial Ca^{2+}, Mg^{2+}, phosphate, and PTH levels. Hypocalcemia can also present with rapid onset of weakness and airway compromise.

Hypoparathyroidism

Hypoparathyroidism is associated with other endocrine disorders and neoplasias or may result from surgical removal of the parathyroid glands. Hypocalcemia is the major acute result of inadvertent removal of the parathyroid glands. Hypocalcemic tetany can manifest as painful spasms of the facial muscles and extremities and laryngeal muscle spasm with upper airway obstruction. ECG changes associated with hypocalcemia include prolonged QT interval and possible heart block. Pseudohypoparathyroidism is not due to reduced PTH levels, but instead to reduced target sensitivity to PTH due to a receptor defect. Patients exhibit low plasma Ca^{2+} levels, high phosphate levels, and high PTH levels. Depending on the type of receptor defect, patients with pseudohypoparathyroidism demonstrate either complete, systemic resistance to PTH (and present with short stature and skeletal abnormalities) or simply manifest renal resistance to PTH.

There are few anesthetic considerations for the patient with a history of hypoparathyroidism presenting for surgery. The patient should have baseline Ca^{2+}, phosphate, and Mg^{2+} levels and an ECG to determine QT interval. Hypocalcemia can be treated with

TABLE 35.3 Thyroid Cell Types and Functions

Cell Type	Function
Follicular cells	Thyroid hormone (T_3 and T_4) synthesis
Endothelial cells	Line capillaries Provide blood supply to follicles
Parafollicular cells (also called C cells)	Produce and secrete calcitonin
Fibroblasts, lymphocytes, and adipose tissue	Structural support for the thyroid

T_3, Triiodothyronine; *T_4*, thyroxine.

calcium gluconate or calcium chloride in order to maintain serum Ca^{2+} levels.

Thyroid Physiology

The thyroid gland is an acinar gland positioned in the neck, just anterior to the trachea with a rich vascular supply from the superior and inferior thyroid arteries. Weighing up to 25 g, the thyroid gland has a right and left lobe connected by the thyroid isthmus. Table 35.3 reviews the various cell types found within the thyroid gland and their corresponding functions. Other structures close to the thyroid gland include the trachea and esophagus as well as the recurrent laryngeal nerves and superior laryngeal nerve.

Thyrotropin-releasing hormone (TRH) is produced in the hypothalamus and released in response to decreased free circulating thyroid hormone. TRH binds to a G protein–coupled receptor in the anterior pituitary, causing an increase in intracellular Ca^{2+}. Increased intracellular Ca^{2+} then causes release of TSH into the bloodstream, which stimulates the thyroid gland to increase the synthesis and release of T_4 and T_3 into the systemic circulation. T_4 and T_3 inhibit further secretion of TSH by inhibiting secretion of TRH. Thus, thyroid hormone production and secretion are regulated via negative feedback by the hypothalamic-pituitary-adrenal (HPA) axis. Other mediators that inhibit TSH release include dopamine, somatostatin, and glucocorticoids.

Iodide is required for thyroid hormone synthesis. The body readily absorbs the necessary iodine from dietary sources, which is converted to iodide before being absorbed by the thyroid gland.[14] In the follicle of the thyroid, thyroglobulin, a glycoprotein possessing several tyrosine residues, is iodinated, yielding mono-iodinated tyrosine (MIT) and di-iodinated tyrosine (DIT) residues. MIT and DIT ultimately are synthesized to T_3 and T_4 via thyroid peroxidase. The thyroid gland releases more T_4 than T_3, and T_4 is converted to T_3, primarily in the liver, as a result of the deiodination of T_4. T_4 is less active than T_3 in that it has decreased affinity for the thyroid hormone receptor, but both T_3 and T_4 are stored in the thyroid gland for a 2- to 3-month supply. Thyroid hormones circulate in the bloodstream bound to proteins, mainly to thyroid-binding globulin but also to albumin. A small amount of each hormone circulates in an unbound, free form ready to enter the cell and bind to the thyroid hormone receptor. T_4 binds more avidly to plasma proteins and thus has a longer half-life of 7 days compared to T_3, which has a half-life of only 1 day. Thyroid hormone metabolism involves the sequential removal of iodine. Thus, T_4, a relatively inactive thyroid hormone, is deiodinated to T_3, the active thyroid hormone. Removal of an additional iodine molecule to T_2 yields a completely inactive product. In addition, thyroid hormones can be conjugated in the liver to increase solubility and allow for biliary excretion.

Thyroid hormone receptors are found in virtually all tissues. Thyroid hormones play a chief role in cellular energy metabolism and are involved in the following[15]:

- Transcription of cell membrane sodium-potassium adenosine triphosphatase (ATPase), leading to increase in oxygen consumption
- Transcription of uncoupling protein (UCP)
- Fatty acid oxidation and heat generation with production of ATP
- Protein synthesis and breakdown
- Epinephrine-induced glycogenolysis and gluconeogenesis with effects on insulin-induced glycogen synthesis and glucose utilization
- Cholesterol synthesis and lipoprotein receptor regulation

Thyroid hormone plays a major role in normal growth and development. Specific systems to note include the skeletal system, in which thyroid hormone is essential for bone growth, and the cardiovascular system, in which thyroid hormone has inotropic and chronotropic effects. These effects are evidenced by increased cardiac output and effects on blood volume and systemic vascular resistance. Thyroid hormone differentiates adipose tissue and regulates triglyceride and cholesterol metabolism in the liver. Thyroid hormone also regulates production of pituitary hormones and expression of genes involved in central nervous system myelination, cell differentiation, migration, and signaling.

Thyroid disease and dysfunction occurs as a result of alterations in thyroid hormone levels, impaired metabolism of thyroid hormones, or resistance to effects of thyroid hormones. The thyroid gland can undergo changes that contribute to altered thyroid function. Thyroid hyperplasia or enlargement occurs in Graves disease and thyroid destruction occurs in Hashimoto thyroiditis. Table 35.4 differentiates hypothyroidism from hyperthyroidism based on laboratory values and clinical manifestations.

Hypothyroidism

Hypothyroidism is divided into primary and secondary hypothyroidism. Primary hypothyroidism refers to disease at the level of the thyroid gland itself. In adults, this is most often owing to autoimmune disease causing destruction of thyroid tissue. Surgical excision or radioactive iodine therapy are iatrogenic causes of hypothyroidism and require thyroid hormone replacement. Secondary hypothyroidism implies dysfunction outside of the thyroid gland, most commonly in the hypothalamus or pituitary gland, resulting in decreased TSH secretion from the pituitary gland and, thus, decreased thyroid hormone release from the thyroid gland. Medications such as lithium, amiodarone, iron, and cholestyramine can be iatrogenic causes of hypothyroidism.[16] Symptoms of hypothyroidism are vague and nonspecific, including fatigue, lethargy, painful joints and muscles, cold intolerance, constipation, change in voice quality (rough or gravelly), bradycardia, low voltage of ECG, and heart failure symptoms.

Myxedema coma refers to severe hypothyroidism characterized by decreased mental status and coma, hypothermia, bradycardia, hyponatremia, heart failure, and respiratory failure. Myxedema coma is rare, and most commonly presents in the postoperative period after a trigger such as infection, exposure to cold temperatures, and excessive sedation and analgesic medications.[16] A patient

TABLE 35.4 Disorders of Thyroid Function

	Hypothyroidism	Hyperthyroidism
Laboratory values	Low free T_4 Low or normal T_3 High TSH	High T_4 High T_3 Low TSH
Clinical manifestations	Fatigue, lethargy	Hyperactivity, irritability
	Impaired memory, depression	Anxiety, insomnia
	Cold intolerance	Heat intolerance
	Bradycardia, ventricular arrhythmias	Tachycardia, palpitations, arrhythmias
	Prolonged QT interval, ventricular arrhythmias	Arrhythmias (often atrial fibrillation)
	Decreased blood volume	Increased blood volume
	Decreased stroke volume	Increased stroke volume
	Decreased cardiac output	Increased cardiac output
	Narrowed pulse pressure	Widened pulse pressure
	Muscle cramps	Proximal muscle weakness
	Delayed reflexes	Hyperreflexia, fine tremor
	Weight gain	Weight loss
	Constipation	Diarrhea
	Brittle nails, dry skin	Warm, moist skin; excessive sweating
	Abnormal menses	Decreased or absent menses
	Dry hair, hair loss	Fine hair, hair loss
	Periorbital edema	Exophthalmos

TSH, Thyroid-stimulating hormone.

with myxedema coma should be treated in the intensive care unit with supportive therapy and urgent administration of intravenous levothyroxine and glucocorticoids for likely concomitant adrenal insufficiency, as well as aggressive volume replacement.[16–18]

Hyperthyroidism

Hyperthyroidism refers to excessive thyroid gland function such that excess thyroid hormone is produced and released. Patients most commonly experience increased metabolism and autonomic nervous system disturbances. For adults, the most common cause of hyperthyroidism is Graves disease or diffuse toxic goiter, an autoimmune disease in which thyroid hormone is produced in an autonomous fashion owing to TSH receptor stimulation by antibodies. Patients with Graves disease often have thyroid eye disease, which is characterized by exophthalmos (protrusion of the eyeballs) owing to lymphocyte and fibroblast infiltration of the extraocular tissues and eye muscles. Other conditions leading to hyperthyroidism include toxic nodular goiter, toxic adenomatous disease of the thyroid, administration of excessive thyroid hormone, excess iodine intake, thyroiditis, follicular carcinoma, and TSH-producing tumor of the pituitary gland. Clinical features of hyperthyroidism or thyrotoxicosis include weight loss, tremor, heat intolerance, sweating, diarrhea, nausea, vomiting, anxiety, irritability, insomnia, and depression. Cardiovascular manifestations of hyperthyroidism include tachycardia, cardiac arrhythmias (commonly atrial fibrillation), and increases in blood volume, stroke volume, and cardiac output, which may ultimately lead to severe systolic ventricular dysfunction without appropriate management.[19]

Patients with hyperthyroidism are typically treated with antithyroid drugs to achieve a euthyroid state. The antithyroid drugs propylthiouracil (PTU) and methimazole both work by inhibiting thyroid peroxidase. At high doses, PTU also decreases peripheral T_4 conversion to T_3.[20] While PTU has traditionally been the first-line antithyroid drug, a US Food and Drug Administration (FDA) warning issued in 2010 associated PTU with potential severe liver dysfunction.[21] Thus, methimazole is now the most common antithyroid drug used to treat patients with hyperthyroidism. PTU is generally reserved for treatment of pregnant patients in the first trimester because methimazole has been associated with birth defects.[20]

Thyroid storm presenting in the perioperative period can mimic malignant hyperthermia (MH). Thus, anesthesiologists need to be aware of and vigilant for this concerning complication of undiagnosed or undertreated hyperthyroidism. Initiation of antithyroid therapy (i.e., with methimazole) and preoperative β blockade has significantly decreased the incidence of thyroid storm, though has not completely eliminated it. Symptoms are nonspecific and similar to those of MH: hyperpyrexia (up to 41°C), tachycardia, weakness, and delirium. Treatment requires intensive care and is mainly supportive. Beta blockers such as propranolol help reduce the adrenergic surge whereas antithyroid medications and iodine aim to reduce thyroid gland output.[22–24] Useful cooling measures include administration of antipyretics, cool fluids, and application of cooling blankets. As these patients are typically intubated and mechanically ventilated, increased carbon dioxide production during thyroid storm may be counteracted with increasing the patient's minute ventilation.[22]

Sick euthyroid syndrome affects patients with chronic nonthyroid medical conditions and diseases as patients appear euthyroid clinically but have evidence of thyroid dysfunction on laboratory testing. Usually, patients have decreased T_3 and T_4, decreased T_4 binding to thyroid-binding globulin, but normal TSH and otherwise normal imaging of the thyroid gland itself.[15] Factors known to precipitate sick euthyroid syndrome include stress, starvation, malnutrition, surgical trauma, myocardial infarction, chronic renal failure, diabetic ketoacidosis, cirrhosis, sepsis, and hyperthermia. Medications such as propranolol and amiodarone can also induce sick euthyroid syndrome, as they impair conversion of T_4 to T_3.[16]

Thyroiditis

Thyroiditis, or inflammation of the thyroid gland, can be acute or chronic and can lead to abnormalities of thyroid function. Acute thyroiditis is rare and infectious. Patients present with a painful thyroid gland, chills, and fever and appear hyperthyroid. Chronic thyroiditis (otherwise known as Hashimoto thyroiditis, chronic lymphocytic thyroiditis, or autoimmune thyroiditis) is an autoimmune condition of the thyroid gland in which there is lymphocytic infiltration of the thyroid gland and circulating autoimmune antibodies. The antibodies prevent iodide uptake and thyroid hormone synthesis. Autoimmune thyroiditis is the most common cause of adult hypothyroidism.[16] Early in the course of the disease, patients can have variable levels of T_3, T_4, and TSH, but usually

have antibodies to thyroid peroxidase and thyroglobulin. Once chronic hypothyroidism develops, patients manifest low T_3 and T_4 and high TSH levels, although the increased TSH usually dissipates over time.

Although hypothyroidism does not reduce the minimum alveolar concentration (MAC) for volatile anesthetics, hypothyroid patients presenting for surgery can be more sensitive to the effects of anesthetic agents and can have a prolonged recovery from anesthesia. Patients with mild to moderate hypothyroidism are at low risk for complications when undergoing surgery and anesthesia.[10,25] If possible, patients should be rendered euthyroid before surgery and patients should receive their thyroid supplementation medication on the day of surgery. It is important to maintain body temperature in hypothyroid patients because hypothermia puts patients at risk for such complications as delayed recovery from anesthesia, impaired wound healing, and coagulopathy.

Major anesthetic considerations for patients with history of hyperthyroidism include determining their current thyroid status and obtaining a medication history. It is important to review the most recent thyroid function tests and inquire about symptoms of hyperthyroidism, such as tachycardia, atrial fibrillation, diarrhea, and weight loss. In patients presenting for thyroid surgery, it is vital to consider the size of the thyroid gland and elicit from patients whether they have experienced compressive symptoms due to an enlarged gland or goiter, such as dysphagia, or respiratory symptoms, such as dyspnea, stridor, or respiratory distress. Imaging of the neck may be helpful to reveal tracheal compression or deviation as well as retrosternal extension of the thyroid gland.[22] Patients with severe tracheal compression may require awake, fiberoptic intubation with maintenance of spontaneous ventilation. Thyroid surgery for patients with retrosternal extension may require sternal splitting and partial sternotomy. In patients having emergency surgery in which there is concern for possible untreated or inadequately treated hyperthyroidism, a short-acting β blocker, such as esmolol, can be used to control tachycardia. During surgery in the neck, manipulation of the carotid sinus and bodies can induce hemodynamic instability that may not be well tolerated by patients who have coexistent cardiovascular disease. Other anesthetic considerations for the intraoperative and postoperative period, especially with regard to vocal cord dysfunction, are reviewed in the earlier section on anesthetic considerations, in the parathyroid disease discussion.

Postoperative complications related to thyroid surgery are critical for every anesthesiologist to be vigilant of and understand how to treat quickly. Airway obstruction owing to hemorrhage in the neck, recurrent laryngeal nerve injury, and tracheal compression must be treated immediately. Hemorrhage or hematoma is the most common cause of airway obstruction within the first 24 hours after surgery. It is best treated by opening the neck, allowing drainage of the blood and clot, with consideration given to early endotracheal reintubation. Stitch and staple removers should be present at the bedside of every patient after thyroid surgery.[22] After release of the airway compression, the neck wound can be explored and the hemorrhage treated surgically. The most common cause of airway obstruction occurring more than 24 hours after surgery is hypocalcemia, which occurs secondary to inadvertent parathyroid injury or removal. Hypocalcemia is treated with intravenous calcium, as described earlier.

Adrenal Gland Physiology

The adrenal glands are small (3–5 cm in length) and are located just superior to each kidney. There are 2 parts to each adrenal gland: the outer adrenal cortex derives from mesodermal tissue and the inner medulla derives from neural crest cells. The cortex makes up 90% of the adrenal mass and produces the steroid hormones glucocorticoids, mineralocorticoids, and androgens (cortisol, aldosterone, and dehydroepiandrosterone) as a result of HPA stimulation. The medulla makes up the remaining 10% of adrenal mass and synthesizes and releases the catecholamines epinephrine and norepinephrine as a result of sympathetic stimulation. Blood supply of the adrenal glands comes from branches of the suprarenal arteries. The venous drainage includes a renal vein for each adrenal gland. Steroid hormones are all synthesized from the same initial first step, the conversion of cholesterol to pregnenolone by cytochrome P450 enzymes.

Adrenal Cortex Physiology

Cortisol is released from the adrenal gland in a pulsatile fashion—following a circadian rhythm sensitive to light, sleep, stress, and disease—owing to stimulation by ACTH from the anterior pituitary gland. Cortisol is mainly bound to a carrier protein called *transcortin*; some cortisol is also bound to albumin and a minimal amount of cortisol circulates unbound, which is the biologically active portion. Glucocorticoids such as cortisol have a multitude of actions, such as protein breakdown and gluconeogenesis, fatty acid mobilization, and prevention of muscle protein synthesis (Table 35.5). The main effect of glucocorticoids is to increase serum glucose concentration. At high circulating levels, glucocorticoids cause catabolism and breakdown of lean body mass, including bone and muscle. They also affect the immune response by exerting an antiinflammatory effect.

Aldosterone is synthesized and released from the adrenal cortex zona glomerulosa, regulated not by the HPA axis but instead by the renin-angiotensin-aldosterone system, which is responsible for maintaining salt and water homeostasis. When intravascular volume and renal perfusion are decreased, renin is released and, through the angiotensin-converting enzyme (ACE), angiotensin II is released, which binds to a G protein–coupled receptor and stimulates aldosterone release. Aldosterone increases Na^+ and water absorption through the kidneys and K^+ is excreted. The other main stimulant for aldosterone release is K^+. Aldosterone helps maintain K^+ homeostasis and is responsible for preventing hyperkalemia by increasing K^+ excretion via the kidneys, gastrointestinal tract, diaphoresis, and salivation.

Cushing Syndrome

Glucocorticoid excess (Cushing syndrome) can occur for a number of reasons, including overproduction of cortisol by an adrenal mass, excessive stimulation of a normal adrenal gland to produce cortisol due to excessive ACTH production by the pituitary gland, or iatrogenic administration of glucocorticoids. Cushing syndrome manifests initially by a large increase in weight, usually central in the abdominal region. Patients also can appear to have moon facies and a buffalo hump of adipose tissue at the posterior cervical region. Other characteristics of Cushing syndrome include hypertension, glucose intolerance, decreased or absent menses in women, decreased libido, spontaneous ecchymoses, muscle wasting and weakness, thin friable skin, and osteoporosis due to bone resorption.

Anesthetic considerations for patients with Cushing syndrome revolve around managing the effects of glucocorticoid excess during the perioperative period. The resultant obesity often portends increased risk of difficult airway management and problems with positioning. Osteoporosis also presents risk during positioning of

TABLE 35.5 Glucocorticoid Effects

Metabolism	Hemodynamic	Immune Function	Central Nervous System
Muscle protein breakdown	Maintains vascular integrity	Increases antiinflammatory cytokines	Regulates perception and emotion
Increases nitrogen excretion	Maintains vascular reactivity	Decreases proinflammatory cytokines	Decreases corticotropin-releasing hormone
Increases gluconeogenesis	Maintains responsiveness to catecholamines	Decreases inflammation	Decreases adrenocorticotropic hormone release
Increases plasma glucose	Maintains fluid volume	Inhibits prostaglandin and leukotriene production	
Increases hepatic glycogen synthesis		Inhibits bradykinin and serotonin inflammatory effects	
Decreases glucose utilization		Decreases eosinophil, basophil, and lymphocyte counts	
Decreases amino acid utilization		Impairs cell-mediated immunity	
Increases fat mobilization		Increases neutrophil, platelet, and red blood cell counts	
Redistributes fat			

inadvertent bony fractures. Patients can have preexisting muscle weakness and be sensitive to the effects of neuromuscular blocking agents. Patients with Cushing syndrome tend to be hypervolemic with hypokalemic metabolic alkalosis. Many patients are on chronic diuretic therapy with potassium replacement.

Glucocorticoid Deficiency

Glucocorticoid deficiency (Addison disease) is less common and results from dysfunction of the adrenal gland (primary deficiency) or from lack of ACTH stimulation of adrenal glucocorticoid production (secondary deficiency). Clinical manifestations include weakness, fatigue, hypoglycemia, hypotension, and weight loss. Exogenous administration of glucocorticoids in the treatment of many chronic medical conditions results in downregulation of corticotropin-releasing hormone and ACTH. Thus, sudden withdrawal of exogenous glucocorticoids during a stressful period or critical illness can precipitate an Addisonian crisis (acute adrenal failure), which is a medical emergency. Patients can experience circulatory collapse, fever, hypoglycemia, and mental obtundation as a result of the acute decrease in cortisol and the inability to secrete cortisol in response to stress.

Anesthetic considerations for patients with glucocorticoid deficiency (whether chronic or acute) mainly focus on steroid replacement therapy during the perioperative period—a time of acute physiologic stress. Patients given the equivalent dose of prednisone 20 mg for 5 days may experience suppression of their HPA axis and their adrenal glands might not be able to respond to physiologic stress by production of cortisol.[26,27] Exogenous glucocorticoid therapy for a 1-month period places patients at risk for HPA axis suppression for 1 year after the treatment is discontinued.[26,27] Thus "stress-dose" steroids should be considered for these patients during the perioperative period. Historically, stress-dose steroid therapy consisted of hydrocortisone 100 mg every 8 hours. However, this dose can precipitate hyperglycemia and decreased wound healing in some patients. Thus, a lower-dose regimen might be considered: hydrocortisone 25 mg at induction of anesthesia, followed by a total of 100 mg of hydrocortisone over the next 24 hours.[16] This lower-dose regimen decreases the risks of excessive steroid replacement and allows for plasma cortisol levels equal to that of healthy patients undergoing elective surgery. The initial bolus dose of hydrocortisone can be increased based on the urgency and complexity of the surgical procedure.[28]

Hyperaldosteronism

Aldosterone excess can take several forms based on the pathophysiology. Primary hyperaldosteronism, or Conn syndrome, is due to adrenal oversecretion of aldosterone by benign adrenal tumors. Patients exhibit hypertension owing to Na^+ and water retention, and exhibit hypokalemia owing to K^+ excretion, muscle weakness, and metabolic alkalosis. Secondary hyperaldosteronism usually results from another pathologic state that reduces the effective circulating blood volume, such as cirrhosis with ascites or congestive heart failure. This decrease in the effective circulating volume causes continuous stimulation of the renin-angiotensin-aldosterone system with overproduction of aldosterone.[29] Tertiary hyperaldosteronism, or Bartter syndrome, is a renal disorder that leads to increased renin release in order to compensate for excessive Na^+ loss. The excess renin causes excess production of angiotensin II and aldosterone. Anesthetic considerations include correction of fluid and electrolyte abnormalities preoperatively. Potassium-sparing diuretics, such as spironolactone, are often prescribed to help manage the hypokalemia and hypervolemia and to control hypertension.

Hypoaldosteronism

Aldosterone deficiency also can take several forms. Primary hypoaldosteronism, or Addison disease, occurs as a result of destruction of the adrenal gland due to infection, injury, autoimmune problems, or genetic disorders. In Addison disease, renin activity is increased, which helps differentiate primary hypoaldosteronism from the other forms of deficiency. Clinical manifestations include hyponatremia, hypovolemia, hypotension, hyperkalemia, and metabolic acidosis. Secondary hypoaldosteronism results from

decreased renin stimulation, usually from renal insufficiency, but the adrenal glands function normally. Anesthetic considerations include preoperative mineralocorticoid therapy, such as fludrocortisone, which helps correct the hypovolemia and hyperkalemia.

Adrenal Medulla Physiology

The adrenal medulla is the inner part of the adrenal gland and is highly vascular, made up of 2 types of chromaffin cells: those that produce epinephrine and those that produce norepinephrine. Catecholamines such as epinephrine and norepinephrine are made from the amino acid tyrosine through multiple enzymatic conversions:

Tyrosine ⇒ L-DOPA (L-3,4-dihydroxyphenylalanine) ⇒ dopamine ⇒ norepinephrine ⇒ epinephrine

The synthesis of catecholamines can be regulated by changes in the first enzymatic reaction of the pathway (tyrosine hydroxylase) such that the enzyme is inhibited acutely by increase in catecholamine production and chronically by an increase in tyrosine hydroxylase synthesis. Catecholamines are released in direct response to sympathetic nervous stimulation of the adrenal medulla. Acetylcholine released from the preganglionic sympathetic nerve terminals binds to nicotinic receptors in the chromaffin cells of the adrenal medulla. Depolarization of these cells leads to activation of Ca^{2+} channels. The influx of Ca^{2+} causes the vesicles containing the catecholamines to release their contents, including the catecholamines and other molecules, such as chromogranins, ATP, and various peptides. Catecholamines have a very short half-life, on the order of just 10 seconds up to about 2 minutes, and undergo uptake at extraneuronal sites and degradation by catechol-*O*-methyltransferase (COMT) or monoamine oxidase (MAO). The degradation by COMT and MAO of norepinephrine and epinephrine, mostly in the liver, produces the metabolite vanillylmandelic acid (VMA), which is excreted in the urine and can be measured as an index of cumulative catecholamine secretion.

The physiologic effects of the catecholamines epinephrine and norepinephrine are mediated by G protein–coupled receptors found in many tissues (Table 35.6, and see Chapter 13). α-Adrenoreceptor activation causes activation of phospholipase C, which then activates protein kinase C via diacylglycerol. This causes an increase in intracellular Ca^{2+} and corresponding increase in smooth muscle contraction. β-Adrenoceptor stimulation leads to an increase in cyclic adenosine monophosphate (cAMP) and, depending on which subtype of β receptor is stimulated, effects vary from increasing myocardial contractility, vasodilation, bronchial smooth muscle relaxation, and lipolysis. Sympathetic stimulation leads to secretion of catecholamines, which play a chief role in the stress response to perceived or real physical or psychological injury, including hemorrhage, severe hypoglycemia, trauma, surgical trauma, and fear. The basic physiologic effects attributed to catecholamine secretion are mental arousal and alertness, pupillary dilation, diaphoresis, bronchial smooth muscle dilation, tachycardia, reduced activity of gastrointestinal tract, sphincter constriction, and uterine muscle relaxation. Catecholamines activate catabolism for the expenditure of energy in order to provide substrate for the stress response. As such, glucose is mobilized from the liver through glycogen breakdown and fat breakdown.

TABLE 35.6 Physiologic Effects of Adrenergic Stimulation

α-Adrenergic Receptor Stimulation	β-Adrenergic Receptor Stimulation
Vasoconstriction	Vasodilation
Intestinal relaxation	Intestinal relaxation
Bladder and intestinal sphincter contraction	Bladder wall relaxation
Pilomotor contraction	
Bronchoconstriction	Bronchodilation
Uterine smooth muscle contraction	Uterine relaxation
Increased cardiac contractility	Increased chronotropy, increased dromotropy, increased contractility
Hepatic glucose production	Glycogenolysis, lipolysis
Iris dilation	

Pheochromocytoma

Pheochromocytoma represents the most significant disease associated with adrenal medullary tissue. This tumor causes overproduction of catecholamines. As a result, patients with pheochromocytoma present with severe (sustained or paroxysmal) hypertension, headaches, sweating, and palpitations. Most pheochromocytomas are benign and located unilaterally in an adrenal gland, but approximately 10% can be malignant and 10% can be bilateral/extra-adrenal in origin.[30] Unrecognized pheochromocytoma can present intraoperatively due to sympathetic stimulation or surgical stimulation in the area of the undiagnosed tumor. Under general anesthesia, the signs of undiagnosed pheochromocytoma include tachycardia and hypertension.

Preoperative evaluation and assessment should concentrate on treatment with α-adrenergic blockers and volume replacement. Arterial blood pressure, orthostatic blood pressure measurements, heart rate, and ECG are critical and might warrant further cardiovascular evaluation, including echocardiography. At the time of diagnosis, patients with pheochromocytoma are usually hypovolemic with a normal to elevated hematocrit. Preoperative α-adrenergic blocker therapy with phenoxybenzamine or phentolamine helps correct the hypertension and vasoconstriction as well as reduce the intravascular volume deficit. A drop in hematocrit usually signals adequate α blockade. Beta-blocker therapy is typically started after initiation of α-adrenergic blocker therapy to help control heart rate and blood pressure.[31] There is a theoretical risk of unopposed α-adrenoreceptor agonism with massive vasoconstriction if β-blocker therapy is initiated prior to α-adrenoreceptor antagonists.[16] Some studies have questioned the primacy of α-adrenergic blocker therapy in favor of treatment with Ca^{2+} channel blockers with favorable results.

Management of pheochromocytoma resection mandates intraarterial blood pressure monitoring for immediate evaluation of rapid changes in blood pressure, which may aid in titration of any necessary vasopressor or vasodilator therapy, and frequent laboratory analysis to assess acid–base status, hematocrit, and electrolyte values. Central venous access may be helpful to allow infusion of vasoactive substances and large volumes of fluid and blood products if required. Induction should proceed thoughtfully, with strict blood pressure control. A deep plane of anesthesia should be established prior to laryngoscopy and endotracheal intubation in order to prevent

sympathetic activation. Intraoperative hypertension can be treated with phentolamine, nitroprusside, or nicardipine. Phentolamine blocks α-adrenergic receptors, is relatively short acting, and prevents effects of catecholamines. Nitroprusside is easily titratable, with rapid onset and offset, but can result in cyanide accumulation with high doses. Potential anesthetic drugs to avoid include those that stimulate sympathetic nervous system activity or block parasympathetic activity, such as ketamine, ephedrine, and pancuronium. After the tumor is resected, hypotension can complicate the intraoperative and postoperative course owing to a decrease in circulating catecholamines and residual antihypertensive therapies. However, in some patients, hypertension continues to be problematic and requires treatment.[32] If present, the resultant hypotension is usually responsive to fluid resuscitation and adrenergic agonist therapy if necessary. Persistent hypertension is treated with antihypertensive medications as well as serial surveillance for recurrence of the pheochromocytoma.[32]

Pancreas Physiology

The pancreas plays a key role in digestion, metabolism, utilization, and storage of energy substrate with exocrine and endocrine capacities. The pancreas is located in the retroperitoneal space, near the duodenum. Most of the mass of the pancreas is made up of exocrine cells, which secrete an alkaline digestive fluid into the pancreatic duct and duodenum. Comprising 1% to 2% of the mass of the pancreas, within the pancreatic lobules, are small clusters of endocrine cells—the islets of Langerhans—which include α, β, and δ cells. The β cells make up about 75% of the total mass of the islets and secrete insulin. Of endocrine cells, 18% to 20% are α cells, which secrete glucagon, and the remaining 5% are δ cells, which secrete somatostatin. The arterial blood supply to the pancreas consists of branches from the splenic artery and the superior and inferior pancreaticoduodenal arteries. The islets receive 10% to 15% of the pancreatic blood flow; thus, their rich vascularization allows easy access for the hormones to be secreted by the islet cells into the bloodstream. Venous drainage leads directly to the portal vein of the liver; therefore, the pancreatic hormones undergo first-pass metabolism in the liver before being released into the systemic circulation.

Insulin synthesis begins with an inactive protein, pre-proinsulin, which undergoes cleavage to proinsulin and then to insulin by cleavage of the C-peptide linkage structure. Insulin is thus made up of 2 amino acid peptides, α and β linked by a disulfide bond. The insulin and C peptide make up secretory granules that are stored in β cells and released in response to increased blood glucose. Glucose enters β cells via the GLUT-2 receptor, where it is used to generate ATP. ATP causes closure of the ATP-sensitive K^+ channels, membrane depolarization, and Ca^+ influx, which then triggers exocytosis of insulin secretory granules into the circulation. Overall, insulin has an anabolic effect on target organs and stimulates the synthesis of carbohydrates, fats, and proteins (Table 35.7). Glucose transporters play a key role in the utilization of glucose mediated by insulin. There are several glucose transporters with variable tissue distributions and functions.[33] Table 35.8 reviews the specific glucose transporters along with their primary locations and functions.

Glucagon is an amino acid polypeptide hormone secreted by the α cells of the islets of Langerhans and plays a vital role in glucose homeostasis by antagonizing the effects of insulin. Glucagon release is stimulated by hypoglycemia, high amino acid levels after amino acid–rich food intake, epinephrine, and vagal stimulation and is inhibited by increased blood glucose levels and somatostatin. The primary target tissues for the effects of glucagon are the liver

TABLE 35.7 Effects of Insulin

	Glucose Transport Into Fat and Muscle	Glycogen Breakdown in Muscle and Liver
Carbohydrate metabolism	Glycolysis in fat and muscle Glycogen synthesis in fat, muscle, and liver	Glycogenolysis and gluconeogenesis in liver
Lipid metabolism	Fatty acid synthesis Uptake of triglycerides from circulation into fat and muscle Cholesterol synthesis in liver	Lipolysis in fat (causes decreased plasma fatty acids) Fatty acid oxidation in muscle and liver Ketogenesis
Protein metabolism	Amino acid transport into tissues Protein synthesis in muscle, fat, and liver	Protein breakdown in muscle Urea formation

TABLE 35.8 Glucose Transporters

Transporter	Location	Function
GLUT-1	Widely distributed; highest concentration in red blood cells and endothelial cells of the brain	Glucose uptake by skeletal muscle and fat under basal conditions; allows glucose to cross blood–brain barrier
GLUT-2	Pancreatic β cells, liver, small intestine, kidney	Ensures that glucose uptake by β cells and hepatocytes occurs only when serum glucose concentration is elevated
GLUT-3	Neurons, placenta	Glucose uptake under basal conditions; allows glucose to cross blood–brain barrier
GLUT-4	Skeletal and cardiac muscle, adipose tissue	Mediates insulin-stimulated glucose transport into striated muscle cells and adipocytes
GLUT-5	Spermatozoa, small intestine	Transports fructose primarily; very low affinity for glucose

and adipose tissues. The main effect of glucagon is to increase serum glucose concentration by causing hepatic gluconeogenesis and glycogen breakdown. The effects of glucagon on adipose tissue primarily occur during periods of stress and food deprivation.

Diabetes Mellitus

DM results from impaired secretion of insulin from the pancreas and/or reduced tissue sensitivity. Type 1 DM has been referred to as insulin-dependent DM owing to the destruction of the β cells in the pancreas, thus necessitating administration of exogenous insulin to avoid diabetic ketoacidosis. It is associated with onset in younger-age patients and makes up 2% to 5% of cases of DM. Type 2 DM is more frequent and results from loss of normal regulation of insulin secretion from the pancreas and insulin sensitivity. It is associated with adult onset, obesity, mild levels of hyperglycemia, and insulin resistance. The mean normal blood glucose is about 72 mg/dL (4 mM). The diagnosis of DM is made when fasting serum glucose is greater than 126 mg/dL (7 mM), or random glucose levels are greater than 200 mg/dL (11 mM) with associated symptoms of DM such as polyuria, polydipsia, and polyphagia. With type 1 DM, there is impaired insulin release such that cells cannot take up glucose as energy substrate; thus, serum glucose levels are elevated. Increased serum glucose concentrations cause elevated plasma osmolarity and glycosuria, accompanied by water and Na^+ loss in the urine (polyuria). Patients become very dehydrated; increased thirst (polydipsia) as well as hunger (polyphagia) are compensatory mechanisms for the "starving" cells that are unable to utilize glucose.

Diabetic ketoacidosis (DKA) can occur perioperatively; it is an acute event that anesthesiologists must understand and for which they must be vigilant. DKA is characterized by elevated blood glucose, ketone body formation (both acetoacetate and β-hydroxybutyrate), and anion gap metabolic acidosis that result from decreased availability of insulin and elevated levels of the counter-regulatory hormones glucagon, catecholamines, cortisol, and growth hormone. Lactic acidosis can coexist with the anion gap metabolic acidosis with DKA. DKA can be precipitated by infection, stress, surgery, inadequate doses of exogenous insulin, and untreated DM. Patients manifest tachypnea, severe abdominal pain, nausea, vomiting, and altered mental status. Treatment of DKA involves aggressive fluid volume resuscitation, insulin to treat the hyperglycemia, and replacement of K^+ deficit. Patients with DKA require intensive care and frequent laboratory analysis for glucose, K^+, serum ketones, and acid–base status.

There are 3 main defects involved in type 2 DM. First, there is inadequate response of the β cells of the pancreas to glucose loads. That is, at basal conditions, patients produce and secrete insulin; however, with serum glucose elevation (such as with meals), there is much less secretion of insulin than in normal patients. Second, type 2 DM patients also have a decreased response of peripheral tissues to the actions of insulin. Third, patients with type 2 DM have increased hepatic glucose production.[34] These impairments contribute to an overall higher fasting glucose level. Approximately 80% of patients with type 2 DM are considered obese and have a sedentary lifestyle, both of which are well-known risk factors.[35,36]

Anesthetic considerations for patients with DM include a thorough preoperative evaluation to determine whether the patient requires insulin and to determine end-organ damage. Hemoglobin A_{1C} levels are helpful in preoperative evaluation for identifying patients at risk for perioperative hyperglycemia and further complications. Hemoglobin A_{1C} levels less than 6% are considered normal (with good glycemic control); those patients with levels greater than 8% are considered to have poorly controlled DM and often have postoperative complications.[37,38] Patients with DM are at high risk for cardiovascular complications, including myocardial ischemia and infarction; thus, a preoperative ECG should be obtained. Diabetic autonomic dysfunction has many implications for the patient undergoing surgery and anesthesia, as it limits the ability of the myocardium to compensate for changes in volume status (such as reduced preload) and predisposes patients to cardiovascular instability, hypotension, and sudden cardiac death. Delayed gastric emptying and risk for aspiration can also be attributed to autonomic dysfunction and the attendant gastroparesis. Long-standing DM also places patients at risk for renal dysfunction and failure. Additionally, patients with DM have decreased immune system function and microvascular disease. Consequently, they are at risk for infections and delayed or impaired wound healing.

The intraoperative care of the patient with DM focuses on control of blood glucose. There has been controversy surrounding what level of glucose should be targeted for patients with DM undergoing surgery. Hyperglycemia in surgical patients is a common problem in the perioperative period for patients with and without known DM. There are many reasons postulated for this hyperglycemia, including poorly controlled DM preoperatively, insulin resistance, increased inflammatory response associated with surgical trauma, increased stress response characterized by increased secretion of counter-regulatory hormones, and requirement for catecholamine-based vasopressors, such as epinephrine.[16,39,40] The effects of these changes lead to increased gluconeogenesis, glycogenolysis, and insulin resistance in the periphery.

Multiple studies have illustrated the importance of good glycemic control in surgical patients. The Portland Diabetes Project demonstrated the connection between hyperglycemia in the perioperative period and increased morbidity in the form of increased infections and deep sternal wound infections as well as increased mortality.[41,42] In addition, intensive insulin therapy to control serum glucose to levels less than 110 mg/dL (6.1 mM) in the intensive care unit population was shown to significantly reduce morbidity and mortality.[43] However, concerns over tight glycemic control have surfaced as a result of studies showing that intensive glucose control intraoperatively led to an increased incidence of stroke and death.[44,45]

Thus, no single, generalizable serum glucose goal exists for all patients with DM. One approach for serum glucose management in this patient population involves learning about each patient's glycemic control before surgery. If a patient has a hemoglobin A_{1C} of 9%, there is likely very poor control and rapidly controlling that patient's blood glucose to a narrow, strict or "low" target range could lead to complications, such as severe hypoglycemia and even stroke or death. Instead, a patient whose DM is poorly controlled can be treated in a moderate fashion, aiming to reduce the blood glucose slowly over time to less than 180 mg/dL (10 mM) intraoperatively via an insulin infusion. Insulin infusions are more physiologic, rapidly titratable, and easier to control than intravenous insulin boluses.[46] Currently, there is a paucity of evidence-based data to demonstrate that strict glucose control is superior to more moderate control intraoperatively. Refer to several other sources on blood glucose management.[16,17,45,47]

Emerging Developments

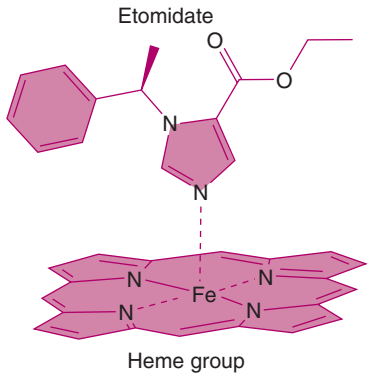
Etomidate is an intravenous anesthetic agent typically used for the induction of general anesthesia, with the advantage of maintenance

of hemodynamic stability. Etomidate's hypnotic effects are believed to result from enhancement of γ-aminobutyric acid type A (GABA-A) receptor function. Etomidate has been shown to suppress adrenocortical function through inhibition of 11β-hydroxylase, which is a required enzyme to produce cortisol, corticosterone, and aldosterone.

The mechanism underlying etomidate's well-described suppression of adrenal steroid synthesis relates to the imidazole ring in its chemical structure. Some imidazole ring–containing drugs are known to produce a "chemical adrenalectomy" that can be long lasting. In the case of etomidate, x-ray crystallographic studies suggest that the nitrogen molecule on the imidazole ring forms a "coordination bond" with the heme iron of the 11β-hydroxylase enzyme, thus occupying the enzyme's active site and preventing the enzyme from interacting with its usual substrates (Fig. 35.2).[48]

Recent work has resulted in the development of etomidate analogs that retain the hemodynamic stability of etomidate yet reduce the risks of adrenal suppression.[48] Investigators have characterized the hypnotic potency of etomidate and 22 other etomidate analogs using in vivo and in vitro assays and found that the hypnotic potencies were significantly correlated with GABA-A receptor potencies.[49] Several structural elements in the etomidate analogs can be modified with GABA-A receptor enhancement leading to an increase in the hypnotic potency of these etomidate analogs.[49]

These investigators also developed a strategy to reduce the problem of adrenocortical steroid suppression associated with etomidate. They synthesized and evaluated cyclopropyl methoxycarbonyl metomidate (CPMM) and carboetomidate, etomidate analogs that have similar hypnotic effects to etomidate but are either broken down rapidly to a metabolite with low affinity for 11β-hydroxylase (CPMM) or bind poorly to 11β-hydroxylase (carboetomidate).[50] CPMM leads to reduced adrenocortical suppression as compared to etomidate because it is metabolized more rapidly and binds to 11β-hydroxylase with less affinity than etomidate.[50] Carboetomidate and other intravenous anesthetics—such as dexmedetomidine, ketamine, and propofol—bind to 11β-hydroxylase with very low affinity. Thus, at hypnotic doses, they produce nominal adrenocortical suppression.[50] Carboetomidate was found to elicit 3 orders of magnitude less potent inhibition of cortisol synthesis by adrenocortical cells as compared to etomidate.[48] This reduced binding affinity for 11β-hydroxylase likely relates to carboetomidate's inability to bind with the heme iron on the active site of the enzyme, as with other imidazole ring–containing drugs. Thus, alterations in the structure of the basic etomidate molecule represent a path toward increased hypnotic potency, shorter-acting clinical profile, and less adrenal suppression.



• **Fig. 35.2** A proposed mechanism for the adrenocorticoid suppression associated with etomidate. The interaction between the basic nitrogen in the imidazole ring of etomidate and the heme iron at the active site of 11β-hydroxylase forms a coordination bond that prevents the active site of the enzyme from interacting with its usual substrates. (Adapted from Cotten JF, Forman SA, Laha JK, et al. Carboetomidate: a pyrrole analog of etomidate designed not to suppress adrenocortical function. *Anesthesiology*. 2010 Mar;112(3):637–644.)

Key Points

- The most important hormones produced by the anterior pituitary include ACTH, TSH, GH, PRL, and the 2 gonadotropins, LH and FSH.
- The balance of releasing factors secreted by the hypothalamus and inhibiting factors secreted by each hormone's target organ control the secretion of each hormone produced by the anterior pituitary.
- Cardiac disease, hypertension, and ventricular hypertrophy are the most important causes of morbidity and mortality in acromegalic patients.
- ADH, produced by the posterior pituitary gland in response to a very mild increase in osmolarity, binds to vasopressin receptors on the renal collecting ducts and causes an increase in water reabsorption.
- The end result of the interactions between PTH, calcium, vitamin D, and calcitonin is to maintain normal plasma calcium concentration, which, in turn, helps maintain normal cellular function, nerve transmission, membrane stability, bone integrity, coagulation, and intracellular signaling.
- Thyroid hormones play a major role in normal growth and development, controlling the rate of metabolism and many body functions.
- Glucocorticoids, such as cortisol, have a multitude of actions, including protein breakdown and gluconeogenesis, fatty acid mobilization, and prevention of muscle protein synthesis.
- Sympathetic stimulation leads to secretion of catecholamines (e.g., epinephrine and norepinephrine), which are produced in the adrenal medulla. Catecholamine release plays a crucial role in the stress response to perceived or real physical or psychological injury, including hemorrhage, severe hypoglycemia, trauma, surgical trauma, and fear.
- Insulin, secreted by the β cells of the pancreas, has an anabolic effect on target organs and stimulates the synthesis of carbohydrates, fats, and proteins.
- Type 2 DM involves 3 main defects in glucose and insulin metabolism: inadequate response of the pancreatic β cells to glucose, decreased response of the peripheral tissues to effects of insulin, and increased hepatic glucose production.
- Alterations in the structure of the etomidate molecule may represent a path toward the development of an etomidate analog associated with less adrenocortical steroid suppression.

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Endocrine Pharmacology

MARK T. KEEGAN

CHAPTER OUTLINE

Drugs to Treat Disorders of the Endocrine Pancreas
- **Insulin**
  - Basic Pharmacology
  - Clinical Pharmacology
  - Individual Insulin Preparations
    - *Regular Insulin*
    - *Rapidly Acting Insulin Analogues*
    - *Intermediate-Acting Insulin*
    - *Long-Acting Insulins*
    - *Inhaled Insulin*
  - Clinical Application
- **Oral Hypoglycemic Agents: Sulfonylureas, Biguanides, Thiazolidinediones**
  - Basic Pharmacology
    - *Sulfonylureas*
    - *Biguanides*
    - *Thiazolidinediones*
  - Clinical Pharmacology and Clinical Application
    - *Sulfonylureas*
    - *Biguanides*
    - *Thiazolidinediones*
- **Other Oral Hypoglycemic Agents**
- **Glucagon**
  - Basic Pharmacology
  - Clinical Pharmacology and Clinical Application
- **Somatostatin Analogs**
  - Basic and Clinical Pharmacology
  - Clinical Application

Drugs to Treat Disorders of the Hypothalamic-Pituitary-End-Organ Axis
- **Thyroid Hormones**
  - Basic Pharmacology
  - Clinical Pharmacology
  - Clinical Application
- **Thioureylene Antithyroid Drugs**
  - Basic and Clinical Pharmacology
  - Clinical Application
- **Other Antithyroid Drugs**
  - Preparing a Patient With Hyperthyroidism for Surgical Intervention
- **Drugs Used in the Treatment of Pheochromocytoma**
  - Basic and Clinical Pharmacology
    - *α Antagonists*
    - *α-Methyl-para-tyrosine (Metyrosine)*
  - Clinical Application
- **Corticosteroids**
  - Basic Pharmacology
  - Clinical Pharmacology
    - *Adverse Effects*
  - Clinical Application
    - *Adrenal Insufficiency*
    - *Reactive Airways Disease*
    - *Corticosteroid Therapy in Neurologic Critical Care*
    - *Nausea and Vomiting*
    - *Immunosuppression*
    - *Treatment of Inflammatory Conditions*
    - *Airway Edema*
    - *Allergy*
    - *Perioperative Steroid Supplementation*
- **Adrenocorticotropic Hormone and Steroid Antagonists**
- **Posterior Pituitary Hormones, Analogs, and Antagonists**
  - Basic and Clinical Pharmacology
    - *Vasopressin and Desmopressin*
    - *Oxytocin*
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Abstract

Dysfunction of the complex physiologic processes of the endocrine systems can lead to significant and potentially life-threatening problems. Administration of exogenous hormones or drugs that mimic or antagonize hormonal effects to manipulate the metabolic milieu is important in many therapies. Endocrine pharmacotherapeutics range from simple supplementation of a missing hormone, such as insulin in the case of patients with type 1 diabetes mellitus (DM), to careful manipulation of physiologic processes with advanced pharmaceuticals in the case of assisted reproduction techniques. Many of these agents have implications for the practice of anesthesia, critical care, and pain medicine.

Keywords

Endocrinology
Pharmacology
Diabetes mellitus
Thyroid
Adrenal
Hormones

Dysfunction of the complex physiologic processes of the endocrine systems can lead to significant and potentially life-threatening problems. Administration of exogenous hormones or drugs that mimic or antagonize hormonal effects to manipulate the metabolic milieu is important in many therapies. Endocrine pharmacotherapeutics range from simple supplementation of a missing hormone, such as insulin in the case of patients with type 1 diabetes mellitus (DM), to careful manipulation of physiologic processes with advanced pharmaceuticals in the case of assisted reproduction techniques. Many of these agents have implications for the practice of anesthesia, critical care, and pain. Historical perspectives are highlighted with the discussion of individual drug classes.

DRUGS TO TREAT DISORDERS OF THE ENDOCRINE PANCREAS

Insulin

The discovery of insulin by Banting and Best represents a major milestone in modern medicine.[1] Within a few years of its discovery insulin had been purified and crystallized. Its amino acid sequence was established by Sanger in 1960. The protein was synthesized in 1963 and its three-dimensional structure elucidated in 1972. The first biosynthetic human insulin was approved by the U.S. Food and Drug Administration (FDA) in 1982.[2]

Basic Pharmacology

Insulin is synthesized in β cells of the pancreatic islets of Langerhans. Pre-proinsulin (a single-chain, 110–amino acid precursor) is initially formed. Subsequently the N-terminal 24–amino acid peptide is cleaved to form proinsulin. Removal of four basic amino acids and a connecting (C) peptide gives rise to insulin itself. The insulin molecule contains A and B peptide chains, usually composed of 21 and 30 amino acid residues, respectively. In most species a single insulin gene gives rise to a single protein product.

When pancreatic β cells are stimulated, insulin and C-peptide are released into the circulation in equimolar amounts. Therefore functional activity of pancreatic β cells is reflected by plasma C-peptide concentrations. It is also possible to differentiate endogenous from exogenous insulin by evaluating plasma C-peptide content. Human insulin, made by recombinant DNA techniques, is used exclusively in the United States. "Purified" insulin contains less than 10 ppm of proinsulin. Refrigeration is recommended but is not crucial.

Insulin is a member of a family of peptides known as *insulin-like growth factors* (IGFs). IGFs are produced in many tissues and regulate cellular growth and metabolism. Specific insulin receptors in the plasma membrane are similar to IGF receptors. The insulin receptor is a large transmembrane glycoprotein that mediates its actions through intracellular tyrosine kinase activity. Insulin binding leads to autophosphorylation of intracellular insulin receptor sites, causing recruitment of numerous enzymes and mediating molecules that are activated or inactivated, leading to a myriad of intracellular events. Importantly, glucose transporters type 4 are translocated to the plasma membrane where they facilitate diffusion of glucose into cells. Other signals activate glycogen synthase, stimulate uptake of amino acids and protein synthesis, and regulate gene expression (see Chapter 30 for more information on the physiology of insulin).

TABLE 36.1 Hypoglycemic Actions of Insulin

Liver	Muscle	Adipose Tissue
Inhibits hepatic glucose production (decreases gluconeogenesis and glycogenolysis)	Stimulates glucose uptake	Stimulates glucose uptake (amount is small compared to muscle)
Stimulates hepatic glucose uptake	Inhibits flow of gluconeogenic precursors to the liver (e.g., alanine, lactate, pyruvate)	Inhibits flow of gluconeogenic precursors to liver (glycerol) and reduces energy substrate for hepatic gluconeogenesis (nonesterified fatty acids)

Modified from Table 60.2 in Brunton LL, ed. *Goodman and Gilman's The Pharmacologic Basis of Therapeutics*. 11th ed. New York, NY: McGraw Hill; 2006.

Insulin's hypoglycemic actions on liver, muscle, and adipose tissue are most important (Table 36.1).

When injected intravenously, insulin has a plasma half-life of 5 to 6 minutes. It is degraded in liver, kidney, and muscle. When renal function is severely impaired, insulin requirements decrease because of reduced breakdown. Liver metabolism of insulin operates at near-maximal capacity and cannot compensate for loss of renal function. Although insulin is cleared relatively quickly from the circulation, its biologic effects persist for 30 to 60 minutes because it binds tightly to insulin receptors. Subcutaneous injection of insulin leads to slow release into the circulation and a sustained pharmacologic effect.

Clinical Pharmacology

Insulin is most commonly administered subcutaneously, but it can also be administered intravenously. In contrast to physiologic secretion of insulin, subcutaneous administration delivers insulin to the peripheral tissues rather than the portal system, and the pharmacokinetics do not reproduce a normal rise and fall associated with ingestion of nutrients. Nonetheless, insulin treatment is lifesaving for patients with DM.

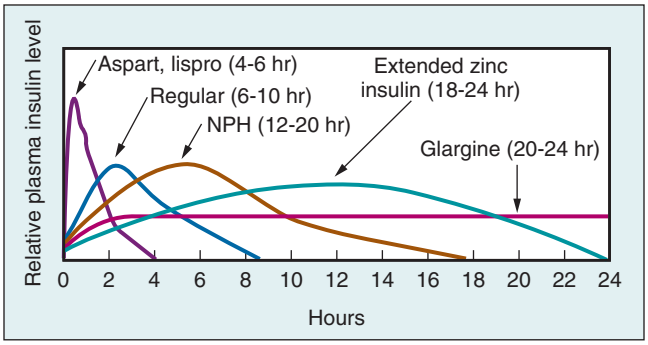
Insulin preparations are characterized by their duration of action or their species of origin. This latter classification is less relevant now owing to the wide availability of synthetic human preparations. For historical reasons, doses and concentrations of insulin are expressed in units. In the past, preparations of the hormone were impure and were standardized by bioassay. One unit of insulin is equal to the amount of insulin required to reduce blood glucose concentration in a fasting rabbit to 45 mg/dL (2.5 mM). Insulin is supplied in solution or suspension at a concentration of 100 units/mL. Typically, a patient with type 1 DM requires between 20 and 60 units of exogenously administered insulin per day. Higher-concentration insulin preparations are available for patients who are resistant to insulin. Table 36.2 details currently available insulin preparations, and Fig. 36.1 shows typical pharmacokinetic profiles of insulin and insulin analogs following subcutaneous administration.

Insulin is among the drugs highlighted by the Institute for Safe Medication Practices as having an increased risk for patient harm

TABLE 36.2 Insulin Preparations

Preparation		Onset (hr)	Peak (hr)	Effective Duration (hr)
Short-acting				
	Aspart	<0.25	0.5–1.5	3–4
	Glulisine	<0.25	0.5–1.5	3–4
	Lispro	<0.25	0.5–1.5	3–4
	Regular	0.5–1.0	2–3	4–6
Intermediate-acting				
	NPH	1–4	6–10	10–16
Long-acting				
	Detemir	1–4	—[a]	20–24
	Glargine	1–4	—[a]	20–24
Insulin combinations				
	75/25–75% protamine lispro, 25% lispro	<0.25	1.5	Up to 10–16
	70/30–70% protamine aspart, 30% aspart	<0.25	1.5	Up to 10–16
	50/50–50% protamine lispro, 50% lispro	<0.25	1.5	Up to 10–16
	70/30–70% NPH, 30% regular	0.5–1	Dual[b]	10–16

NPH, Neutral protamine Hagedorn.
[a]Glargine and detemir have minimal peak activity.
[b]Dual: two peaks, one at 2 to 3 hours; the second one several hours later.
Copyright 2004 American Diabetes Association. Adapted with permission from Skyler JS. Insulin treatment. In: Lebovitz HE, ed. *Therapy for Diabetes Mellitus.* Alexandria, VA: American Diabetes Association; 2004.



• **Fig. 36.1** Pharmacokinetic profiles of human insulin and insulin analogs. The approximate relative duration of action of the various forms of insulin is shown. Duration varies widely both between and within individuals. (From Hirsch IB. Insulin analogues. *N Engl J Med*. 2005;352:174–183.)

when used in error. The administration of insulin is prone to error because of the variety of preparations used and the difficulty associated with administration of a small number of units.

Hypoglycemia is the most common adverse reaction associated with insulin administration. It can occur as the result of administration of an inappropriately large dose of insulin, when peak insulin effect does not coincide with carbohydrate intake, or because of superimposed factors such as exercise. Patients in the perioperative period are especially vulnerable to the development of hypoglycemia because of interruption of oral intake and alterations in insulin dosing regimens. The incidence of hypoglycemia increases when "tighter" glycemic control goals are adopted. Symptoms and signs of hypoglycemia include tachycardia, diaphoresis, tremor, palpitations, anxiety, and hunger. These can be absent during anesthesia. Neuroglycopenia can cause dizziness, blurred vision, and loss of consciousness, potentially progressing to coma, seizures, and even death. Lipodystrophy can occur at the sites of subcutaneous insulin injection, leading to alterations in subcutaneous fat. Lipoatrophy is probably secondary to an immune response to insulin. Enlargement of subcutaneous fat deposits (lipohypertrophy) can also occur and is thought to be due to the lipogenic action of insulin. Allergic reactions to insulin were more common before the use of recombinant human insulin or highly purified insulin preparations, although such reactions still occur. Local reactions cause erythema and induration, and are usually mediated by immunoglobulin (Ig) E. Systemic reactions are less frequent and are usually IgG antibody mediated. Prolonged use of neutral protamine Hagedorn (NPH) insulin can lead to protamine sensitization that can manifest when a large dose of protamine is administered, as in the setting of cardiopulmonary bypass. Doses of subcutaneous insulin of more than 100 units/day can indicate insulin resistance, which can be due to antiinsulin antibodies or target cell receptor dysfunction. As with allergic reactions, the incidence of insulin resistance owing to antibodies is decreasing with use of recombinant and highly purified preparations.

As detailed in Chapters 13 and 30, several hormones antagonize the effects of insulin. These include epinephrine, which inhibits the secretion of insulin and stimulates glycogenolysis, and adrenocorticotrophic hormone (ACTH), glucagon, and estrogens, which tend to cause hyperglycemia. Certain drugs (e.g., tetracycline, salicylates) can increase the duration of action of insulin.

Individual Insulin Preparations

Regular Insulin

Regular insulin is a crystalline zinc insulin preparation, the effect of which appears within 30 minutes of subcutaneous injection. Regular insulin should be injected subcutaneously 30 to 45 minutes before meals. This causes the blood glucose to fall rapidly, reaching a nadir in 20 to 30 minutes.

Rapidly Acting Insulin Analogues

Regular insulin monomers form hexamers in currently available insulin preparations. The hexameric form delays absorption and onset of action. Insulin analogs have been developed that maintain a monomeric or dimeric configuration, increasing their speed of absorption and reducing time to onset to 5 to 15 minutes. They are identical to human insulin except for substitutions of amino acids at one or two positions. Such rapidly acting insulin preparations include insulin lispro, insulin aspart, and insulin glulisine. The use of insulin lispro rather than regular insulin can decrease the incidence of hypoglycemia and improve glycemic control. In clinical trials, insulin aspart has effects similar to insulin lispro on hypoglycemia frequency and glycemic control and causes less nocturnal hypoglycemia than regular insulin.[3] Insulin glulisine has similar properties.

Intermediate-Acting Insulin

Intermediate-acting insulins are designed to dissolve gradually when administered subcutaneously. NPH (or isophane) insulin is a soluble crystalline zinc insulin combined with protamine zinc insulin. Lente insulin is a mixture of crystallized (ultralente) and amorphous (semilente) insulins in an acetate buffer. Their onset of action is delayed to 2 to 4 hours with a peak response at 8 to 10 hours; duration of action is less than 24 hours.

Long-Acting Insulins

Ultralente insulin (an extended insulin zinc suspension) has a slower onset of action and a prolonged peak effect. It provides a low basal concentration of insulin throughout the day and is often used in combination with other insulin preparations. The desire for insulin preparations without peak effects prompted the development of long-acting insulin analogs including insulin glargine and insulin detemir. They lack a peak effect and have durations of action of 17 to 24 hours. Insulin glargine is produced by the addition of two arginine residues to the C-terminus of the insulin B chain and replacement of a single asparagine residue with a glycine in the A chain. The resulting insulin forms a solution with a pH of 4. The low pH stabilizes the hexamer and delays absorption but also means that glargine cannot be mixed with short-acting insulin preparations that are at neutral pH. Another long-acting preparation, insulin detemir, is synthesized by the addition of a saturated fatty acid to the lysine at position B29 in human insulin. Insulin degludec is formed by deleting the last amino acid from the B chain of human insulin and adding a glutamyl linkage to a hexadecanedioic fatty acid, thus allowing the formation of slowly absorbing soluble multihexamers at the injection site. Its duration of action is more than 40 hours. Unlike glargine and detemir, insulin degludec may be mixed with rapidly acting insulins.

Inhaled Insulin

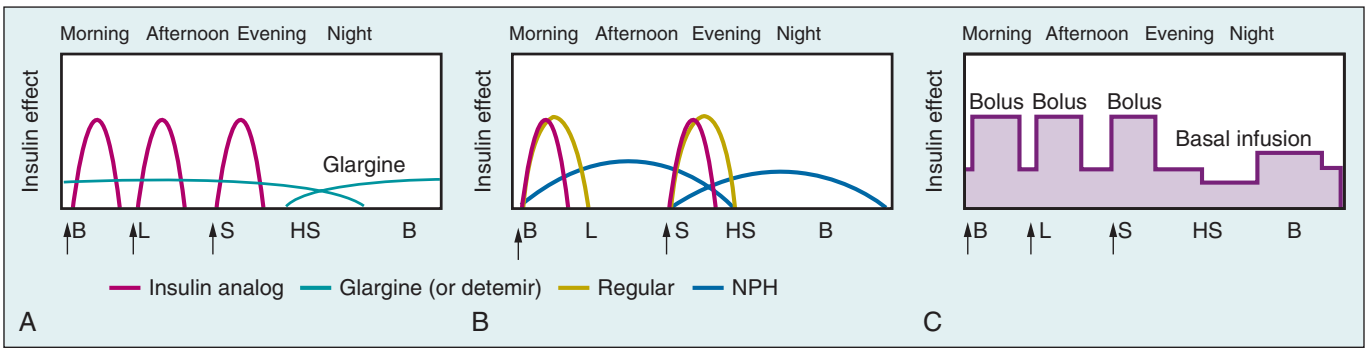
Inhaled insulin is a rapidly acting preparation that can be useful for patients with needle phobias and significant lipodystrophy. The only currently available formulation, Afrezza, was approved by the FDA in 2014. Absorption is inefficient so higher doses of insulin are required, but a very rapid rise of serum insulin concentration can be achieved. Inhaled insulin should be used in combination with a long-acting insulin preparation. It is contraindicated in patients with asthma and chronic obstructive pulmonary disease because of the risk of bronchospasm.

Clinical Application

Subcutaneously administered insulin is the primary therapy for patients with type 1 DM and for many patients with type 2 DM. The American Diabetes Association recommends the following goals of therapy[4]:

- Hemoglobin A1c < 7%
- Preprandial capillary plasma glucose 80 to 130 mg/dL (4.4–7.2 mmol/L)
- Peak postprandial capillary plasma glucose <180 mg/dL (10 mmol/L)

A variety of insulin dosing regimens can be used to achieve these glycemic targets depending on multiple factors, including age, compliance, frequency of significant hypoglycemia and hyperglycemia, and associated medical conditions. Fig. 36.2



• **Fig. 36.2** Commonly used insulin regimens. A, Administration of a long-acting insulin-like glargine (detemir could also be used but often requires twice-daily administration) to provide basal insulin and a short-acting insulin analog before meals. B, A less intensive insulin regimen with twice-daily injection of neutral protamine Hagedorn *(NPH)* insulin providing basal insulin and regular insulin or an insulin analog providing mealtime insulin coverage. Only one type of shorting-acting insulin would be used. C, The insulin level attained after subcutaneous insulin (short-acting insulin analog) by an insulin pump programmed to deliver different basal rates. At each meal, an insulin bolus is delivered. *Upward arrows* show insulin administration at mealtime. *B,* Breakfast; *HS,* bedtime; *L,* lunch; *S,* supper. (Copyright 2008 American Diabetes Association. From Kaufman FR, ed. *Medical Management of Type 1 Diabetes*. 5th ed. Modified with permission from the American Diabetes Association.)

illustrates three potential regimens. Although the route is not FDA approved, regular insulin is often administered intravenously during the perioperative period, during labor and delivery, for the treatment of diabetic ketoacidosis, and as an infusion in the intensive care unit (ICU). The rapidly acting insulin analogs can be injected immediately before or after a meal, allowing for smoother glycemic control because the insulin dose can be titrated to the amount of food actually consumed. In addition, the rapidly acting insulin preparations are commonly used in insulin pumps. Intermediate-acting insulins are usually given once daily (often before breakfast) or twice daily. Long-acting insulin glargine can be administered at any time during the day, has a sustained absorption profile without a peak, and provides better once-daily glycemic control with less hypoglycemia than NPH or ultralente. It is sometimes combined with oral hypoglycemic agents (OHAs; see later text) in patients with type 2 DM. Insulin detemir is administered subcutaneously once or twice daily and delivers glycemic control that is smoother and safer than NPH insulin.

Oral Hypoglycemic Agents: Sulfonylureas, Biguanides, Thiazolidinediones

In the 1940s it was discovered that some sulfonamide antibiotics cause hypoglycemia. Subsequently, more than 20 members of the related sulfonylureas have been developed and used as OHAs. Other major classes of OHAs include the biguanides, the thiazolidinediones, the α-glucosidase inhibitors, and the meglitinides. OHAs are used in patients with type 2 DM.

Basic Pharmacology

Sulfonylureas

There are two generations of sulfonylurea drugs based on an arylsulfonylurea backbone, to which substitutions at the para position on the benzene ring and at a nitrogen residue in the urea moiety are made. First-generation agents include tolbutamide, chlorpropamide, tolazamide, and acetohexamide. Second-generation sulfonylureas are more potent and include glyburide, gliclazide, glipizide, and glimepiride. They act by increasing insulin secretion by stimulating pancreatic β cells. Sulfonylureas inhibit adenosine triphosphate (ATP)-dependent potassium ion (K^+ [K_{ATP}]) channels in the β cells, causing calcium ion (Ca^{2+}) entry and release of insulin storage granules. They can also decrease hepatic clearance of insulin and have other minor extrapancreatic effects.

Biguanides

The biguanides reduce serum glucose by decreasing hepatic glucose output (presumably by decreasing gluconeogenesis) and by sensitizing peripheral tissues such as muscle and fat to the effects of insulin. They do not stimulate insulin release from the pancreas and so are very unlikely to cause hypoglycemia. As such, they are considered to be antihyperglycemic rather than hypoglycemic agents.

Thiazolidinediones

The thiazolidinediones act at extrapancreatic sites to increase insulin sensitivity. They selectively stimulate nuclear peroxisome-proliferator–activated receptor-γ, thus activating insulin-responsive genes that regulate carbohydrate and lipid metabolism. The drugs also decrease hepatic glucose production. They are especially effective in obese patients, although the thiazolidinediones can cause weight gain as edema fluid.

Clinical Pharmacology and Clinical Application

Sulfonylureas

Sulfonylurea drugs are used in patients with type 2 DM in whom diet alone is insufficient to achieve glycemic control. They are absorbed from the gastrointestinal tract where food can interfere with their absorption, so sulfonylureas with short half-lives should be taken 30 minutes before eating. They are weakly acidic and highly protein bound, especially to albumin. Because they are metabolized by the liver with urinary excretion of metabolites, they should be used cautiously in the presence of renal or hepatic dysfunction; if used in such patients, second-generation agents are typically chosen. Specific drugs have considerable variation in their duration of action and metabolism. Glyburide has significant fecal excretion. The metabolism of chlorpropamide is incomplete, with 20% excreted unchanged in the urine. Second-generation sulfonylureas are approximately 100 times more potent than the first-generation agents. Despite their relatively short half-lives of 3 to 5 hours, they have hypoglycemic effects for 12 to 24 hours, and once daily dosing is possible for some.

The sulfonylureas can cause hypoglycemia, potentially leading to coma, especially in elderly patients who have renal or hepatic dysfunction. For first-generation sulfonylureas, the risk of hypoglycemia is greatest for drugs with a longer duration of action (e.g., chlorpropamide). This is not true of the second-generation agents, however. For example, glimepiride causes hypoglycemia in 2% to 4% of patients, whereas glyburide causes hypoglycemia in 20% to 30% of patients, even though the drugs have similar durations of action. It appears that during hypoglycemia, protective mechanisms (inhibition of insulin secretion and promotion of glucagon secretion) are preserved in the presence of glimepiride but not in the presence of glyburide. Drugs that interfere with metabolism or excretion of sulfonylureas and drugs that displace them from plasma proteins can increase the risk of hypoglycemia. Sulfonylurea drugs can also cause cholestatic jaundice, aplastic and hemolytic anemias, agranulocytosis, hypersensitivity reactions, rashes, and nausea and vomiting. Chlorpropamide can cause flushing in association with alcohol ingestion. The sulfonylureas can also cause hyponatremia by potentiating the renal effects of antidiuretic hormone. They are not typically used in pregnant or lactating women.

The degree of cardiovascular risk associated with long-term use of sulfonylureas is controversial. The University Group Diabetes Program demonstrated a slightly higher incidence of cardiovascular events in patients with type 2 DM treated with tolbutamide compared with insulin or placebo. However, multiple other studies, including the large United Kingdom Prospective Diabetes Study Group, demonstrated the absence of increased cardiovascular mortality in sulfonylurea users.[5] Indeed, glimepiride might decrease cardiovascular morbidity, in that it has beneficial effects on ischemic preconditioning. A more recent study, the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial, using the newer agent gliclazide, provided reassuring data on cardiovascular risk.[6]

Biguanides

Metformin, approved for use in the United States in 1995, is the only biguanide in common use today. It is indicated for patients with type 2 DM in whom it was shown to reduce macrovascular complications in the United Kingdom Prospective Diabetes Study Group.[7] It is administered orally and is subsequently absorbed from the small intestine. Metformin is excreted unchanged in the urine

and is relatively contraindicated in patients with renal impairment. It is not bound to plasma proteins. Its half-life in plasma is 2 to 4 hours, and it is administered two to three times daily. The drug is sometimes administered in combination with other OHAs. Metformin leads to a mild weight reduction in obese patients and has beneficial effects on lipid profiles (decreasing plasma triglycerides and cholesterol). The drug is also used in polycystic ovary syndrome.[8]

Phenformin, a similar compound to metformin, was withdrawn from the market because of its predisposition to cause lactic acidosis. Metformin is also associated with lactic acidosis but the incidence (<1 per 10,000 patient-years) is 10 to 20 times lower than that associated with phenformin. The mechanism is thought to be related to interaction with mitochondria that leads to decreased intracellular ATP, causing glucose to be metabolized anaerobically to lactate. In addition to cautions associated with renal impairment, a history of lactic acidosis, significant liver disease, cardiac failure, chronic hypoxic lung disease, and administration of radiographic iodinated contrast agents are relative or absolute contraindications. Metformin should be stopped if the patient develops sepsis or myocardial infarction because of the risk of lactic acidosis. It should also be stopped if plasma lactate is greater than 3 mM. It has been recommended that metformin should not be given on the day of surgery because of concern for the development of lactic acidosis. Some advocate that it be held for 48 hours before surgery. However, in a study comparing a cohort of 443 patients who took metformin preoperatively and a group of 443 patients who did not, there was no difference between groups in hospital mortality, cardiac, renal, or neurologic morbidities.[9] Metformin is also associated with nausea, taste disturbances, abdominal discomfort, diarrhea, and anorexia, although fewer than 5% of patients have side effects severe enough to warrant cessation of the drug.

Thiazolidinediones

Thiazolidinediones include pioglitazone and androsiglitazone. They are used in patients with type 2 DM, either alone or, more often, in combination with insulin or other OHAs. Maximum clinical effect does not occur for 6 to 12 weeks after initiation of therapy. They are taken orally, usually once daily, and are metabolized in the liver via the cytochrome P450 system. Drugs that interfere with cytochrome P450 enzymes alter their rate of metabolism.

Hepatic transaminase levels should be measured regularly in patients taking thiazolidinediones because these drugs can induce liver dysfunction, and hepatic disease is a contraindication to their use. In fact, another thiozolidinedione, troglitazone, was withdrawn because of associated severe hepatic dysfunction. If elevations of transaminases or other signs of hepatic dysfunction occur during therapy, treatment should be stopped. The cardiovascular effects of the thiazolidinediones have also come under scrutiny. Some patients have developed significant peripheral edema and even overt heart failure. Patients who have hypertension and/or diastolic dysfunction are especially at risk. The effects of rosiglitazone on the risk of myocardial infarction and other adverse cardiovascular events remain uncertain despite metaanalyses and data from the Rosiglitazone Evaluated for Cardic Outcomes and Regulation of Glycemia in Diabetes (RECORD) study.[10,11] It appears that thiazolidinediones decrease bone density and increase fracture risk, especially in women, although the absolute risk is small.

Other Oral Hypoglycemic Agents

Both the meglitinide analog repaglinide and the D-phenylalanine derivative nateglinide inhibit K_{ATP} channels in pancreatic β cells to stimulate insulin production. Compared with the sulfonylureas, these drugs have faster onset and shorter duration of action. Repaglinide is administered orally, peak blood levels are obtained within 1 hour, and the half-life is about 1 hour. It can be given multiple times per day before meals. It should be used with caution in patients with liver dysfunction because it is hepatically excreted, although a small portion is renally metabolized. Nateglinide is used to reduce postprandial hyperglycemia in patients with type 2 DM. It is given 1 to 10 minutes before meals. The drug is metabolized by the liver, with a smaller portion excreted unchanged in the urine. Nateglinide is less likely to cause hypoglycemia than repaglinide. Neither drug should be administered when fasting.

The α-glucosidase inhibitors (e.g., miglitol and acarbose) decrease gastrointestinal digestion of carbohydrates and absorption of disaccharides through their action at the intestinal brush border. They are usually administered in combination with insulin or other OHAs, although they can be used as single-agent therapy in patients with predominantly postprandial hyperglycemia or in older adults. They do not cause hypoglycemia unless administered in combination with other glucose-lowering agents. α-Glucosidase inhibitors should be administered at the start of a meal. The drugs can be very effective in patients with type 2 DM who are severely hyperglycemic, although they have more modest effects in those with mild to moderate hyperglycemia. Gastrointestinal side effects can be problematic, although a slow up-titration of the dose lessens these symptoms.

Incretins are gastrointestinal hormones that augment glucose-dependent insulin secretion. They include glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP-1). Both are rapidly broken down by dipeptidyl peptidase IV (DPP-4). Agonists of GIP and GLP receptors and inhibitors of DPP-4 are potentially useful in patients with type 2 DM to amplify glucose-induced insulin release. These agents improve glycemic control and do not usually cause hypoglycemia in the absence of other hypoglycemic agents. Clinically useful synthetic GLP-1 receptor agonists are resistant to the effects of DPP-4. They include exenatide, liraglutide, albiglutide, dulaglutide, taspoglutide, and lixisenatide.[12] The GLP-1 receptor antagonists are injected and are usually combined with oral agents or insulin. They should not be used in patients with type 1 DM or in patients with a history of pancreatitis. Side effects are primarily gastrointestinal. Weight loss is often seen. DPP-4 inhibitors are administered orally, usually as second- or third-line agents, but are only moderately effective. They include sitagliptin, saxagliptin, linagliptin, and alogliptin, and the individual drugs are often combined with metformin. The relationships between DDP-4 inhibitors and heart failure and pancreatitis are subjects of ongoing investigation.

Amylin is co-secreted with insulin from pancreatic β cells. This 37–amino acid peptide decreases gastric emptying, glucagon secretion, and appetite. Pramlintide, an injectable analog of amylin, has been approved for the treatment of patients whose type 1 or type 2 DM is inadequately controlled despite insulin therapy. Drugs that interact with gastrointestinal hormones can predispose patients to increased postoperative nausea and vomiting, their effects on gastric emptying can increase the likelihood of aspiration, and their hypoglycemic effects can lead to dangerously low plasma glucose in the perioperative period.[13] It is recommended that they be held on the day of surgery if possible. Table 36.3 compares agents used for the treatment of DM.

TABLE 36.3 Therapeutic Agents for Diabetes Mellitus

	Mechanism of Action	Examples	HbA1c Reduction (%)[a]	Agent-Specific Advantages	Agent-Specific Disadvantages	Contraindications
Oral						
Biguanides[b]	↓ Hepatic glucose absorption	Metformin	1–2	Weight neutral Do not cause hypoglycemia Inexpensive	Diarrhea Nausea Lactic acidosis	GFR < 50 mL/min, congestive heart failure, radiographic contrast studies, seriously ill patients, acidosis
α-Glucosidase inhibitors[b]	↓ GI glucose absorption	Acarbose, miglitol	0.5–0.8	Reduce postprandial glycemia	Flatulence Liver function tests	Renal/liver disease
Dipeptidyl peptidase-4 inhibitors[b]	Prolong endogenous GLP-1 action	Saxagliptin, sitagliptin, vildagliptin	0.5–1.0	Do not cause hypoglycemia		Reduce dose with renal disease
Insulin secretagogues -sulfonylureas[b]	↑ Insulin secretion	See text	1–2	Inexpensive	Hypoglycemia Weight gain	Renal/liver disease
Insulin secretagogues-nonsulfonylureas[b]	↑ Insulin secretion	Repaglinide, nateglinide	1–2	Short onset of action Lower postprandial glucose	Hypoglycemia	Renal/liver disease
Thiazolidinediones[b]	↓ Insulin resistance ↑ Glucose utilization	Rosiglitazone, pioglitazone	0.5–1.4	Lower insulin requirements	Peripheral edema CHF Weight gain Fractures Macular edema Rosiglitazone may increase risk of CV disease	CHF, liver disease
Bile acid sequestrants[b]	Bind bile acids; mechanism of glucose lowering not known	Colesevelam	0.5		Constipation Dyspepsia Abdominal pain Nausea ↑ Triglycerides Interfere with absorption of other drugs Intestinal obstruction	
Parenteral						
Insulin	↑ Glucose utilization ↓ Hepatic glucose production and other anabolic actions	See text	Not limited	Known safety profile	Injection Weight gain Hypoglycemia	
GLP-1 agonists[b]	↑ Insulin ↓ Glucose Slow gastric emptying Satiety	Exenatide, liraglutide	0.5–1.0	Weight loss	Injection Nausea ↑ Risk of hypoglycemia with insulin secretagogues Pancreatitis	Renal disease, agents that also slow gastrointestinal motility, pancreatitis
Amylin agonists[b,c]	Slow gastric emptying ↓ Glucagon	Pramlintide	0.25–0.5	Reduce postprandial glycemia Weight loss	Injection Nausea ↑ Risk of hypoglycemia with insulin	Agents that also slow gastrointestinal motility
Medical nutrition therapy and physical activity[b]	↓ Insulin, resistance ↑ Insulin secretion	Low-calorie, low-fat diet, exercise	1–3	Other health benefits	Compliance difficult Long-term success low?	

GFR, Glomerular filtration rate; *CHF,* congestive heart failure; *CV,* cardiovascular; *GI,* gastrointestinal; *GLP-1,* glucagon-like peptide 1.

[a]A1c reduction (absolute) depends partly on starting A1c value.

[b]Used for treatment of type 2 diabetes mellitus.

[c]Used in conjunction with insulin for treatment of type 1 diabetes mellitus.

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Glucagon

Basic Pharmacology

Glucagon is a 29–amino acid single-chain polypeptide secreted, like insulin, by the islets of Langerhans, but by the α cells rather than β cells.[2,14] Glucagon is important in the regulation of glucose and ketone body metabolism. Like insulin, glucagon is synthesized as a pro-hormone. Pre-proglucagon is a 180 amino acid polypeptide that gives rise to glucagon, GLP-1 and GLP-2, and glicentin-related pancreatic peptide. Pre-proglucagon is processed differently according to the tissue in which the hormone is secreted, and a variety of glucagon analogs of varying potency can be produced. Glucagon acts on a glycoprotein receptor on target cells that mediates its action through a G-protein cyclic adenosine monophosphate (cAMP)/protein kinase A–mediated mechanism. Glucagon activates glycogen phosphorylase, the rate-limiting step in glycogenolysis, leading to increased glucose concentrations. Glycolysis is also inhibited. Glucagon is active in the liver (to regulate glucose levels), adipose tissue (where it increases lipolysis), heart (where it acts as an inotrope), and the gastrointestinal tract (where it causes relaxation). Glucagon secretion is influenced by diet and by insulin. Both glucagon and insulin release are stimulated by ingestion of amino acids, presumably to minimize hypoglycemia if a pure protein meal is taken. In normal individuals, glucagon release is stimulated by hypoglycemia, a defense mechanism to maintain serum glucose concentration homeostasis. This response is attenuated in the presence of type 1 DM.

Clinical Pharmacology and Clinical Application

Clinical preparations of glucagon are extracted from bovine and porcine pancreas because there is no structural difference between these preparations and human glucagon. The half-life of glucagon in plasma is 3 to 6 minutes, because it is broken down quickly in liver, kidney, plasma, and other sites.

Glucagon is used to treat severe hypoglycemia, especially in patients with DM when oral or intravenous (IV) administration of glucose is not possible. Intramuscular (IM), subcutaneous, or IV glucagon can be administered at a dose of 1 mg, with clinical improvement within 10 minutes. The anti-hypoglycemic effects of glucagon depend on the presence of adequate hepatic glycogen stores. The effect of glucagon is transient and steps should be taken to prevent recurrence of hypoglycemia after the initial effect has waned. Side effects include nausea and vomiting. Glucagon is also used to relax the gastrointestinal tract to improve imaging procedures and to treat biliary spasm and intussusception. It has also been used for its cardiac inotropic effects in instances of β-blocker overdose. It is contraindicated in patients with pheochromocytoma in that it can stimulate release of catecholamines from the tumor.

Somatostatin Analogs

Basic and Clinical Pharmacology

The somatostatins are actually a group of related peptides and include the original 14–amino acid peptide somatostatin, a 28–amino acid peptide, and a 12–amino acid peptide. They are released by pancreatic islets (delta cells), in the central nervous system, and in the gastrointestinal tract. The somatostatins act as inhibitors of the release of thyroid-stimulating hormone (TSH) and growth hormone (GH) from the pituitary, of insulin and glucagon from the pancreas, and of a number of vasoactive peptides from the gastrointestinal tract. Somatostatin has a half-life of less than 6 minutes, but longer-acting analogs such as octreotide and lanreotide have been developed.

Clinical Application

Somatostatin analogs are used to block hormone release in endocrine tumors. Octreotide and lanreotide are used for the treatment of carcinoid tumors, glucagonomas, VIPomas, and GH-secreting tumors. Octreotide, which has been available for longer in the United States, can be given intravenously or subcutaneously and is useful in the perioperative period. The drug is administered in 50- or 100-μg aliquots, either prophylactically or in response to hemodynamic instability, bronchospasm, or other manifestations thought to be secondary to release of vasoactive mediators. Long-term somatostatin analog use can lead to biliary abnormalities and gastrointestinal symptoms.

DRUGS TO TREAT DISORDERS OF THE HYPOTHALAMIC-PITUITARY-END-ORGAN AXIS

Thyroid Hormones

The physiology of the thyroid gland and of the hypothalamic-pituitary-thyroid axis is discussed in Chapter 30.

Basic Pharmacology

The endogenous thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) can be used as pharmacologic agents. T_4 is the pro-hormone product of the thyroid gland.[15,12] The thyroid secretes 80 to 100 μg of T_4 daily; its half-life in the circulation is 6 to 7 days. Thus missing a morning dose of replacement T_4 on the morning of surgery has minimal impact. T_4 is metabolized to biologically active T_3 or biologically inactive reverse T_3. T_3 (3,5,3-triiodothyronine) is formed by extrathyroidal deiodination of T_4 (80%) and by direct thyroid secretion (20%). It is more potent and less protein bound than T_4; its half-life in the circulation is 24 to 30 hours. T_3 mediates most of the effects of thyroid hormones.

Clinical Pharmacology

Thyroxine (levothyroxine sodium) (T_4) is the hormone of choice for thyroid hormone replacement owing to its consistent potency and its duration of action. Usually given orally, 50% to 80% of the administered dose of thyroxine is absorbed in the small intestine. Absorption is increased by fasting and decreased by administration of a number of drugs including sucralfate, cholestyramine, and mineral supplements. Levothyroxine supplementation is monitored by assay of serum TSH levels, with a goal of achieving a normal TSH concentration. Most patients require 75 to 150 μg/day. Dose adjustments take approximately 5 weeks to induce a new serum steady state. In older patients and patients with cardiac disease, low-dose thyroxine supplementation should be started initially, with subsequent slow titration upward to avoid myocardial ischemia or arrhythmias. If enteral access is not possible, thyroxine can be prepared from a lyophilized powder and administered intravenously at 50% of the enteral dose.

Liothyronine sodium (T_3) is the salt of triiodothyronine. It is available in tablet and injectable forms. The average daily dose is 50 to 75 μg. Liothyronine is usually not used as primary replacement therapy because of its relatively short half-life.

Thyrotropin alfa is recombinant TSH and is administered intramuscularly. It is used as an adjunctive diagnostic tool for testing of serum thyroglobulin and in association with radioiodine for ablation of remnants of thyroid tissue in patients with thyroid cancer. Common adverse effects include nausea and headache, paresthesias, arrhythmias, and hypersensitivity reactions.

Clinical Application

Myxedema coma is a rare, extreme form of hypothyroidism. It usually occurs in older women with undiagnosed hypothyroidism, especially in the setting of intercurrent illness. It can present with mental status changes and severe metabolic derangements, including hyponatremia and hypoglycemia, and can lead to hypotension and hypoventilation. Myxedema coma is associated with relatively high mortality. Therapy includes mechanical ventilation and rewarming and administration of IV levothyroxine and hydrocortisone, the latter because 5% to 10% of patients also have adrenal insufficiency.

Thioureylene Antithyroid Drugs

Basic and Clinical Pharmacology

Clinically used antithyroid drugs belong to the thioureylene class and include propylthiouracil (PTU), methimazole, and carbimazole. Carbimazole, used in Europe, is a prodrug of methimazole.[15] Thioureylenes interfere with the incorporation of iodine into tyrosyl residues of thyroglobulin and inhibit the coupling of tyrosyl residues to form iodotyrosines. Blockade of the peroxidase enzyme prevents oxidation of iodide or iodotyrosyl groups to the active state. The coupling reaction might be more sensitive to antithyroid drugs than the iodination reaction. Inhibition of thyroid hormone synthesis leads to depletion of thyroid hormone stores and subsequently to a decrease in serum concentrations. PTU, but not methimazole, also inhibits peripheral conversion of T_4 to T_3 and has theoretical advantages in thyroid storm wherein such blockade of peripheral T_3 production is useful. Both PTU and methimazole must be given enterally.

Both drugs, but especially methimazole, can produce agranulocytosis, which seems to be dose related and can develop rapidly. The development of fever or pharyngitis in patients taking antithyroid medication should prompt evaluation including a complete blood cell count. The most common adverse effect of these drugs, however, is a mild, urticarial rash. Joint pain, headache, paresthesias, nausea, alopecia, and rarely vasculitis can also occur. Both drugs cross the placenta and appear in breast milk, although transfer is lower with PTU, making PTU the preferred agent in parturients and breastfeeding mothers.

Clinical Application

Antithyroid drugs are used as definitive treatment for hyperthyroidism, in conjunction with radioiodine for the treatment of Graves disease, and to control hyperthyroidism in preparation for surgical treatment. PTU is started at a dose of 100 mg every 8 hours or 150 mg twice daily. Methimazole, because of its relatively long duration of action, is given as a single daily dose. Doses of greater than 300 to 400 mg of PTU or 30 to 40 mg of methimazole are usually not required. Thyrotoxicosis usually improves within 3 to 6 weeks. Pretreatment serum T_3 concentrations, size of the goiter, and dose of medication administered all affect the rate of resolution of symptoms. Once the patient is euthyroid, typically within 3 months, the dose of antithyroid medication can be reduced. The drugs are usually not stopped, however, to reduce risk of recurrence of hyperthyroidism. Hypothyroidism can develop and necessitates reduction in dosage or even the administration of thyroid hormone supplementation. Some have advocated a "block and replace" technique, which involves administration of a full dose of antithyroid medication to completely suppress the thyroid gland, followed by supplementation with thyroid hormone once a euthyroid state has been reached. Neither the "gradual dose titration" nor the "block and replace" technique is unequivocally superior.

Thyroid storm is a rare life-threatening exacerbation of hyperthyroidism that can be precipitated by surgical stress or intercurrent illness. It is more likely to occur with undiagnosed or untreated hyperthyroidism. It manifests as hyperthermia, agitation, confusion, and tachycardia. Patients can develop arrhythmias, myocardial ischemia, and congestive heart failure. The differential diagnosis includes pheochromocytoma and malignant hyperthermia, and light anesthesia can mimic some of the features. Treatment of thyroid storm often requires multiple antithyroid agents administered simultaneously.

Other Antithyroid Drugs

β Blockers (see Chapter 13) can be used as adjunctive therapies to improve the signs and symptoms of hyperthyroidism. β Blockers blunt tachycardia, tremor, and anxiety associated with the condition but do not affect synthesis or secretion of T_3 or T_4. They should not be used as single-agent therapy except for brief periods before sodium iodide [^{131}I] administration or before surgery.

Iodide has been used for many years for the treatment of hyperthyroidism and was the only therapy available before the introduction of the antithyroid drugs. Administration of large doses of iodide acutely inhibits synthesis of iodotyrosines and thyroid hormones (known as the Wolff-Chaikoff effect). The mechanism of the acute Wolff-Chaikoff effect is unclear but might be due to antagonism of TSH and cAMP-stimulated thyroid hormone release or generation of organic iodo-compounds within the thyroid.

Inorganic iodine (e.g., Lugol's solution, which contains 5% iodine and 10% potassium iodide, or saturated solution of potassium iodide) is used in preparation for thyroidectomy in patients with thyrotoxicosis. Administered enterally, iodine is converted to iodide in the intestine. It can be given alone, but is usually given 7 to 10 days immediately preoperatively after thyrotoxicosis has been controlled with an antithyroid drug. Doses are determined empirically and range from 1 to 5 drops three times per day. Inorganic iodide decreases the uptake of radioactive iodine, with uptake being inversely proportional to serum iodine concentration. Iodide was administered to populations at risk after the Chernobyl nuclear accident as protection against thyroid cancer.

Iodinated contrast agents (e.g., iopanoic acid, ipodate sodium) can be used as temporary treatment for hyperthyroidism of any cause. These agents block peripheral conversion of T_4 to T_3 and are useful for very symptomatic hyperthyroidism and thyroid storm. They are not currently available in the United States. Of the radioisotopes of iodine, ^{131}I has been used most commonly as an antithyroid medication.[16] It has a half-life of 8 days, meaning that the vast majority of its radioactivity has decayed within 60 days.

It emits both β particles and gamma rays. ^{131}I is administered orally in capsule or solution form, is taken up into the thyroid in the same manner as nonradioactive iodide, and is incorporated into monoiodotyrosine and diiodotyrosine and subsequently into thyroid hormones that are stored in the thyroid follicles. Radioactivity damages thyroid parenchymal cells. Carefully chosen doses of radioactive iodine cause destruction of the thyroid gland without damage to adjacent tissues. ^{131}I is used to treat hyperthyroidism and is often the therapy of choice for Graves disease, especially in older patients and those in whom the disease has been difficult to control. Complete ablation of the thyroid is often recommended, with subsequent supplementation with L-thyroxine. More than half of patients to whom ^{131}I is administered require only one dose, but in others second or subsequent doses are required. Even when complete ablation of the thyroid gland is not desired, many patients develop hypothyroidism. Administration of PTU, but not methimazole, reduces the effectiveness of ^{131}I, presumably by blocking incorporation into thyroid hormone. ^{131}I is contraindicated in pregnancy because of concern for damage to the fetal thyroid gland. Theoretically the drug can cause cancer, and so there are concerns about its administration to younger patients. However, extensive experience with ^{131}I, as documented in the Cooperative Thyrotoxicosis Therapy Follow-up Study Group, has not demonstrated an increase in cancer mortality after ^{131}I treatment for Graves disease.[17] Another radioisotope of iodine, ^{129}I, primarily emits gamma rays, has a shorter half-life than ^{131}I, and is used for imaging of the thyroid gland.

Preparing a Patient With Hyperthyroidism for Surgical Intervention

The steps to be taken to prepare a patient with hyperthyroidism for surgical intervention will depend on the urgency of the procedure. If emergency surgery is required, initiation of an esmolol infusion may be all that time allows, with titration to heart rate and blood pressure control. If cases are urgent rather than emergent, antithyroid medications may be administered, followed a few hours later by iodide. Elective surgery may be prepared for by administration of antithyroid drugs, Lugol's iodine, and oral β blockers.

Drugs Used in the Treatment of Pheochromocytoma

Basic and Clinical Pharmacology

α Antagonists

Phenoxybenzamine is a nonselective α-adrenergic receptor antagonist used in patients with pheochromocytoma or paraganglionoma. The drug blunts the effects of catecholamines released from the tumor and is usually administered preoperatively in preparation for pheochromocytoma resection. Phenoxybenzamine can cause a reflex tachycardia by inhibition of presynaptic α_2 adrenoceptors at postganglionic neurons, resulting in increased release of norepinephrine. It also causes orthostatic hypotension, which can be mitigated by liberal salt and fluid intake. Despite the use of phenoxybenzamine, significant elevations of blood pressure can still occur, especially with intraoperative tumor manipulation. Once a pheochromocytoma has been isolated from the circulation and removed, hypotension is common, and the residual effects of phenoxybenzamine contribute to this hypotension as drug effects dissipate over about 36 hours. Phenoxybenzamine is usually administered in the outpatient setting at an initial dose of 10 mg orally twice daily, increased in 10-mg increments daily until arterial blood pressure has stabilized and symptoms have reduced. Average dose is 44 mg/day (range 10–240 mg/day), and most patients require 10 to 14 days of therapy.[18]

Selective α_1-receptor antagonists include terazosin and prazosin. They do not cause reflex tachycardia, decreasing the need for preoperative β-receptor antagonists. They have a shorter duration of action, allowing adjustment before surgery and a shorter duration of hypotension after pheochromocytoma resection. In addition to their use in the management of patients with pheochromocytoma, selective α_1 antagonists can also be used in the treatment of benign prostatic hyperplasia. Side effects include dizziness and muscle weakness.

Doxazosin is a long-acting α_1 blocker administered once daily. Use of doxazosin before pheochromocytoma resection provides hemodynamic control similar to phenoxybenzamine.[19]

Phentolamine is an α_1 antagonist that can be given intravenously or intramuscularly. It can be used for management of hypertension associated with pheochromocytoma, especially in the perioperative period, when it is given intravenously in 5-mg doses. It has also been used for pralidoxime-associated hypertension. Phentolamine can also be administered subcutaneously in diluted form to decrease the effects of extravasation of α-adrenergic agonists and to reverse the effects of subcutaneously administered local anesthetics. The drug is metabolized in the liver and excreted in the urine.

α-Methyl-para-tyrosine (Metyrosine)

α-Methyl-para-tyrosine is a competitive inhibitor of tyrosine hydroxylase, the rate-limiting enzyme in the production of catecholamines. Administration reduces tumor stores of catecholamines, and can be used in the long-term management of patients with pheochromocytoma when surgery is contraindicated or when long-term management of malignant pheochromocytoma is required. It can also be used in the preoperative preparation of patients with pheochromocytoma. Metyrosine can be especially useful for patients with congestive heart failure in whom α blockers cause tachycardia and β blockers worsen congestive heart failure. The dose is 0.5 to 4 mg/day.

Clinical Application

The optimal regimen for the preoperative preparation of a patient undergoing pheochromocytoma or paraganglionoma resection is controversial. Preoperative α blockade is widely—although not universally—considered necessary to minimize extreme perioperative hypertension and allow for a smoother perioperative course.[20,21] The agents decrease blood pressure, prevent paroxysmal hypertensive episodes, increase intravascular volume, decrease myocardial dysfunction, and are thought to allow resensitization of adrenergic receptors. Published guidelines from the Endocrine Society recommend the use of α antagonists, but there have been reports (including a large case series) of successful pheochromocytoma resections in the absence of α blockade.[20,21] Whether to use a selective or nonselective α blocker is also uncertain. Weingarten et al. compared preoperative regimens using either the nonselective agent phenoxybenzamine or a selective agent (prazosin, doxazosin, or terazosin) and found differences in the need for intraoperative pressors and volume administration but no differences in surgical outcome or length of hospital stay.[22]

Achieving satisfactory hemodynamic and symptom control in patients with pheochromocytoma can also involve use of calcium channel antagonists and β blockers. β Blockers are usually administered after α blockade has been established. They are

contraindicated in the absence of α_1 blockade because vasoconstriction may occur without opposition by vasodilating β_2 receptors. β Blockade should be used cautiously in patients with catecholamine-induced cardiomyopathy. Calcium antagonists may be used on the basis that calcium is essential for catecholamine release from the adrenal medulla and norepinephrine-mediated transmembrane calcium influx influences tone in vascular smooth muscle.

An international group described two different preoperative preparatory regimens for pheochromocytoma resection.[23] The authors advocated for the use of combination therapy with phenoxybenzamine, α and β blockers, and perhaps α-methyl paratyrosine in "high-risk" patients. In "low-risk" patients, α-methyl paratyrosine and calcium channel blockers might be sufficient.[22]

Intraoperative blood pressure control often requires use of readily titratable, rapidly acting vasodilators such as sodium nitroprusside and nicardipine (see Chapter 24) in addition to esmolol and the combined α and β antagonist, labetalol.

Corticosteroids

In the 1940s, Kendall and Hench at Mayo Clinic used products of the adrenal gland, especially cortisol (hydrocortisone), to treat rheumatoid arthritis, opening the door to widespread use of "steroids" in medicine.[24] The physiology of the hypothalamic-pituitary-adrenal axis (HPAA) is described in Chapter 35.

Basic Pharmacology

All steroids, both endogenous and synthetic, are based on the cyclopentanophenanthrene ring, to which side group substitutions can be added to alter the pharmacodynamic and pharmacokinetic profile. The adrenal cortex synthesizes two classes of steroids: the corticosteroids and the androgens. Corticosteroids have traditionally been divided into glucocorticoids and mineralocorticoids according to their relative effects on carbohydrate metabolism, sodium ion (Na^+) retention, and inflammation. Glucocorticoids have more effect on carbohydrate metabolism and more potent antiinflammatory effects, whereas mineralocorticoids more powerfully cause distal renal tubular absorption of Na^+. Many steroids have both properties. Hydrocortisone is synthetically produced cortisol, the primary glucocorticoid in humans, and is used as the reference steroid (Table 36.4).

Transport of the steroid into the cytoplasm allows binding to cytoplasmic receptors, which translocate to the nucleus where they interact with glucocorticoid response elements in genes. Glucocorticoids repress or activate specific genes, interact with other transcription factors, modulate messenger ribonucleic acid, and alter protein production.[25]

Clinical Pharmacology

Corticosteroid effects include alterations in protein, carbohydrate and lipid metabolic processes, preservation of cardiovascular and metabolic homeostasis, and actions on the nervous, endocrine, and immune systems.[26] Steroids increase blood glucose, promote hepatic glycogen synthesis, and decrease sensitivity to insulin. Muscle tissue can be degraded, leading to negative nitrogen balance. Antiinflammatory effects are mediated by stabilization of lysozymes, diminishing leucocyte response to local inflammation, promoting the formation of inhibitor of nuclear factor κB ($I_\kappa B$), and inhibition of proliferation of activated T cells (Fig. 36.3).

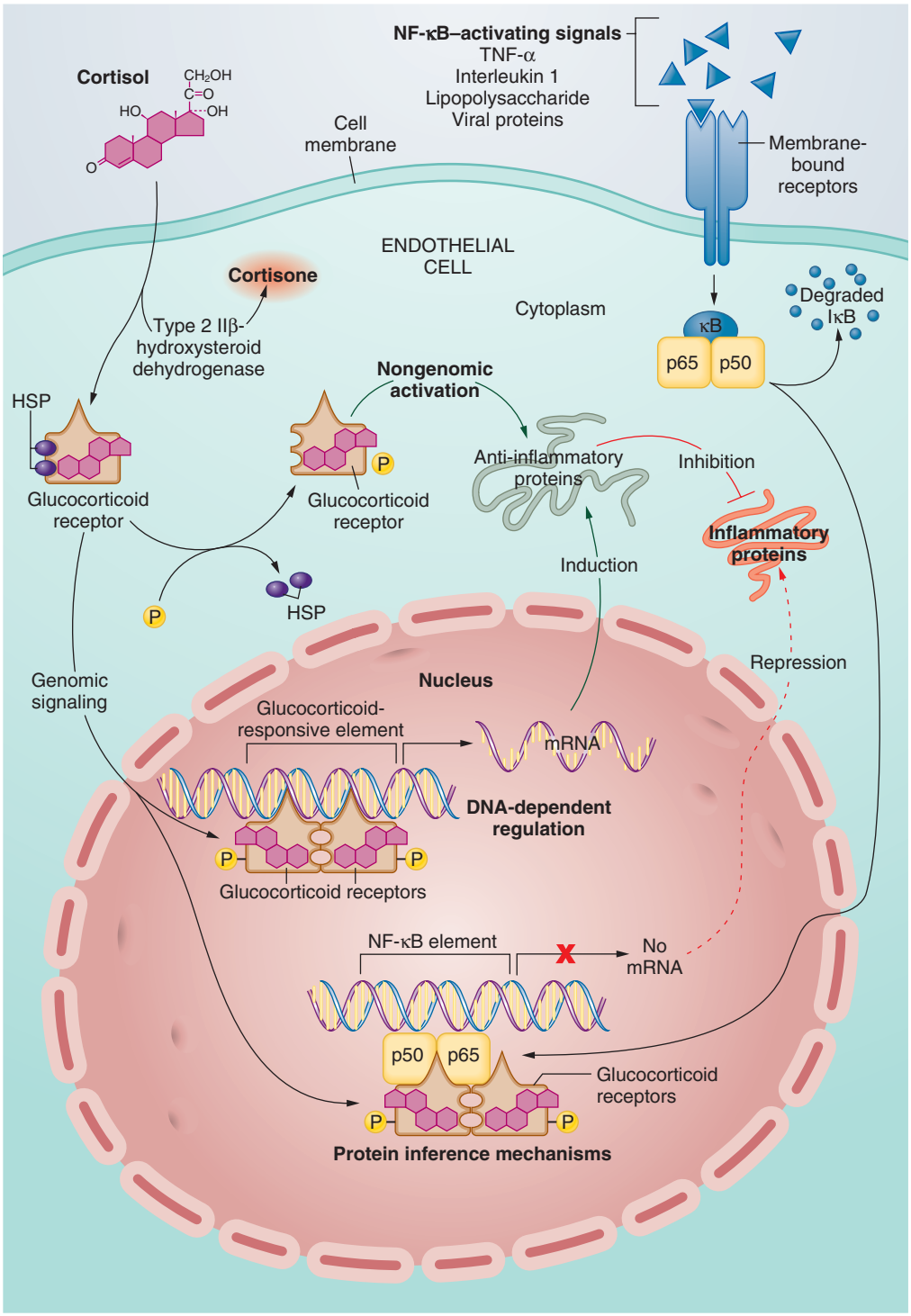
In plasma, glucocorticoids are bound to albumin and transcortin, the levels of which are altered by states such as liver disease or pregnancy. Free, unbound glucocorticoid exerts physiologic effects. Glucocorticoids are metabolized primarily in the liver where they undergo oxidation-reduction reactions to form dihydrocortisol and tetrahydrocortisol. These metabolites are conjugated with glucuronide or sulfate to water-soluble metabolites that are excreted in the urine. A small proportion of the water-soluble metabolites are eliminated via the intestine.

The serum half-lives of the synthetic glucocorticoids vary considerably. Hydrocortisone has a half-life of 80 minutes, whereas dexamethasone has a half-life of 270 minutes. The duration of physiologic effects is determined by the effects on gene regulation, which usually last significantly longer than the half-life. Glucocorticoids can be

TABLE 36.4 Pharmacokinetics and Pharmacodynamics of Commonly Used Steroids

Steroid	Antiinflammatory Potency	Equivalent Dose (mg)	Elimination Half-Time (hr)	Duration of Action (hr)	Sodium-Retaining Potency	Route of Administration
Cortisol	1	20	1.5–3.0	8–12	1	O, T, IV, IM, IA
Cortisone	0.8	25	0.5	8–36	0.8	O, T, IV, IM, IA
Prednisolone	4	5	2–4	12–36	0.8	O, T, IV, IM, IA
Prednisone	4	5	2–4	12–36	0.8	O
Methylprednisolone	5	4	2–4	12–36	0.5	O, T, IV, IM, IA, E
Betamethasone	25	0.75	5	36–54	0	O, T, IV, IM, IA,
Dexamethasone	25	0.75	3.5–5.0	36–54	0	O, T, IV, IM, IA
Triamcinolone	5	4	3.5	12–36	0	O, T, IV, IM, E
Fludrocortisone	10	2		24	250	O, T, IV, IM
Aldosterone	0				3000	

E, Epidural; *IA,* intraarticular; *IM,* intramuscular; *IV,* intravenous; *O,* oral; *T,* topical.
From Elisha S, Ouellette RG, Joyce J. *Pharmacology for Nurse Anesthesiology.* Sudbury, MA: Jones and Bartlett Learning; 2011. Table 18.3.



• **Fig. 36.3** Antiinflammatory mechanisms of action of glucocorticoids. The three major antiinflammatory mechanisms are (1) nongenomic activation mediated by cytoplasmic glucocorticoid receptors, (2) genomic signaling involving DNA-dependent gene regulation via glucocorticoid receptor interaction with glucocorticoid response elements, and (3) protein interference mechanisms (e.g., nuclear factor kappa B *[NF-κB]* elements). *Black arrows* denote activation; the *red line* denotes inhibition; the *red dashed arrows* denote repression; and the *red X* denotes lack of product (i.e., no mRNA). *HSP,* Heat shock protein; *mRNA,* messenger RNA; *P,* phosphate; *TNF,* tumor necrosis factor. (From Rhen T, Cidlowski JA. Anti-inflammatory action of glucocorticoids—new mechanisms for old drugs. *N Engl J Med*. 2005;353:1711–1723.)

TABLE 36.5 Tissue-Specific Side Effects of High-Dose or Prolonged Glucocorticoid Therapy

Tissue	Side Effects
Adrenal gland	Adrenal atrophy, Cushing syndrome
Cardiovascular system	Dyslipidemia, hypertension, thrombosis, vasculitis
Central nervous system	Changes in behavior, cognition, memory, and mood (i.e., glucocorticoid-induced psychoses, cerebral atrophy)
Gastrointestinal tract	Gastrointestinal bleeding, pancreatitis, peptic ulcer
Immune system	Broad immunosuppression, activation of latent viruses
Integument	Atrophy, delayed wound healing, erythema, hypertrichosis, perioral dermatitis, petechiae, glucocorticoid-induced acne, striae rubrae distensae, telangiectasia
Musculoskeletal system	Bone necrosis, muscle atrophy, osteoporosis, retardation of longitudinal bone growth
Eyes	Cataracts, glaucoma
Kidney	Increased sodium retention and potassium excretion
Reproductive system	Delayed puberty, fetal growth retardation, hypogonadism

From Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. *N Engl J Med.* 2005;353:1711–1723.

administered orally, intravenously, and intramuscularly. Preparations are specifically designed for topical use, and steroids can also be administered into the epidural space, synovial spaces, conjunctiva, and respiratory tract. If the enteral route is not available, an equivalent dose can be administered intravenously. The intravenous route is used as first-line therapy for allergic reactions (including anaphylaxis), and in severely ill patients. Inhaled steroids are commonly used for reactive airways disease (usually by metered-dose inhaler), epidural steroids are a mainstay of therapy in certain pain disorders, and topical steroid preparations are used in dermatologic conditions.

Fludrocortisone is the mineralocorticoid most commonly used in clinical practice. It is administered in association with glucocorticoids for primary and secondary adrenocortical insufficiency and for treatment of salt-losing adrenogenital syndrome. It is administered orally, and absorption is rapid and complete. The dose is 0.05 to 0.2 mg/day, although there is considerable interpatient variability. Its half-life is 18 to 36 hours. Side effects include congestive heart failure, hypertension, and edema.

Adverse Effects

High-dose and/or long-term corticosteroid therapy can cause side effects in many organs (Table 36.5). Hypertension is caused by renal Na^+ retention and potentiation of vasopressor responses to angiotensin II and catecholamines. In children, corticosteroids interfere with the proliferation and longevity of chondrocytes, thus slowing longitudinal growth. In adults, osteoporosis and an increased risk of fracture occur owing to adverse effects on osteoblast function. Corticosteroid-induced immunosuppressant effects on lymphocytes predispose to infection and interfere with wound healing. Although corticosteroids are used in the treatment of allergic reactions, patients can have allergic reactions to synthetic steroids. An allergy to a specific steroid can mean that the patient has an allergy to other synthetic steroids.

Negative feedback effects of exogenous steroids can blunt the function of the HPAA, leading to absolute or relative adrenal suppression. This can lead to problems in stressful situations, such as during illness or in the perioperative period (see later text).

Clinical Application

Adrenal Insufficiency

Corticosteroid therapy is vital in patients with Addison disease. Hydrocortisone, a short-acting agent, is often used. Dosing recommendations include 5 mg/m^2 body surface area three times per day, 10 mg in the morning and 5 mg in the evening, and 15 to 25 mg per day administered in two or three doses. These dosing regimens attempt to mimic physiologic steroid secretion, but early morning relative adrenal insufficiency can still occur. Longer-acting steroid preparations (prednisone, dexamethasone) can also be used, especially in those who are noncompliant with multiple dose regimens. Mineralocorticoids might also need to be administered, usually in the form of fludrocortisone, as mentioned earlier.

Reactive Airways Disease

Asthma and chronic obstructive pulmonary disease are inflammatory conditions in which corticosteroids are often used. Inhaled glucocorticoids are the agents of choice in the treatment of persistent asthma according to the National Asthma Education and Prevention Program. Regular treatment with steroids reduces symptom frequency, improves quality of life, decreases risk of serious exacerbations, and modulates bronchial hyperresponsiveness. In randomized controlled trials, inhaled budesonide decreases the incidence of asthma exacerbations more than placebo and inhaled terbutaline.[27,28] Inhaled glucocorticoids can be administered by metered-dose inhaler, dry powder inhaler, or nebulizer. Oral and intravenous corticosteroids are also administered for exacerbations of asthma and chronic obstructive pulmonary disease, and oral agents can be used on a long-term basis for severe reactive airways disease.

Corticosteroid Therapy in Neurologic Critical Care

Glucocorticoids (usually dexamethasone) are administered in relatively large doses for the treatment and prevention of cerebral edema in patients with brain tumors and certain patients with bacterial meningitis.[29] Despite encouraging experimental results, they have not been shown to improve outcome when administered to patients with ischemic stroke, intracerebral hemorrhage,

aneurysmal subarachnoid hemorrhage, and traumatic brain injury. Previously, methylprednisolone was often administered in the acute phase of spinal cord injury, although the evidence to support this was controversial, and current guidelines recommend against such practice.[30–32]

Nausea and Vomiting

Dexamethasone is often used as prophylaxis against nausea and vomiting in the perioperative setting and in patients receiving chemotherapy, a practice supported by clinical trials and meta-analyses.[33] In the perioperative period it works best when administered early in the surgical procedure, suggesting that its effects might be due to a decrease in the inflammatory effects of surgery.[34] Modulation of endorphins might also play a role. Dexamethasone might also have a central effect on the chemoreceptor trigger zone.

Immunosuppression

Corticosteroids are used extensively for induction of immunosuppression in patients receiving solid organ transplants. They are given in high doses (e.g., methylprednisolone 500 mg) in the operating room and continued at lower doses for an indefinite period.

Treatment of Inflammatory Conditions

Steroids are used to treat rheumatoid arthritis, connective tissue diseases (e.g., polyarteritis nodosa, Goodpasture syndrome, Wegener granulomatosis), ocular inflammation (e.g., iritis, uveitis), myasthenia gravis, inflammatory bowel disease, and cutaneous disorders. In addition to systemic therapy, steroids can be administered rectally and topically for bowel and cutaneous disorders, respectively. Steroids are usually used in conjunction with other immunosuppressants to allow use of the lowest effective dose of each agent to minimize side effects.

Airway Edema

Corticosteroids (usually dexamethasone) are often administered prophylactically in the setting of surgical procedures that cause airway swelling (e.g., tonsillectomy, maxillofacial procedures) to decrease swelling and avoid airway compromise. Dexamethasone can also be administered as a treatment for airway compromise following extubation. A metaanalysis suggested that such a practice is supported by clinical data.[35]

Allergy

Corticosteroids are important in the treatment of allergic reactions. In the perioperative and critical care setting, intravenous administration of hydrocortisone is a key component in the treatment of anaphylaxis.

Perioperative Steroid Supplementation

Worldwide, 1% to 3% of adults use long-term corticosteroids to manage a chronic condition. As many as 20% of these patients have taken oral glucocorticoids for more than 6 months and almost 5% of patients continue oral steroid therapy for more than 5 years.[36] Such patients are at risk of adrenal suppression causing relative adrenal insufficiency in the perioperative period.

Major surgery increases the daily production of cortisol from the usual 15 to 20 mg to 75 to 150 mg. There is considerable debate about the necessity of administering perioperative "stress" doses of steroids. Since the 1950s, there have been reports of perioperative deaths in patients with adrenal insufficiency. The incidence of hypotensive crises caused by adrenal insufficiency is low (1%–2%), but steroid supplementation has been justified on the basis that the risk of death is significant. Many have expressed concern, however, that perioperative steroid supplementation is overused.

Patients can be divided into those likely or unlikely to have suppression of the HPAA. Patients taking the equivalent of 20 mg of prednisone per day or more or those who have a cushingoid appearance are likely to have adrenal suppression and should receive perioperative steroid supplementation. On the other hand, those taking steroids for less than 3 weeks and those using long-term alternate-day therapy are unlikely to have suppression of the HPAA axis and do not need perioperative supplementation. For intermediate doses of steroids when the state of the HPAA axis is indeterminate, consideration can be given to the performance of an ACTH test or patients can simply receive perioperative steroid supplementation. Recommended doses for steroid supplementation depend on the nature of the surgical procedure.[37–39] For minor procedures (e.g., hernia repair) the usual morning steroid dose should be taken and no additional supplementation is required. For patients undergoing a procedure associated with moderate surgical stress (e.g., joint replacement), hydrocortisone 50 mg can be given before the procedure, and hydrocortisone 25 mg given every 8 hours for 24 hours postoperatively. Subsequently the patient should receive the usual steroid dose. If a major surgical procedure is being performed (e.g., esophagectomy), 100 mg of hydrocortisone should be given before induction and hydrocortisone 50 mg IV administered every 8 hours for 24 hours. Subsequent steroid supplementation should be tapered relatively quickly to baseline levels.

Adrenocorticotropic Hormone and Steroid Antagonists

Corticotropin or ACTH is used diagnostically in the ACTH test for adrenal insufficiency and therapeutically for a variety of conditions, including acute exacerbations of multiple sclerosis, infantile spasms, and many rheumatologic and connective tissue diseases. Adverse effects are similar to those of the corticosteroids and include adrenal insufficiency after acute withdrawal.

Spironolactone is a potassium-sparing diuretic that acts to antagonize the actions of aldosterone on distal renal tubules.[40] It is used in the treatment of congestive heart failure, primary hyperaldosteronism, hypertension, and peripheral edema. Side effects include hyperkalemia, renal impairment, and gynecomastia. It is associated with tumor development in animals. Eplerenone is another aldosterone antagonist used to modify the renin-angiotensin-aldosterone system in patients with heart failure. It lacks the sexual side effects of spironolactone but might be more likely to cause hyperkalemia.

Metyrapone and aminoglutethimide inhibit steroid synthesis. Metyrapone inhibits the 11-β-hydroxylation reaction, leading to a decrease in cortisol secretion and accumulation of 11-deoxycortisol. Mineralocorticoid deficiency does not occur because production of 11-deoxycorticosterone (a mineralocorticoid) is increased. It can be used in situations of excess glucocorticoid production from adrenal or extraadrenal tumors. Aminoglutethimide inhibits cholesterol side-chain cleavage enzyme (a desmolase), leading to a decrease in both cortisol and aldosterone production. Like metyrapone it is used in the treatment of tumor-induced steroid excess. The commonly used induction agent etomidate blunts steroid production by inhibiting 11-β-hydroxylation, and there has been considerable controversy regarding the appropriateness of its use in patients with septic shock, with metaanalyses producing conflicting results.[41–43]

Posterior Pituitary Hormones, Analogs, and Antagonists

The posterior pituitary (neurohypophysis) secretes oxytocin and antidiuretic hormone. The latter is also known as arginine vasopressin (AVP) or vasopressin. These agents, their analogs, and their antagonists are used in clinical practice, especially in obstetrics and critical care.

Basic and Clinical Pharmacology

Vasopressin and Desmopressin

AVP, a 9–amino acid peptide with a 6–amino acid ring and 3–amino acid side chain, is a powerful vasoconstrictor that works by stimulating specific G-protein–coupled receptors (V_1 receptors) in the vasculature. It also acts on the renal collecting ducts where it increases permeability to water and results in the production of more concentrated urine. This effect is mediated by V_2 receptors. V_3 receptors (formerly called V_{1b} receptors) are found in the anterior pituitary and are coupled to various second-messenger systems. They have a role in the secretion of ACTH.[34,44] Other vasopressin-like receptors regulate the release of factor VIII and von Willebrand factor. Desmopressin acetate (also known as DDAVP) is a long-acting synthetic analog of vasopressin that has a much more pronounced antidiuretic effect and much weaker vasopressor properties than vasopressin. Compared with vasopressin, in desmopressin the first amino acid has been deaminated and the arginine at the eighth position is the *dextro* rather than *levo* form. Vasopressin can be administered intramuscularly or intravenously. It has a half-life in the circulation of about 15 minutes and is metabolized in the kidneys and the liver. Desmopressin can be given intravenously, subcutaneously, orally, or intranasally. It has a half-life of 1.5 to 2.5 hours. Oral bioavailability is less than 1%, but when given by the nasal route it is 3% to 4%. Adverse effects associated with use of vasopressin include headache and agitation. Abdominal pain and nausea can occur as the result of stimulation of abdominal smooth muscle and increased peristalsis. Allergic reactions, which include rashes, urticaria, and anaphylaxis, are rare. Hyponatremia with subsequent seizure activity can occur if an inappropriately high dose is administered. Thrombocytopenia can be caused by AVP-induced platelet aggregation mediated by V_1 receptors.[45] Extravasation can lead to skin necrosis and gangrene. Myocardial ischemia can occur at relatively high doses.

Oxytocin

Oxytocin is a cyclic nonapeptide structurally similar to AVP. The hormones differ by only two of their nine amino acids. An oxytocin precursor is produced by the paraventricular and supraoptic nuclei of the hypothalamus. After proteolysis, oxytocin is secreted by the posterior pituitary. There is also minor oxytocin release from regions of the hypothalamus, brainstem, and spinal cord. Oxytocin is synthesized to a significantly lesser extent in the ovary, uterus, and placenta. It is released in response to cervical dilation and suckling at the breast. Oxytocin plays an important role in pregnancy and labor, in which it stimulates the force and frequency of uterine contractions and milk ejection. It acts through G-protein–coupled receptors that are closely related to vasopressin receptors (see Chapter 30). Oxytocin is used to induce or augment labor in selected pregnant women.[46,47]

Adverse effects of oxytocin include water retention and hyponatremia; when used at high doses in patients to whom hypotonic fluids are administered, this can lead to seizures and coma. Intravenous administration of oxytocin causes vasodilation with subsequent hypotension and reflex tachycardia. Hypotension can be severe in hypovolemic patients and in patients under anesthesia in whom compensatory reflexes are blunted. In contrast to the effects on the systemic vasculature, coronary vasoconstriction can occur.

Clinical Application

Vasopressin and Desmopressin

Both vasopressin and desmopressin can be used for treatment of pituitary DI, which can occur as the result of disruption of the posterior pituitary after neurosurgery or trauma or in the setting of postpartum hemorrhage. Desmopressin is typically used in a dose of 10 to 40 μg/day in two or three divided doses delivered by intranasal spray. It can also be given orally or intravenously. In the ICU it can be given intravenously in a dose of 1 to 4 μg once or twice daily as needed to treat polyuria, polydipsia, and hypernatremia of pituitary origin.

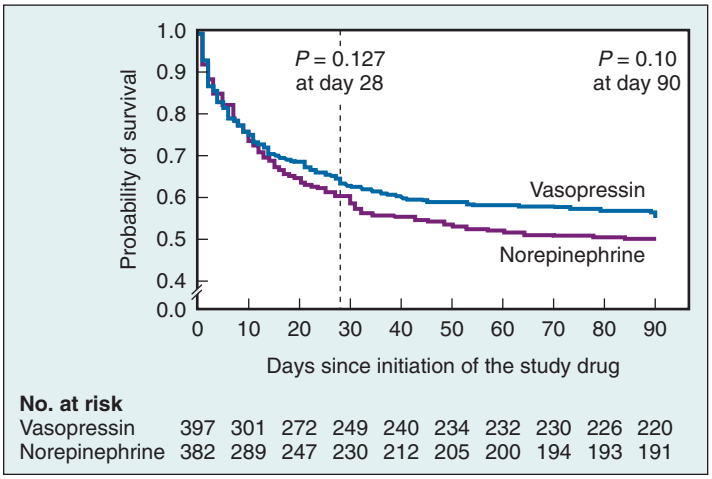
Vasopressin has also been used in critically ill patients with bleeding esophageal varices or bleeding colonic diverticula. The doses required are relatively high and can cause coronary ischemia. Alternative therapies are more typically used now.

In doses larger than those used for the treatment of DI, vasopressin causes vasoconstriction and increases in both systemic and pulmonary blood pressure by direct effects on vascular smooth muscle. When vascular tone is low, the vasoconstrictive effects are more powerful. Studies of AVP serum concentrations in shock states have shown there is relative AVP deficiency in patients with vasodilatory shock states such as sepsis. Administration of vasopressin in vasodilatory shock caused a dramatic increase in systemic blood pressure, even with acidemia, in which the effectiveness of catecholamines is reduced.[48] Vasopressin use in critically ill patients has increased over the past 2 decades. It is used as an infusion at a dose of 0.03 units/min in septic shock. Its exact role has been debated; recommendations are that it be used as an adjunct to catecholamines rather than as a first-line single agent.[49–51] The results of a large prospective study (Vasopressin and Septic Shock Trial [VASST]) comparing low-dose vasopressin to norepinephrine in patients with septic shock failed to show a significant difference in 28-day mortality (Fig. 36.4).[52] Vasopressin was introduced into algorithms for the treatment of cardiac arrest based on a prospective study that demonstrated effectiveness similar to that of epinephrine.[53] A subsequent randomized control trial in patients who had sustained an out-of-hospital cardiac arrest, however, failed to demonstrate improved survival with vasopressin, and the drug has been removed from the most recent cardiac arrest management algorithms.[50,54,55]

In addition to its role in the treatment of DI, desmopressin is also used in patients with uremia, liver disease, and some types of hemophilia to improve hemostatic function. It releases von Willebrand factor, prostaglandins, and tissue plasminogen activator from endothelial cells via V_2 receptors, increasing platelet adhesiveness. It can be used in the treatment of hemophilia A, mild to moderate von Willebrand disease type 1, and uremic platelet dysfunction. It is also used in the perioperative period, although the effectiveness of such therapy is debatable.[56]

Oxytocin

Oxytocin is administered by intravenous infusion. A starting dose of 0.5 to 2 mU/min can be titrated upward in increments of 1 to 2 mU/min until the desired contraction pattern is established, and decreased when a satisfactory contraction pattern and adequate cervical dilation are present. Infusion rates of 6 mU/min provide



• **Fig. 36.4** Kaplan-Meier survival curves for patients with septic shock randomly asigned to receive vasopressin or norepinephrine. The *dashed vertical line* marks day 28. There was no significant difference in mortality rate calculated with the log-rank test. (From Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358:877–887.)

oxytocin levels similar to those of spontaneous labor; rates greater than 9 to 10 mU/min are rarely required, although high-dose oxytocin strategies have been used with doses of more than 20 mU/min. As increased uterine contraction occurs, so too does an increase in the associated pain, and additional analgesia or adjustment of epidural analgesia might be required. Hyperstimulation leads to very frequent or sustained uterine contractions that can necessitate discontinuation of the infusion. Cessation of the infusion usually leads to rapid resolution of hyperstimulation because the plasma half-life of intravenous oxytocin is about 3 minutes. A low-dose oxytocin infusion administered as an "oxytocin challenge test" is performed in some pregnant women to assess fetal well-being.

Oxytocin is also used as a therapy for postpartum hemorrhage.[57] Ten units can be given intramuscularly, or 20 to 40 units diluted in a liter of crystalloid can be administered intravenously. If oxytocin fails to cause uterine contraction and postpartum hemorrhage is ongoing, administration of methylergonovine and/or prostaglandin F_2 might be required.

Other Agents

Terlipressin is a vasopressin analog, not currently available in the United States, with a longer duration of action than vasopressin. It is used with albumin administration for treatment of hepatorenal syndrome. Although it can improve short-term renal function and survival in patients with type 1 hepatorenal syndrome, there is a paucity of evidence demonstrating an effect on overall mortality.[58,59]

Vaptans are relatively new drugs that antagonize the effects of AVP.[60] Tolvaptan selectively antagonizes the effects of AVP at V_2 receptors in the renal collecting ducts, causing a marked, dose-dependent increase in solute-free water excretion.[61] In two multicenter trials, oral tolvaptan was effective in patients with euvolemic or hypervolemic hyponatremia, and is approved for the treatment of hyponatremia and heart failure.[45,62] Conivaptan antagonizes V_1a and V_2 receptors, which, in conditions associated with increased vasopressin levels, decreases renal water excretion. It is used to treat hyponatremia and has been used successfully to treat hyponatremia in liver transplant candidates.[63] Use of vaptans for the treatment of hyponatremia allows avoidance of fluid restriction and continuation of natriuretic diuretics (for treatment of ascites) and prevents development of hepatic encephalopathy. Conivaptan is not approved for treatment of congestive heart failure. The most frequent side effect of the vaptans is thirst. They can also theoretically cause rapid hypernatremia and renal failure owing to depletion of intravascular water.

Carbetocin is an analog of oxytocin, still under investigation, that has a longer duration of action than oxytocin. Atosiban is a peptide agent that antagonizes the actions of oxytocin for the treatment of preterm labor. Its clinical utility is still under consideration. Neither drug is currently available in the United States.[64]

GROWTH HORMONE, PROLACTIN, AND RELATED DRUGS

Growth Hormone

Basic Pharmacology

GH is secreted from the anterior pituitary in a pulsatile manner. Secretion is high in childhood, maximal around the time of puberty, and decreases with age. Pituitary secretion is under the control of GH-releasing hormone (GHRH) and somatostatin from the hypothalamus, which increase and decrease GH secretion, respectively. Ghrelin (from the stomach) and IGF-1 (which mediates GH effects in the periphery) negatively feed back on GH release. GH is actually a mixture of peptides. A polypeptide of 191 amino acids is most prominent, and a 176–amino acid polypeptide makes up approximately 10% of secreted GH. These are bound to a number of GH-binding proteins. GH binds to specific cell surface receptors that are widely distributed. The hormone stimulates the longitudinal growth of bones, increases bone density when the epiphyses have closed, stimulates chondrocyte formation, and increases muscle mass. GH acts on the liver to stimulate gluconeogenesis and on fat cells to promote fat breakdown. It stimulates production of IGF-1 in liver and many tissues, and it is through IGF-1 that its anabolic action is mediated.

Clinical Pharmacology

Pharmaceutical GH is now produced by recombinant techniques, which has increased the safety of administration. Pharmacologic preparations include somatropin whose sequence matches that of native GH, and somatrem, a GH derivative. They have similar biologic activity but differ slightly in their method of preparation. The half-life of GH is less than 30 minutes, but its biologic half-life is up to 18 hours. GH is administered subcutaneously, once daily, or every second day, usually in the evening. Some preparations can also be given intramuscularly.

Adverse effects of GH administration include raised intracranial pressure manifesting as nausea, vomiting, headache, and visual changes. This is a rare complication but warrants periodic ophthalmoscopy to assess for the presence of papilledema. There could be an increased risk of cancers including leukemia, although the link is tenuous. GH is antagonistic to insulin and administration increases the risk of type 2 DM. Scoliosis and epiphyseal injuries have been associated with excessively rapid growth. In adults, arthralgias, myalgias, carpal tunnel syndrome, and peripheral edema can occur.

Clinical Application

GH is used as replacement therapy in children with short stature and severe GH deficiency. In addition, GH can be used in other conditions associated with short stature, including Prader-Willi syndrome, Turner syndrome, and (somewhat controversially) in idiopathic short stature. It is also used in wasting associated with AIDS and for patients with short bowel syndrome.

Measurement of serum IGF-1 levels is used to monitor response in the initial phase of administration; later, change in height is assessed. The duration of GH therapy must be individualized, although some children with GH deficiency require continuation of GH supplementation into adulthood.

Drugs Related to Growth Hormone

Sermorelin acetate is a synthetic analog of GHRH also available for treatment of GH deficiency. It is less effective than GH and not suitable for GH deficiency of pituitary origin. Recombinant human IGF-1 is also available for use in patients with GH resistance. Mecasermin is a complex of recombinant human IGF-1 and recombinant human IGF-binding protein-3 (rhIGFBP-3) used to treat children with severe IGF-1 deficiency unresponsive to GH. The rhIGFBP-3 is used to maintain an adequate half-life of the biologically active IGF-1. Subcutaneous administration can cause hypoglycemia and so should be given only around food ingestion. Elevations in intracranial pressure and liver blood tests can also occur. Pegvisomant is a GH receptor antagonist used in the treatment of acromegaly.[65] It is administered subcutaneously once daily with dosage adjusted to serum IGF-1 levels. It can cause liver dysfunction and, theoretically, loss of negative feedback of GH and IGF-1 can lead to increased growth of GH-secreting tumors. Tesamorelin is an analog of GHRH used to treat HIV-associated lipodystrophy.

Drugs Affecting Prolactin Physiology

Dopamine acts as an inhibitory transmitter for prolactin release. The release of prolactin from prolactin-secreting adenomas is also inhibited by dopamine and dopamine receptor agonists. Bromocriptine and cabergoline are ergot derivatives that act as dopamine-receptor agonists. Usually administered orally, they are useful in the treatment of hyperprolactinemia caused by prolactin-secreting pituitary tumors and in Parkinson disease, and can also be of use at higher doses in the suppression of GH release in acromegaly.[66] The half-life of bromocriptine (7 hours) is shorter than that of cabergoline (65 hours). Longer-acting preparations of bromocriptine are available outside the United States. Side effects of dopamine agonists include headache, nausea and vomiting, postural hypotension, digital vasospasm, nasal congestion, nightmares, and insomnia. At high doses, pulmonary infiltrates and cardiac valvulopathies can develop. Bromocriptine was used for suppression of lactation and decrease of breast size when breast feeding was not desired, but this is no longer recommended because of the potential for coronary thrombosis and stroke. Pramipexole is a dopamine agonist used in the treatment of Parkinson disease and restless legs syndrome.[67]

Sex Hormones and Related Drugs

Because many of these drugs are essentially identical to their endogenous hormone counterparts, their basic and clinical pharmacology behavior (i.e., structure-activity, mechanism, metabolism, pharmacokinetics, and clinical effects) mimic those of the endogenous hormones. Sex steroids include androgens, estrogens, and progestins. Their physiology is reviewed in Chapter 30.

Basic and Clinical Pharmacology

The Gonadotropins

Gonadotropins include follicle-stimulating hormone (FSH) and luteinizing hormone (LH). They are produced by the gonadotroph cells in the anterior pituitary. In women, both LH and FSH are involved in the production of ovarian steroids and in the regulation of the ovarian cycle. In men, FSH regulates spermatogenesis and supports developing sperm. LH stimulates testosterone production by Leydig cells. Human chorionic gonadotropin (hCG) controls estrogen and progesterone production during pregnancy. The three hormones have identical α chains and unique β chains, although the β chains of LH and hCG are very similar.

The gonadotropins are used in the treatment of infertility. They can stimulate spermatogenesis in men and induce ovulation in women. Preparations of FSH include urofollitropin (a purified preparation of FSH extracted from the urine of postmenopausal women), and follitropin α and follitropin β (recombinant preparations). Lutropin α is recombinant human LH. It is used in association with follitropin α to stimulate follicle development in infertile women with LH deficiency. FSH and LH are also contained in human menopausal gonadotropin, which is another extract obtained from the urine of postmenopausal women. hCG is purified from the urine of pregnant women or made by recombinant techniques when it is known as choriogonadotropin α. The former preparation is administered intramuscularly, the latter subcutaneously. It is typically used to cause final maturation of follicles and timed ovulation in assisted reproduction techniques.

Adverse effects of gonadotropin treatment include depression and emotional lability, headache, edema, and antibody production. Gynecomastia can be associated with gonadotropin treatment in men and is related to the level of treatment-associated testosterone production.

Sex Steroids

Androgens and Androgen Antagonists

Androgens include testosterone, dihydrotestosterone, and related compounds. They act through a specific androgen receptor. Hepatic metabolism limits the systemic availability of orally administered drug, so parenteral preparations are commonly used. Testosterone is used when there is a deficiency of endogenous testosterone, in males with delayed puberty and hypogonadism, and for inoperable breast cancer. A variety of compounds that activate the androgen receptor are also used in clinical practice. Therapeutic uses include catabolic and wasting states and, controversially, enhancement of athletic performance. Male contraception is a potential use for

androgen administration but such therapy is still being refined. Administration of androgens is used to prevent attacks in both male and female patients with angioedema caused by C1-esterase inhibitor deficiency. Stanozolol and danazol, both of which are 17α-alkylated androgens, stimulate hepatic synthesis of the inhibitor. Danazol 200 mg is administered orally two to three times per day initially, with subsequent decrease in the long-term dose. If an attack occurs, dosage is increased by up to 200 mg/day. Side effects include hepatotoxicity and, rarely, benign intracranial hypertension. The drugs are also used to treat endometriosis and fibrocystic breast disease in women.

Nilutamide, bicalutamide, and flutamide are androgen receptor antagonists used in the treatment of metastatic prostate cancer. Nilutamide commonly causes visual changes and is associated with interstitial pneumonitis in 2% of recipients. All three drugs can cause hepatotoxicity and gynecomastia. Cyproterone is a weak antiandrogen used to reduce hirsutism. Finasteride and dutasteride antagonize the enzyme (5α-reductase) that converts testosterone to dihydrotestosterone. They are used in the treatment of benign prostatic hyperplasia and male-pattern baldness. Impotence and gynecomastia can occur as a result of their use.

Estrogens and Estrogen Antagonists

Estrogens and progestins are endogenous hormones that produce numerous physiologic actions, including developmental effects, control of ovulation and cyclical changes in the female reproductive tract, and actions on carbohydrate, protein, lipid, and mineral metabolism.[68]

Estrogens can be administered via oral, parenteral, transdermal, or topical routes. Oral drugs include estradiol, conjugated estrogens (including conjugated equine estrogens), esters of estrone and other estrogens, and ethinyl estradiol. The delivery of estrogens by transdermal patch allows a slow, sustained release of hormone to the systemic circulation. Preparations in oil are most suitable for intramuscular administration and have a prolonged duration of action. Estradiol and preparations of conjugated estrogen have been prepared for topical (vaginal) use. Systemic estrogens are bound to plasma proteins in varying degrees and metabolized in the liver. They also undergo enterohepatic circulation. Adverse effects of pharmacologic estrogen administration include nausea and vomiting, migraine headaches, breast tenderness, exacerbation of endometriosis, alterations in triglyceride and lipoprotein metabolism, increased risk of gynecologic malignancies, and increased risk of thromboembolic disease, especially in smokers.[69,70] In addition to thromboembolic disease, use of oral contraceptives is associated with hypertension, cholelithiasis, and the development of benign hepatomas.

Progestins and Progestin Antagonists

The progestins are compounds with actions similar to those of progesterone.[68] They include progesterone, a naturally occurring hormone, pregnanes (17α-acetoxyprogesterone derivatives), estranes (19-nortestosterone derivatives), and gonanes (norgestrel and related compounds). The progestins are used for contraception, either alone or in association with an estrogen, and are administered with estrogen as hormone replacement therapy in postmenopausal women. Progestins can be used in the diagnosis of secondary amenorrhea and can be used to reduce endometrial hyperplasia induced by unopposed estrogens. Levonorgestrel is used as an emergency contraceptive measure. Mifepristone is an antiprogestin that can be used for termination of pregnancy. It is a derivative of the 19-norprogestin norethindrone and acts as a competitive antagonist at progesterone receptors. Mifepristone is orally active, has good bioavailability, and undergoes liver metabolism and enterohepatic circulation. Effects depend on the phase of the cycle in which it is administered. It can cause breakdown of the decidua, delay or prevent ovulation, and impair the development of a secretory endometrium. Ulipristal is another 19-norprogestin derivative that acts as a selective progesterone receptor modulator. It can be used as an emergency contraceptive for at least 72 hours after unprotected intercourse. Adverse effects include nausea, abdominal pain, and headache.

Clinical Application

Gonadotropins

In women with anovulation (e.g., those with polycystic ovarian syndrome or hypogonadotropic hypogonadism), gonadotropins are used to induce ovulation. They are also used for controlled ovarian hyperstimulation in assisted reproduction techniques. Careful monitoring of their effects using blood hormone concentrations and ultrasound visualization of the ovaries is required as they can cause ovarian hyperstimulation syndrome and multiple pregnancies. Ovarian hyperstimulation occurs in up to 4% of patients and, on occasion, a cycle might need to be abandoned because of the risk of hyperstimulation. Ovarian hyperstimulation results in painful ovarian enlargement, ascites, pleural effusions, and potentially intravascular volume depletion. Fever, ovarian cyst rupture, and thromboembolism can also occur. Treatment of infertility in men who have hypogonadism requires stimulation of FSH and LH by gonadotropins. hCG and human menopausal gonadotropins are administered for this purpose, although recombinant FSH and recombinant LH have been used more recently.

Estrogens

Estrogens are administered to decrease vasomotor symptoms, bone fractures, and urogenital atrophy in menopausal women. The long-term effects of estrogens on cardiovascular risk in postmenopausal women are a matter of debate.[71,72] In addition, estrogens are commonly administered as a component (with progestins) of combination oral contraceptive regimens. The combination of hormones inhibits ovulation by a negative feedback mechanism that prevents release of FSH and LH. A less frequent, but accepted, indication for estrogen treatment is in the setting of failure of ovarian development (e.g., Turner syndrome) in which estrogens are administered to induce puberty.

Selective estrogen receptor modulators are drugs that produce beneficial estrogen effects in some tissues (e.g., bone) and antagonize estrogen effects in others (e.g., breast), also with beneficial intent. Tamoxifen, administered orally, is the hormonal therapy of choice in women with early and advanced breast cancer and is used as palliative therapy in women with advanced breast cancer who have estrogen receptor–positive tumors. Adverse effects include hot flashes and increased risk of thromboembolic disease and endometrial cancer. It is metabolized in the liver by cytochrome P450 and induces the activity of some isoforms. Metabolism to its more potent 4-hydroxy metabolite is influenced by genetic polymorphisms. Toremifene is similar to tamoxifen in structure and activity. Raloxifene is used to reduce the risk of breast cancer in postmenopausal women and in the prevention and treatment of osteoporosis. It inhibits proliferation of estrogen receptor–positive breast cancer cells and has an antiresorptive effect on bone that leads to a reduction in the incidence of vertebral fractures.

Clomiphene and fulvestrant antagonize the action of estrogen in all tissues. The former is used in the treatment of female infertility owing to anovulation. Administered orally, it increases gonadotrophin levels and enhances follicular recruitment. Adverse effects of clomiphene include ovarian hyperstimulation, multiple births, ovarian cysts, hot flashes, and visual changes. Prolonged use might increase the risk of ovarian cancer. Fulvestrant is used in patients with advanced breast cancer.

Hormonal Contraceptives

Most oral contraceptives use a combination of an estrogen and a progestin, with a theoretical efficacy of greater than 99.9%.[68] They are usually presented in 28-day packs, with pills for days 22 to 28 being inert. Preparations are monophasic, biphasic, or triphasic, depending on the relative amounts of estrogens and progestins, in an attempt to more closely mimic the natural menstrual cycle and limit the amount of hormone administered. Most preparations contain 30 to 35 μg of estrogen; those containing less than 35 μg are referred to as "low-dose." Preparations containing a combination of norelgestromin and ethinyl estradiol are available as patches and as an intravaginal ring. Combination contraceptives act by influencing the hypothalamic-pituitary-ovarian axis at multiple levels, but ultimately prevent ovulation, especially by suppressing FSH and LH.

Adverse effects of combination oral contraceptives are related to the dose of estrogen used and newer low-estrogen preparations have decreased risks.[73] Side effects include increased risk of venous thromboembolic disease, especially in women who smoke; myocardial infarction in smokers and those with other risk factors; hepatic adenomas and hepatocellular carcinoma; and cervical cancer in long-term oral contraceptive users who also have human papilloma virus infection. Combination oral contraceptives decrease the risk of endometrial and ovarian cancers. An association with breast cancer is controversial. Combination oral contraceptives are contraindicated in patients with active or previous thromboembolic disease, cerebrovascular disease, myocardial infarction, congenital hyperlipidemia, liver tumors or significant dysfunction, and certain cancers. The risk of cardiovascular side effects is significantly increased if combination oral contraceptives are administered to smokers older than 35 years.

Progestin-only preparations are also available. They block ovulation in only 60% to 80% of cycles but cause a thickening of cervical mucus that decreases sperm penetration and causes endometrial alterations that impair implantation. They have a slightly decreased theoretical efficacy (99%) compared with combination preparations. They are taken in pill form, administered intramuscularly or placed subdermally or intravaginally. Side effects include breakthrough bleeding, headache, and alterations in lipid metabolism. The progestin-only preparations are contraindicated in liver disease, breast cancer, and undiagnosed vaginal bleeding.

Parathyroid Hormone and Drugs Affecting Calcium Metabolism

Parathyroid hormone (PTH) helps regulate extracellular fluid Ca^{2+} concentration.[74] It influences bone osteoclast activity, renal distal tubular reabsorption of Ca^{2+}, and gastrointestinal Ca^{2+} absorption, the latter through its regulation of the synthesis of 1,25 dihydroxycholecalciferol (calcitriol). PTH also affects renal absorption of phosphate and bicarbonate. PTH secretion is regulated primarily by serum [Ca^{2+}] and is influenced by phosphate, magnesium ion, and catecholamine levels.[75] The actions of PTH on metabolism are shown in Fig. 36.5. See Chapter 30 for a more detailed discussion of PTH physiology. PTH is derived from pre-proparathyroid hormone, and subsequently from proparathyroid hormone, neither of which appears in plasma. During periods of hypocalcemia, PTH secretion is increased. The half-life of PTH in the plasma is 2 to 5 minutes. It is cleared mainly by the liver and kidneys. The physiologic effects of PTH on target tissues are mediated by PTH-specific G-protein–coupled receptors.

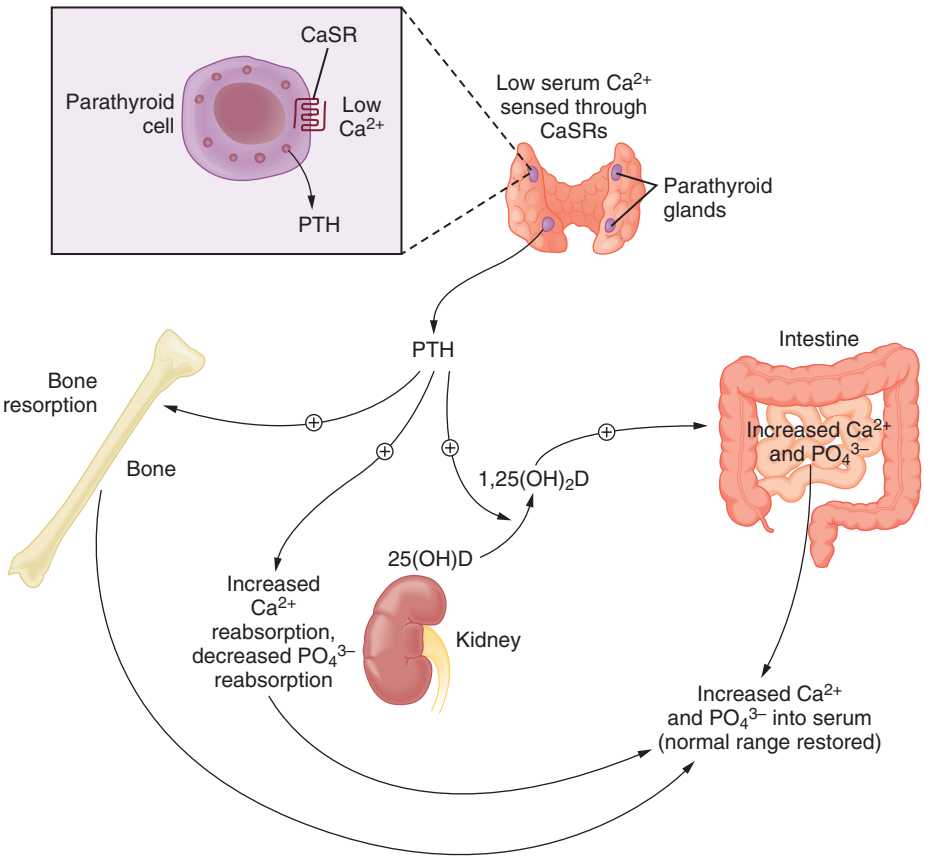
With high levels of circulating PTH (e.g., in primary hyperparathyroidism), bone demineralization and osteopenia occur. PTH can be administered intermittently, however, and this promotes bone growth. Teriparatide is recombinant human PTH 1-34 (a 34–amino acid terminal PTH fragment) used for the treatment of osteoporosis in postmenopausal women at high risk for fracture, as well as hypogonadal or primary osteoporosis in men and osteoporosis resulting from glucocorticoid administration.[76] Teriparatide reduces the risk of vertebral and nonvertebral fractures. Given via the subcutaneous route, it causes an increased serum Ca^{2+} that peaks at 4 to 6 hours. Adverse effects include transient hypercalcemia, orthostatic hypotension, chest pain, and syncope as well as gastrointestinal upset. It is also associated with the development of osteosarcoma in animals.

Vitamin D is used therapeutically for prevention and treatment of osteoporosis; prophylaxis against, and cure of, nutritional rickets; treatment of chronic renal failure metabolic rickets osteomalacia; and hypoparathyroidism. A number of preparations are available. Calcitriol (1,25-dihydroxy cholecalciferol) is administered orally or by injection. Doxercalciferol (1α-hydroxyvitamin D_2) is administered orally or intravenously for the treatment of secondary hyperparathyroidism. It requires activation in the liver by 25-hydroxylation. Dihydrotachysterol is another form of vitamin D that requires activation in the liver. At high doses it mobilizes bone mineral and is used in the treatment of hypoparathyroidism. Ergocalciferol is used for prevention of vitamin D deficiency as well as therapeutically for the treatment of hypoparathyroidism, certain types of rickets, and familial hypophosphatemia.

Calcitonin is a single-chain peptide hormone secreted by the parafollicular C cells of the thyroid. It circulates in very low concentrations in plasma and causes hypocalcemia and hypophosphatemia by inhibition of osteoclastic bone resorption. The actions of calcitonin oppose those of PTH, although it does not appear essential for Ca^{2+} homeostasis. It is used pharmacologically to treat hypercalcemia (especially hypercalcemia related to malignancy), osteoporosis, and Paget disease. The therapeutic agent is derived from salmon or eel and administered subcutaneously, intramuscularly, or intranasally. Side effects are usually associated with the nasal route of administration and include rhinitis, flushing, back pain, and rare allergic reactions.

Cinacalcet mimics the effect of Ca^{2+} to inhibit PTH secretion (i.e., it is a calcimimetic) and lowers the concentration of Ca^{2+} at which PTH secretion is suppressed. It is used for the treatment of secondary hyperparathyroidism owing to chronic renal disease and for patients with hypercalcemia associated with parathyroid carcinoma. Cinacalcet can cause hypocalcemia, which is especially problematic in patients prone to seizures.

Pyrophosphate analogs with two phosphate groups attached to a central carbon are known as bisphosphonates.[77] The bisphosphonates have a strong affinity for bone because their physical structure allows them to chelate Ca^{2+}. They inhibit bone resorption by concentrating at sites of active remodeling where they are absorbed into the bone matrix and subsequently inhibit osteoclasts. They also decrease osteoclast numbers. Members of this class include



• **Fig. 36.5** Control of mineral metabolism by parathyroid hormone. Levels of serum ionized calcium *(Ca^{2+})* are tightly controlled through the action of parathyroid hormone *(PTH)* and 1,25-dihydroxyvitamin D *(1,25[OH]$_2$D)*. Both the rate and magnitude of changes in serum ionized Ca^{2+} concentration are detected by extracellular Ca^{2+}-sensing receptors *(CaSRs)* expressed on parathyroid cells. When ionized Ca^{2+} decreases, release of PTH is triggered. Conversely, when ionized Ca^{2+} levels increase, PTH secretion is suppressed. PTH stimulates bone resorption, which delivers Ca^{2+} and phosphorus *(PO_4^{3-})* into the circulation. In the kidney, PTH stimulates renal reabsorption of Ca^{2+} and promotes phosphate excretion. PTH also enhances the conversion of 25-hydroxyvitamin D *(25[OH]D)* to the active vitamin D metabolite *1,25(OH)2D,* which increases transepithelial transport of Ca^{2+} and PO_4^{3-} through actions in intestinal cells. In concert, these steps restore ionized Ca^{2+} to the normal range, and through the actions of PTH and other factors (e.g., fibroblast-derived growth factor 23) in the kidney, reset the level of serum PO_4^{3-} within the normal range. When the actions of PTH are reduced or lost, subsequent steps in the maintenance of homeostasis are impaired, resulting in hypocalcemia, hyperphosphatemia, and hypercalciuria. (From Shoback D. Clinical practice. Hypoparathyroidism. *N Engl J Med*. 2008;359:391–403.)

etidronate, zoledronate, pamidronate, alendronate, tiludronate, and risedronate. Bisphosphonates have limited bioavailability (1%–6%) when given orally because they are very poorly absorbed from the gastrointestinal tract and can be given intravenously to avoid this problem. Excretion is primarily renal, and poor renal function is a relative contraindication. Zoledronate can be nephrotoxic. The bisphosphonates—especially the first-generation bisphosphonate etidronate— can cause osteomalacia and esophagitis. Although hypocalcemia associated with their use is unusual, it can occur especially in patients with malignancy. Intravenous administration can cause myalgias and fevers. Oral bisphosphonates increase phosphate retention in the tubules. The bisphosphonates are used in postmenopausal osteoporosis, Paget disease, corticosteroid-associated bone loss, and hypercalcemia due to malignancy.[78] They are also used for patients with multiple myeloma and metastatic breast cancer. They can be given as infrequently as weekly or monthly.

Emerging Developments

Glycemic Control in the Perioperative Period and in the Critically Ill

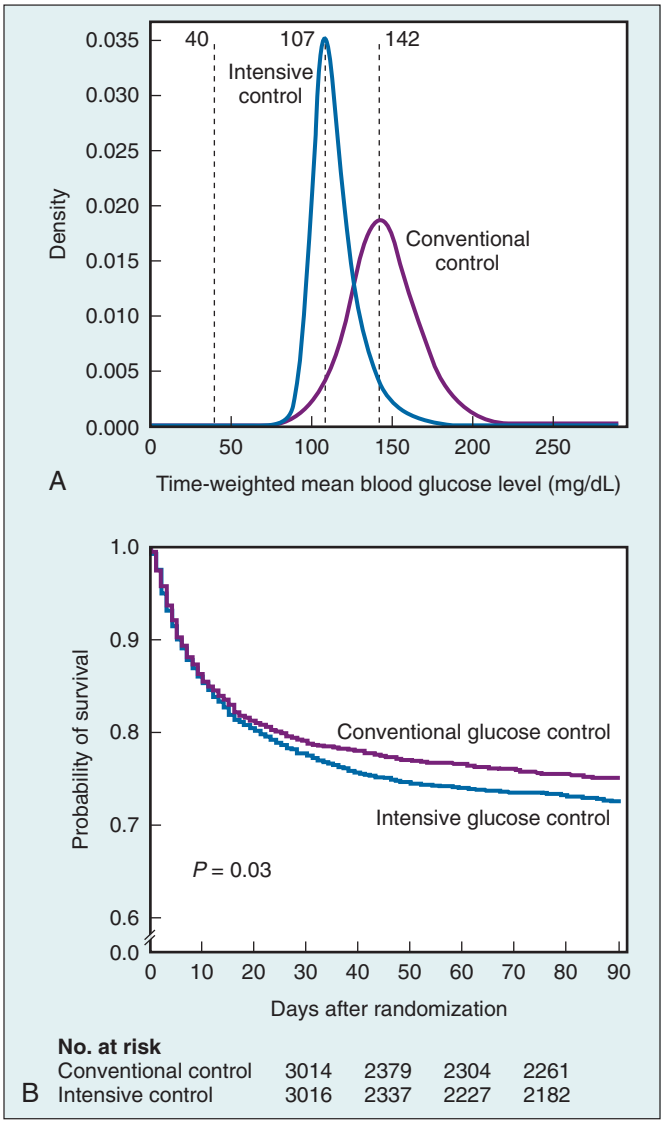
There is considerable controversy regarding optimal blood glucose concentration in the perioperative period and in critically ill patients.[79] Significant hyperglycemia is associated with multiple adverse effects including increased incidence of surgical site infections. Certain patient populations are adversely affected by hyperglycemia (e.g., patients with acute myocardial infarction, neurologic injury). In 2001, a single-center study suggested that targeting "tight" glycemic control (80–110 mg/dL; 4.4–6.1 mM) in critically ill patients improved outcomes.[80] Over the course of the subsequent decade, glycemic control targets were lowered and the use of insulin infusions in the ICU became commonplace. Many practitioners extrapolated these data and targeted tighter

glycemic control in the operating room. Quality initiatives also encouraged tighter glycemic control. However, the potential for hypoglycemia exists when intensive insulin therapy is used. Hypoglycemia is associated with adverse neurologic outcomes and is a feared perioperative complication. Further data suggested that hypoglycemia in critically ill patients was independently associated with poor outcome. A number of studies and metaanalyses failed to demonstrate beneficial effects of "tight" glycemic control and raised the question of whether the practice was, in fact, detrimental. For example, the VISEP (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis) study was stopped early because the use of intensive insulin therapy to maintain normoglycemia was associated with adverse events in patients with sepsis.[81] The NICE-SUGAR (Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) study, a prospective multicenter, multinational randomized controlled trial comparing tight glycemic control (target glucose 81–108 mg/dL; 4.5–6 mM) with conventional glycemic control (target glucose <180 mg/dL; 10 mM) failed to demonstrate a beneficial effect of intensive insulin therapy and, in fact, demonstrated increased mortality in the intensive insulin therapy group (Fig. 36.6).[82] Current guidelines suggest that in-hospital glucose levels should be kept between 140 and 180 mg/dL (7.8–10 mM).[83]

Steroid Supplementation During Critical Illness

Steroid supplementation in the setting of severe sepsis and septic shock has also been a topic of debate over the past decade. Adrenal insufficiency can be a feature of the so-called endocrinopathy of critical illness. A "functional" or "relative" adrenal insufficiency has been described and called critical illness-related corticosteroid insufficiency, though there is considerable debate regarding its definition.[84] Initial data suggested that supplementation with hydrocortisone and fludrocortisone in patients with septic shock improved outcomes.[85] The choice and dose of steroids, the need for performance of an ACTH test (and the dose of ACTH if performed), the duration of steroid use, and the choice of patients in whom steroid supplementation is necessary are controversial. Recent multicenter studies, however, have failed to demonstrate any benefit to steroid administration in septic shock unless the patient has preexisting adrenal insufficiency.[86,87] The CORTICUS (Corticosteroid Therapy of Septic Shock) study was a multicenter, randomized, double-blind placebo controlled trial of 499 patients enrolled within 72 hours of the onset of septic shock. Hydocortisone administration did not improve 28-day mortality overall, nor was there improvement in the subgroups of patients with and without adequate adrenal reserve.[86] Steroid administration lead to a faster reversal of shock but may have contributed to an increased risk of infection. Analysis of data from almost 9000 patients in the Surviving Sepsis Campaign database demonstrated an *increase* in mortality in patients treated with steroids.[88] The HYPRESS (Hydrocortisone for Prevention of Septic Shock) study demonstrated that in patients with sepsis, but without septic shock, use of hydrocortisone did not reduce the risk of shock.[89]

High-dose corticosteroid administration in the early phase of the acute respiratory distress syndrome (ARDS) does not offer significant advantages. Low-dose steroids have been used in the fibroproliferative stage of ARDS to decrease the fibrosing alveolitis. The multicenter LASRS (Late Steroid Rescue Study) demonstrated that in patients in whom ARDS had been present for 7 days, administration of a course of methylprednisolone allowed earlier liberation from mechanical ventilatory support, but ultimately no difference in outcome.[90] Glucorticoids are useful, however, in ARDS caused by certain conditions, including acute eosinophilic pneumonia and engraftment syndrome after hematopoietic stem cell transplantation, when they should be administered in high doses.



• **Fig. 36.6** A, Density plot for the mean time-weighted blood glucose levels for individual patients in the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) study. *Dashed lines* indicate the modes in the intensive control group *(blue)* and the conventional control group *(purple),* as well as the upper threshold for severe hypoglycemia (40 mg/dL). B, Kaplan-Meier plots demonstrating improved survival with conventional glycemic control versus intensive glycemic control ($P = 0.03$) in the NICE-SUGAR study. (From NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283–1297.)

Hormone Supplementation in Potential Organ Donors

Brain death leads to derangement of the hypothalamic-pituitary axis, and hormonal supplementation has been advocated as a means to maintain hemodynamic stability and metabolic homeostasis. Such management might ultimately result in an increase in the number of organs available for procurement from suitable patients and subsequent transplantation.[91] Corticosteroids are thought to attenuate the effects of inflammatory cytokines generated as a result

of brain death and seem to improve oxygenation in donor lungs.[92,93] Whether they improve survival of donor kidneys or hearts is uncertain. Vasopressin has beneficial effects on hemodynamics, and desmopressin is useful in the treatment of DI to help with sodium management. Although numerous case series and retrospective audits reported a beneficial effect of thyroid hormone administration to patients in whom brain death had occurred, a metaanalysis of four placebo-controlled randomized trials failed to show an advantage.[94,95] Nonetheless, the practice continues based on theoretical grounds. In general, there is a paucity of good evidence on which to decide whether or not to administer hormonal supplementation to potential organ donors in whom brain death has occurred. The evidence is further confounded by the variety of drugs and doses that have been used.[96] In an attempt to standardize practice, a consensus statement has been published by critical care and organ procurement organizations.[97] Recommendations include administration of four drugs: methylprednisolone, 15 mg/kg[91]; T_3 (4-μg bolus, then an infusion at 3 μg/hr) or T4 (20 μg bolus, followed by an infusion at 10 μg/hr); arginine vasopressin (0.01–0.04 IU/min) for hemodynamic support and/or desmopressin (initial dose 1–4 μg); and insulin (titrated according to institutional protocols for hyperglycemia).[94] Further data are expected.

Key Points

- Endocrinologic therapeutic interventions range from supplementation of missing endogenous hormones (e.g., insulin in DM) to complex manipulations of hormones and receptors using synthetic drugs (e.g., assisted reproduction techniques).
- Treatments for hyperglycemia include administration of insulin in patients with type 1 and type 2 DM and a variety of insulin secretagogues and other OHAs in patients with type 2 DM.
- Thyroid hormone supplementation includes administration of T_4 (usually) or T_3. Antithyroid medications are used in hyperthyroidism.
- Management of pheochromocytoma and paraganglioma involves the use of α- and β-adrenoreceptor antagonists, inhibitors of catecholamine synthesis, and direct-acting vasodilators.
- Corticosteroids are among the most widely used pharmaceuticals. Perioperatively, careful consideration must be given to appropriate adrenal supplementation in patients with adrenal suppression.
- Oxytocin, a hormonal product of the posterior pituitary, has long been used in obstetric practice. There is considerable recent interest in use of the other posterior pituitary hormone, arginine vasopressin, in patients with hemodynamic instability and septic shock.
- Finely regulated Ca^{2+} homeostasis is influenced by parathyroid hormone and vitamin D analogs and by calcitonin and the bisphosphonates.

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Physiology and Pharmacology of Obstetric Anesthesia

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CHAPTER OUTLINE

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  - *Decreased Systemic Vascular Resistance*
  - *Aortocaval Compression*
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Emerging Developments
- In Utero Anesthetic Exposure and Brain Development

Physiology

Hormone activity, increased metabolic demands, the gravid uterus, and biochemical changes related to the fetoplacental unit result in significant alterations in maternal physiology, anatomy, and pharmacology during pregnancy, as shown in Fig. 37.1. These physiologic changes have a direct impact on maternal pharmacodynamics and anesthetic management considerations during the peripartum period.[1–3]

Cardiovascular Changes

Pregnancy-related changes to the cardiovascular system include an increase in cardiac output, decrease in systemic vascular resistance, increase in blood volume, and presence of supine hypotension. The extent of these physiologic changes varies with gestational age (GA). A summary of these alterations at term is provided in Table 37.1.

Increased Cardiac Output

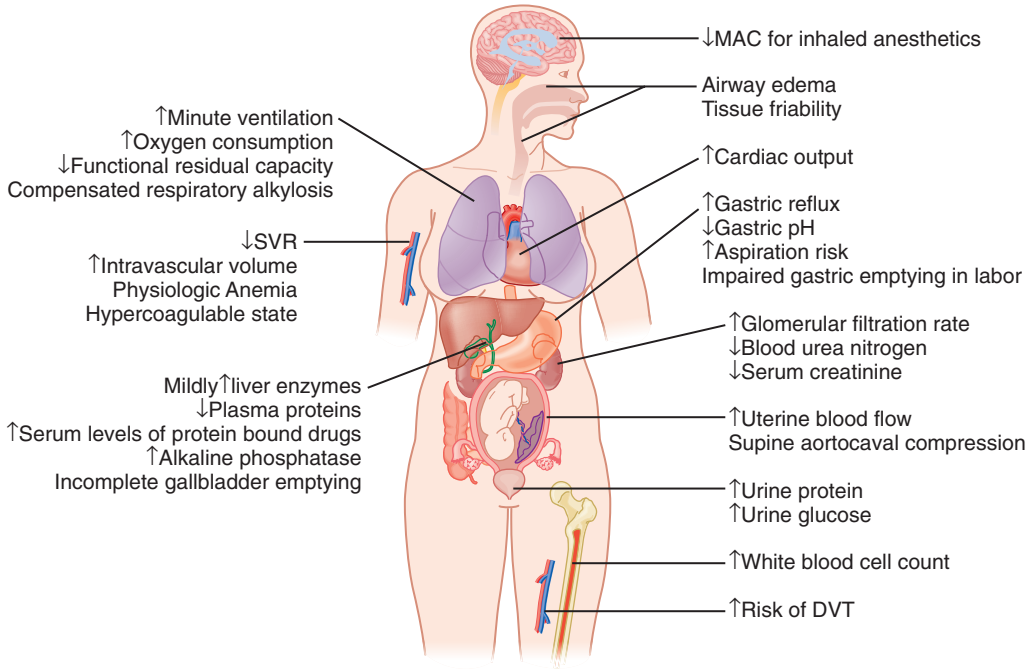
Maternal cardiac output increases to 35% above prepregnancy values by the end of the first trimester, with continued increases up to 50% above prepregnancy values from the end of the second trimester through term gestation. An increase in both stroke volume (by 25%–30%) and heart rate (by 15%–25%) contributes to this increased cardiac output. Further changes are also noted in labor and the postpartum period. During the first stage of labor, cardiac output increases an additional 10% to 25% above term pregnancy levels, and continues to increase to 40% above term cardiac output during the second stage of labor. Immediately after delivery there is an autotransfusion from the contracting uterus, a release of aortocaval compression with decreased systemic vascular resistance, and a return of lower extremity venous blood. These changes result in a maternal cardiac output 80% to 100% greater than prelabor values. Such a dramatic increase in cardiac output can place patients with cardiovascular pathology, such as fixed valvular stenosis, heart failure, or pulmonary hypertension, at significant risk. By approximately 24 hours postpartum, cardiac output has returned to term, prelabor levels, and by 2 weeks postpartum has continued to decline significantly toward prepregnancy values. At 3 to 6 months postpartum, maternal cardiac output has returned to normal prepregnancy levels.

Abstract

The physiologic changes that occur during pregnancy, labor, and the postpartum periods are profound. In addition, the fetus presents a unique component of the circulatory and metabolic systems that must be part of patient care considerations and decision-making. A thorough understanding of these physiologic alterations and fetal considerations is integral to providing safe and optimal anesthetic care for obstetric patients. The field of obstetric anesthesiology commonly uses a variety of medications that are unique within the practice of anesthesiology and require special understanding for use in the obstetric population. All medications administered to the mother have the potential to affect the fetus. A detailed understanding of drug pharmacodynamics, placental transfer, and side effects helps ensure not only optimal patient care but also improved patient counseling in both the peripartum period and for nonobstetric surgery during pregnancy. Obstetric anesthesia creates the need to care simultaneously for two patients, and a comprehensive understanding of the unique physiologic systems as well as pharmacologic management pertinent to pregnant patients will help to ensure safe and appropriate medical care.

Keywords

obstetric anesthesia
fetal anesthesia
pregnancy physiology
fetal physiology
cesarean delivery
labor analgesia
neuraxial anesthesia



• **Fig. 37.1** Selected anatomic, physiologic, and pharmacologic changes in pregnancy at term. Pregnancy results in significant changes to every organ system. In addition to the text in the "Physiology" section of this chapter, refer to Tables 37.1 through 37.4 for more detailed information regarding specific timing and degree of change. *DVT,* Deep vein thrombosis; *MAC,* minimum alveolar concentration; *SVR,* systemic vascular resistance.

TABLE 37.1 Cardiovascular Changes of Pregnancy

Cardiovascular Component	Changes at Term (vs. Prepregnancy Values)
Cardiac output	Increased 40%–50%
Stroke volume	Increased 25%–30%
Heart rate	Increased 15%–25%
Vascular pressures and resistances	
Central venous pressure	No change
Femoral venous pressure	Increased 15%–50%
Pulmonary capillary wedge pressure	No change
Systemic resistance	Decreased 20%
Pulmonary resistance	Decreased 35%
Intravascular volume	Increased 35%–45%
Plasma volume	Increased 45%–55%
Erythrocyte volume	Increased 20%–30%

Created and adapted from information from Cheek TG, Gutsche BB. Maternal physiologic alterations. In: Hughes SC, Levinson G, Rosen MA, et al., eds. *Shnider and Levinson's Anesthesia for Obstetrics.* 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2002:3–18; and Gaiser R. Physiologic changes of pregnancy. In: Chestnut DH, Wong CA, Tsen LC, et al. *Chestnut's Obstetric Anesthesia: Principles and Practice.* 5th ed. Philadelphia: Elsevier; 2014:15–38.

Decreased Systemic Vascular Resistance

A 20% decrease in systemic vascular resistance occurs in an uncomplicated pregnancy at term, resulting in a 5% to 20% decrease in blood pressure by 20 weeks GA (with diastolic blood pressures decreasing to a greater degree than systolic). After midgestation, blood pressures begin to increase toward prepregnancy values. Although there is an increase in femoral venous pressure influenced by the gravid uterus and maternal positioning, central venous pressures and pulmonary capillary wedge pressures do not change significantly during pregnancy.

Aortocaval Compression

Supine hypotension, a decrease in blood pressure caused by aortocaval compression from the gravid uterus in the supine position, occurs in approximately 15% of term gestations. "Supine hypotension syndrome" is defined as a decrease in mean arterial pressure greater than 15 mm Hg and an increase in heart rate greater than 20 beats/min, with symptoms of diaphoresis, nausea, vomiting, and changes in mentation. Significant occlusion of the vena cava in the supine position causes a decrease in stroke volume and cardiac output by 10% to 20%, and contributes to lower extremity venous stasis, edema, varices, and increases the risk of venous thrombosis. Blood return increases through the engorged epidural, azygous, and vertebral veins. Aortoiliac arterial compression is also present in 15% to 20% of women at term.

Increased peripheral sympathetic nervous system activity is a compensatory reflex that reduces supine hypotension in the setting of aortocaval compression by increasing systemic vascular resistance in an effort to maintain blood pressure despite a reduced cardiac output. This sympathetic tone can be impaired in the setting of general or neuraxial anesthesia, resulting in an exacerbation of hypotension related to supine positioning. Maternal blood pressure measured from the upper extremities does not necessarily accurately reflect the reduced arterial pressure of the lower extremity vasculature caused by aortocaval compression. Therefore, even without measured hypotension or symptoms, uterine and placental blood flow may

be significantly impaired. Prolonged impairment may lead to the development of fetal acidosis.

Because of these considerations, the supine position is avoided during neuraxial or general anesthesia.[4] A leftward tilt helps to relieve compression of the inferior vena cava and abdominal aorta by the uterus, thus maintaining uterine and placental blood flow and lessening the degree of hypotension. An elevation of the right hip by 10 to 15 cm using a blanket, wedge, or table tilt can accomplish this.

Intravascular Volume and Hematology

Changes to the renin-angiotensin-aldosterone system during the first trimester result in sodium reabsorption and water retention. A 25% decrease in albumin and a 10% decrease in total protein are observed at term, with a resulting decrease in colloid osmotic pressure from 27 mm Hg to 22 mm Hg.[5] The plasma volume increases approximately 50% above prepregnancy values at term, while the red cell volume increases only about 25%. This results in a "physiologic anemia" of pregnancy, with typical hemoglobin (Hb) levels decreasing toward 11 g/dL at term. Despite this physiologic anemia, total oxygen delivery is not reduced, as the increased cardiac output compensates for the decreased oxygen-carrying capacity. Plasma volume is increased by 1000 to 1500 mL at term, which offsets the 300 to 500 mL blood loss associated with a vaginal delivery or the 800 to 1000 mL blood loss with cesarean delivery. The uterine contraction after delivery results in an autotransfusion of approximately 500 mL and counteracts the delivery blood loss.

A white blood cell (WBC) count greater than 10,000 WBC/mm^3 of blood is normal in pregnancy and unrelated to infectious causes. There is often a neutrophilia at term, which can increase to more than 30,000 WBC/mm^3 during labor. These values normalize 4 to 5 days postpartum.

Pregnancy results in a hypercoagulable state. There is a 20% decrease in prothrombin time and partial thromboplastin time caused by significant increases in factor I (fibrinogen) and factor VII and less substantial increases in other factors (Table 37.2). There are also decreases in factors XI and XIII and antithrombin III. Platelet levels are typically unchanged or slightly (10%) decreased at term secondary to plasma dilution, and "a routine platelet count is not necessary in the healthy parturient."[4] However, 6% to 10% of normal pregnancies are complicated by thrombocytopenia (platelet count <150,000/mm^3). The most common cause is gestational thrombocytopenia, which accounts for more than 70% of these cases.[6] Gestational thrombocytopenia is a diagnosis of exclusion, and other clinically important pathologies such as idiopathic thrombocytopenic purpura, severe preeclampsia, and hemolysis with elevated liver enzymes and low platelet count (HELLP syndrome) should be ruled out. In cases of gestational thrombocytopenia, platelet levels typically remain above 100,000/mm^3 in the majority of cases and rarely decrease below 70,000/mm^3.

Patients with inherited disorders of coagulation (e.g., factor V Leiden, von Willebrand disease) may have significant changes in their clotting profile during pregnancy, and multidisciplinary management with an anesthesiologist, obstetrician, and hematologist is essential for optimal care.

TABLE 37.2 Coagulation Changes of Pregnancy

Procoagulant factors	
Increased	I, VII, VIII, IX, X, XII, von Willebrand factor
Decreased	XI, XIII
Unchanged	II, V
Anticoagulant factors	
Increased	None
Decreased	Antithrombin III, protein S
Unchanged	Protein C

Clinical Examination and Evaluation

The physiologic changes of pregnancy on the cardiovascular system result in changes in clinical findings and studies. Often a benign, grade 2/6 systolic ejection murmur is appreciated over the left sternal border secondary to mild tricuspid regurgitation from annular dilation and increased intravascular volume. Cardiac auscultation demonstrates an accentuated S_1 as well as increased splitting because of the dissociated closures of the tricuspid and mitral valves. An S_3 is often noted in the third trimester, and an S_4 is heard in a minority of patients owing to increased volume and turbulent flow. Neither the S_3 or S_4 typically has clinical significance. Changes in the electrocardiogram and echocardiography are outlined in later text (Table 37.3). Pregnant patients with chest pain, syncope, severe arrhythmias, high-grade murmurs, or clinically significant shortness of breath should undergo appropriate clinical evaluation and workup. In addition, patients with preexisting cardiac disease should have consultation with a multidisciplinary care team including an anesthesiologist and cardiologist early in pregnancy to optimize their care and minimize risk.

Respiratory Changes

Increases in minute ventilation and oxygen consumption, decreased lung reserve, and upper airway changes are seen in normal pregnancies (Table 37.4).

TABLE 37.3 Cardiac Examination Findings in Pregnancy

Clinical Examination in Pregnancy	Findings
Electrocardiography	Increased PR and QT intervals QRS axis shift rightwards (first trimester) QRS axis shift leftwards (third trimester) ST depression (~1 mm) precordial and limb leads Isoelectric T waves precordial and limb leads Small Q-wave and T-wave inversion in lead III
Echocardiogram	Displacement of heart anteriorly and leftward Right chambers increased by ~20% Left chambers increased by ~10% Eccentric LVH Mitral, tricuspid, pulmonic annular dilation Tricuspid and pulmonic valve regurgitation common Mitral regurgitation (27% of patients) Possible small pericardial effusion

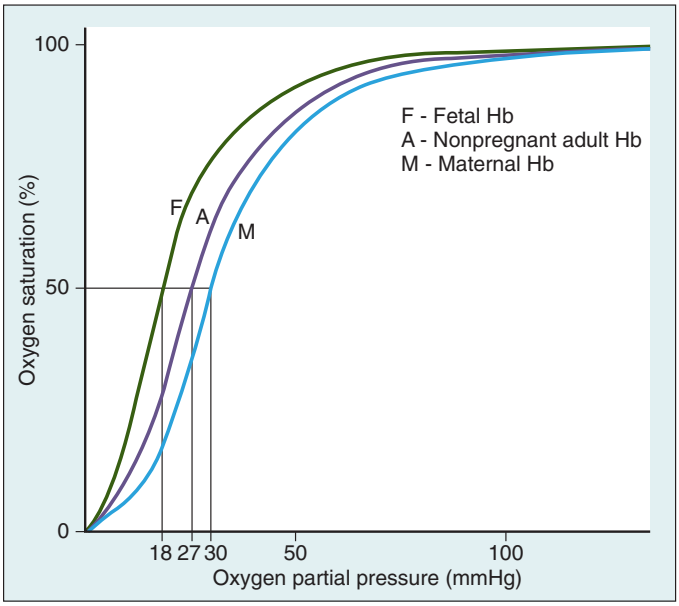
LVH, Left ventricular hypertrophy.

Data from Ain DL, Narula J, Sengupta PP. Cardiovascular imaging and diagnostic procedures in pregnancy. *Cardiol Clin.* 2012;30:331–341.

TABLE 37.4 Pulmonary Changes of Pregnancy

Pulmonary Component	Changes at Term (vs. Prepregnancy Values)
Minute ventilation	Increased 45%–50%
Tidal volume	Increased 40%–45%
Respiratory rate	Increased 0–15%
Oxygen consumption	Increased 20%
Lung capacities and volumes	
Total lung capacity	Decreased 0–5%
Vital capacity	No change
Functional residual capacity	Decreased 20%
Expiratory reserve volume	Decreased 20%–25%
Reserve volume	Decreased 15%–20%

Created and adapted from information from Cheek TG, Gutsche BB. Maternal physiologic alterations. In: Hughes SC, Levinson G, Rosen MA, et al., eds. *Shnider and Levinson's Anesthesia for Obstetrics.* 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2002:3–18; and Gaiser R. Physiologic changes of pregnancy. In: Chestnut DH, Wong CA, Tsen LC, et al. *Chestnut's Obstetric Anesthesia: Principles and Practice.* 5th ed. Philadelphia: Elsevier; 2014:15–38.



• **Fig. 37.2** Oxyhemoglobin dissociation curves. Plots are displayed relating the proportion of oxygen-saturated hemoglobin *(vertical axis)* to the oxygen tension in the blood *(horizontal axis).* Curves are shown for fetal *(F),* maternal *(M),* and nonpregnant adult *(A)* blood. The oxygen partial pressure at which the hemoglobin is 50% saturated (P_{50}) for each of these conditions is noted along the horizontal axis. Compared to nonpregnant adult blood, the relative right shift of the maternal curve and the left shift of the fetal curve illustrate the oxyhemoglobin binding relationships across the placenta that facilitate the transfer of oxygen from mother to fetus. *Hb,* Hemoglobin.

Minute Ventilation and Oxygenation

Minute ventilation is increased by 45% to 50% by the end of the first trimester to compensate for the increased oxygen demand and carbon dioxide production by the fetus and placenta. The respiratory rate is only minimally increased, whereas an increase in tidal volume contributes significantly to the increased minute ventilation. Despite a decrease in maternal arterial partial pressure of carbon dioxide ($PaCO_2$) to 30 mm Hg during the first trimester as a result of these respiratory changes, arterial pH is only slightly alkalotic, at 7.42 to 7.44, because of a compensatory increase in renal excretion of bicarbonate (HCO_3^- 20–21 mEq/L) at term. The increased maternal ventilation results in a room air arterial partial pressure of oxygen (PaO_2) slightly greater than 100 mm Hg early in gestation. However, later during the pregnancy, PaO_2 returns toward prepregnancy values secondary to small airway collapse and intrapulmonary shunting.

These respiratory changes occur during an increased maternal oxygen consumption of 20% at term. During the first stage of labor oxygen consumption increases 40% above term prelabor values, and during the second stage it increases 75% above prelabor values.

With pregnancy, there is an increase in the maternal oxygen partial pressure associated with 50% Hb saturation (P_{50}) from 27 mm Hg to 30 mm Hg as shown in Fig. 37.2. This right shift in the maternal Hb oxygen dissociation curve, combined with the relatively left-shifted fetal P_{50} of 18 mm Hg, facilitates oxygen transfer from the mother to the fetus.

Lung Volumes

As the uterus enlarges during pregnancy, the diaphragm is forced cephalad, resulting in similarly decreased expiratory reserve volume and residual lung volume. These changes cause a decrease in functional residual capacity (FRC) starting after the first trimester, with a 20% decrease in FRC present at term (see Table 37.4). Because closing capacity (CC) remains unchanged, there is a reduced FRC/CC ratio with more small airway closure, reduced lung volumes, and increased propensity for atelectasis in the supine position. Decreased FRC with increased minute ventilation results in a faster rate of alveolar gas exchange and a more rapid change in inhaled anesthetic concentration. Additionally, upon induction of general anesthesia, desaturation occurs more rapidly in a pregnant patient because of decreased oxygen reserve (decreased FRC) as well as increased oxygen consumption. Preoxygenation with 100% oxygen for 3 minutes or four maximal volume breaths immediately before induction is necessary to minimize the chance of significant hypoxia secondary to these physiologic changes.

Airway

Vascular engorgement of the oropharyngeal, laryngeal, and tracheal mucosa results in increased tissue friability and edema, thereby increasing the risk of bleeding with upper airway manipulation and difficulty in intubation and ventilation. Attempts at laryngoscopy should be minimized, and a smaller cuffed endotracheal tube (6.0–6.5 mm) should be used. Suctioning and placement of airways should be done with care to prevent bleeding, and nasal instrumentation should generally be avoided. In patients with preeclampsia, upper respiratory tract infections, and those who have been actively pushing in the second stage of labor, airway edema is often more severe as a result of increased venous pressure. Additionally, the weight gain and increased breast tissue make laryngoscopy more challenging. Positioning should be optimized before laryngoscopy, and backup airway equipment should be immediately available. A recent multiinstitutional database review found the rate of failed intubation for cesarean delivery with general anesthesia to be 1 : 533.[7]

Gastrointestinal Changes

Beyond midgestation the maternal stomach and pylorus are shifted cephalad by the enlarged uterus, thus repositioning the intraabdominal esophagus in the thoracic cavity and decreasing the competence of the esophageal sphincter. Progesterone and estrogen levels contribute to a reduced esophageal sphincter tone. Gastrin is secreted by the placenta, resulting in increased gastric hydrogen ion secretion and decreased gastric pH. These physiologic changes and the increased gastric pressure from the gravid uterus increase the frequency of acid reflux during pregnancy, the risk of aspiration of gastric contents, and development of acid pneumonitis upon induction of general anesthesia.[8] Additionally, gastric emptying is impaired with the onset of labor as well as with pain, anxiety, and opioid administration. The use of epidural local anesthetics alone does not slow gastric emptying, but the use of bolus doses of epidural fentanyl does.[9] Although delayed after delivery gastric emptying returns to prepregnancy function by 18 hours postpartum.[2]

Because of the delayed gastric emptying seen in labor, as well as the physiologic changes detailed above, all women in labor are considered to have a full stomach and are at increased risk for pulmonary aspiration of stomach contents upon induction of general anesthesia. Metoclopramide can significantly decrease gastric volume within 15 minutes of administration. However, prior opioid administration decreases this effect. Some physicians advocate for the use of H_2-histamine receptor blockers, which increase gastric pH within an hour in pregnant women. The combination of antacids and H_2-histamine receptor antagonists is more effective in reducing gastric pH than antacids alone or no pharmacologic intervention. Current American Society of Anesthesiologists guidelines for obstetric anesthesia state "…before surgical procedures (e.g., cesarean delivery or postpartum tubal ligation), consider the timely administration of nonparticulate antacids, H_2-receptor antagonists, and/or metoclopramide for aspiration prophylaxis."[4]

Hepatic and Gallbladder Changes

During pregnancy, aspartate aminotransferase, alanine aminotransferase, and bilirubin levels rise to the upper limits of normal, while plasma protein concentrations are reduced. The decreased protein concentrations can cause elevated free serum levels of highly protein-bound drugs. Alkaline phosphatase levels will double in pregnancy secondary to placental production. Of note, incomplete gallbladder emptying and changes in bile composition increase the risk of gallbladder disease during pregnancy. Although acute cholecystitis is not more common in pregnancy, gallstones are reported in 1% to 3% of pregnant patients and about 0.1% of pregnant patients develop acute cholecystitis.[10]

Butyrylcholinesterase (pseudocholinesterase), which is produced by the liver, is decreased in activity by 25% to 30% starting at the 10th week of gestation through 6 weeks postpartum. This decreased activity is not likely to cause a significant prolongation of neuromuscular blockade achieved with succinylcholine, although muscle strength should be thoroughly assessed before extubation.

Renal Changes

By the end of the first trimester, renal blood flow and glomerular filtration rate are increased by 50% to 60% and remain elevated for 3 months postpartum. The upper limits of blood urea nitrogen and serum creatinine values are about 50% lower during pregnancy, as the clearance of creatinine, urea, and uric acid is increased. Urine protein and urine glucose levels are often elevated from decreased renal tubular resorption capacity, and 300 mg protein or 10 g glucose in a 24-hour urine collection is considered the upper limits of normal during pregnancy.

Neurologic Changes

Pregnant women are considered to have a decreased minimum alveolar concentration (MAC) for inhalational anesthetics, as evidenced by a 40% MAC reduction in animal studies and a 28% MAC reduction in humans during the first trimester.[1,2,11,12] The etiology of this reduction in MAC is unknown but is potentially related to progesterone. In contrast to these findings, an electroencephalographic study suggests that anesthetic effects of sevoflurane on the brain are similar between pregnant and nonpregnant patients.[13] In addition, rates of intraoperative awareness are increased during cesarean delivery with general anesthesia compared with other general anesthesia cases, and reducing standard anesthetic levels in stable obstetric patients may not be prudent.[14]

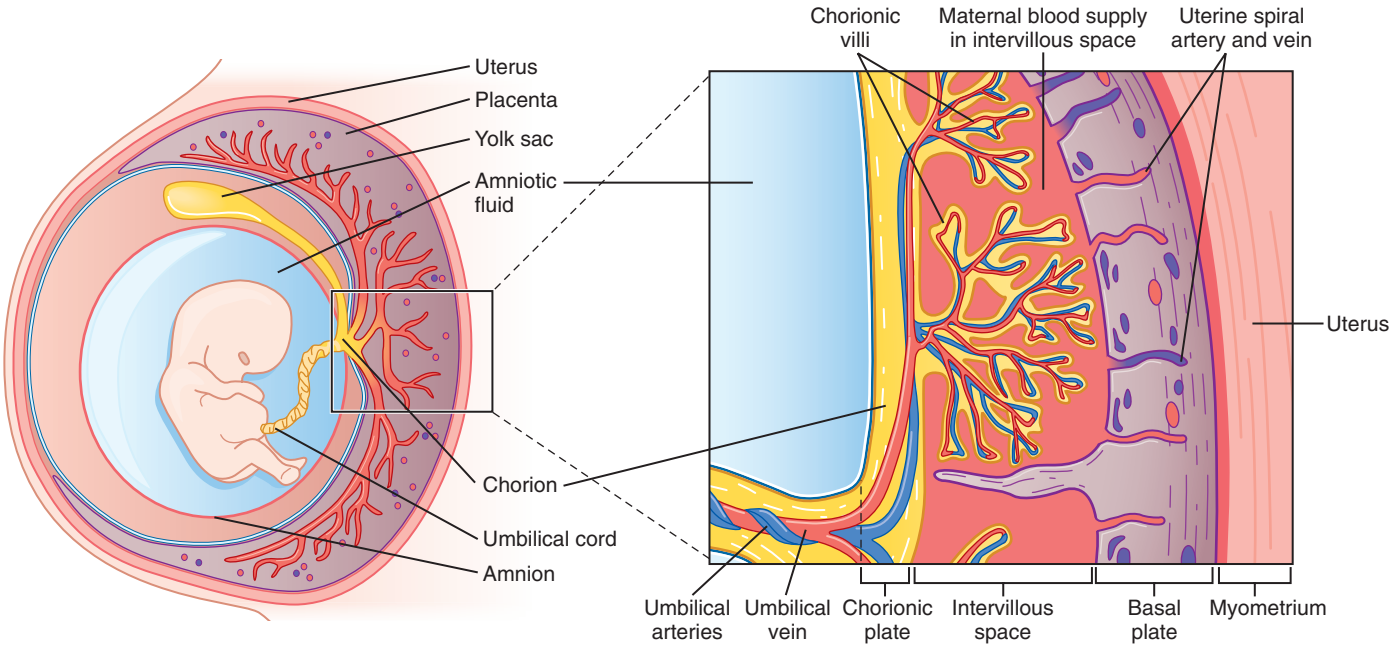
Pregnant patients are also more sensitive to local anesthetics, and a reduced amount is required for neuraxial anesthesia. Anatomic changes to the nervous system during pregnancy include engorgement of the epidural veins, decreased size of the epidural space, and decreased volume of cerebrospinal fluid. The lower volume of these spaces may result in greater spread of local anesthetics. However, research suggests that the decreased local anesthetic requirements observed during pregnancy occur in the first trimester, before significant anatomic changes in the neuraxial system are seen, suggesting a biochemical role for the increased nerve sensitivity. Cerebral spinal fluid pressure remains unchanged until labor, at which point it is increased with contractions and pushing in the second stage.

Uteroplacental Physiology

The placenta, composed of both maternal and fetal tissues, is the means by which physiologic exchange between mother and fetus occurs. It is made up of basal and chorionic plates separated by the intervillous space, into which maternal blood is delivered via the uterine arteries and then the spiral arteries as shown in Fig. 37.3. Two umbilical arteries return fetal blood to the placenta and then become umbilical capillaries that cross the chorionic villi. After placental exchange occurs at the chorionic villi, nutrient-rich and waste-free blood is returned from the placenta to the fetus via an umbilical vein.

Uterine Blood Flow

In the nonpregnant state, uterine blood flow is approximately 100 mL/min. At term, uterine blood flow reaches 700 mL/min, or about 10% of the cardiac output. At term, about 80% of uterine blood flow perfuses the intervillous spaces within the placenta, while the other 20% supports the myometrium. Autoregulation of uterine blood flow is minimal, as the uterine vessels are fully dilated throughout pregnancy. Therefore maternal cardiac output, uterine vascular resistance, and uterine perfusion pressure dictate uterine and placental blood flow. A decrease in systemic vascular resistance, from either general or neuraxial anesthesia, or maternal hypotension from aortocaval compression or hypovolemia, may result in a decreased placental perfusion pressure. In the absence of maternal hypotension, neuraxial anesthesia does not affect uterine blood flow. There may also be a decrease in uterine perfusion



• **Fig. 37.3** Placenta anatomy. Illustration of the placenta showing its structure and components of both fetal and maternal circulation. Maternal arterial blood flows to the uterine spiral arteries, fills the intervillous space, and contacts the fetal chorionic villi. Deoxygenated blood from the fetus flows through the umbilical arteries and branches into chorionic arteries (within the chorionic villi), where oxygen is transferred from the mother and the oxygenated blood returns to the fetus via the umbilical vein. Throughout this process, a placental barrier separates the maternal and fetal circulatory systems. (Modified from original at Anatomy & Physiology, Connexions Web site on Wikimedia Commons (https://commons.wikimedia.org/wiki/File:2910_The_Placenta-02.jpg).

pressure from venocaval compression in the supine position, prolonged or frequent contractions, prolonged Valsalva maneuver during pushing, or significant hypocapnia ($PaCO_2$ < 20 mm Hg) from hyperventilation associated with pain. Decreases in uterine perfusion may result in placental hypoperfusion and cause fetal hypoxemia and acidosis.

Placental Exchange

Oxygen Transfer

In addition to uterine and fetal blood flow, oxygen delivery from mother to fetus is affected by the oxygen partial pressure gradient, diffusion capacity of the placenta, acid-base status of maternal and fetal blood (Bohr effect), and maternal and fetal Hb concentrations and oxygen affinities. Fetal Hb has a greater affinity for oxygen compared with maternal Hb, as shown in Fig. 37.2. These differences create an oxygen transfer gradient to the fetus. The oxygen delivery to the fetus is primarily dependent on the rate of blood flow on each side of the placenta rather than barriers to diffusion. Fetal PaO_2 is typically 20 to 40 mm Hg[15] but can reach up to 60 mm Hg if the mother is breathing 100% oxygen,[16] although typical fetal tissue arterial Hb saturation remains below 65% even with maternal inspired oxygen near 100%.[17,18] This is the maximal fetal PaO_2 because a substantial amount of oxygen is extracted from maternal blood before arrival at the fetoplacental unit. Concern has been expressed for potential fetal harm from generation of free radicals based on chemical markers in the fetal umbilical circulation with maternal hyperoxia.[19,20] However, further studies have noted this concern to be unwarranted, with free radical activity independent of inspired oxygen, but dependent on the labor course and mode of delivery.[21–24] In the setting of decreased oxygen delivery to the fetus, fetal oxygen consumption is maintained by increased oxygen extraction until maternal oxygen delivery is approximately 50% of expected.[25,26] In cases of nonreassuring fetal heart rate patterns, use of maternal supplemental oxygen has been demonstrated to significantly increase fetal oxygenation (based on fetal pulse oximetry)[27] and is likely beneficial, but no randomized clinical trials have addressed the use of maternal oxygen treatment for fetal distress.[28,29]

Drug Transfer

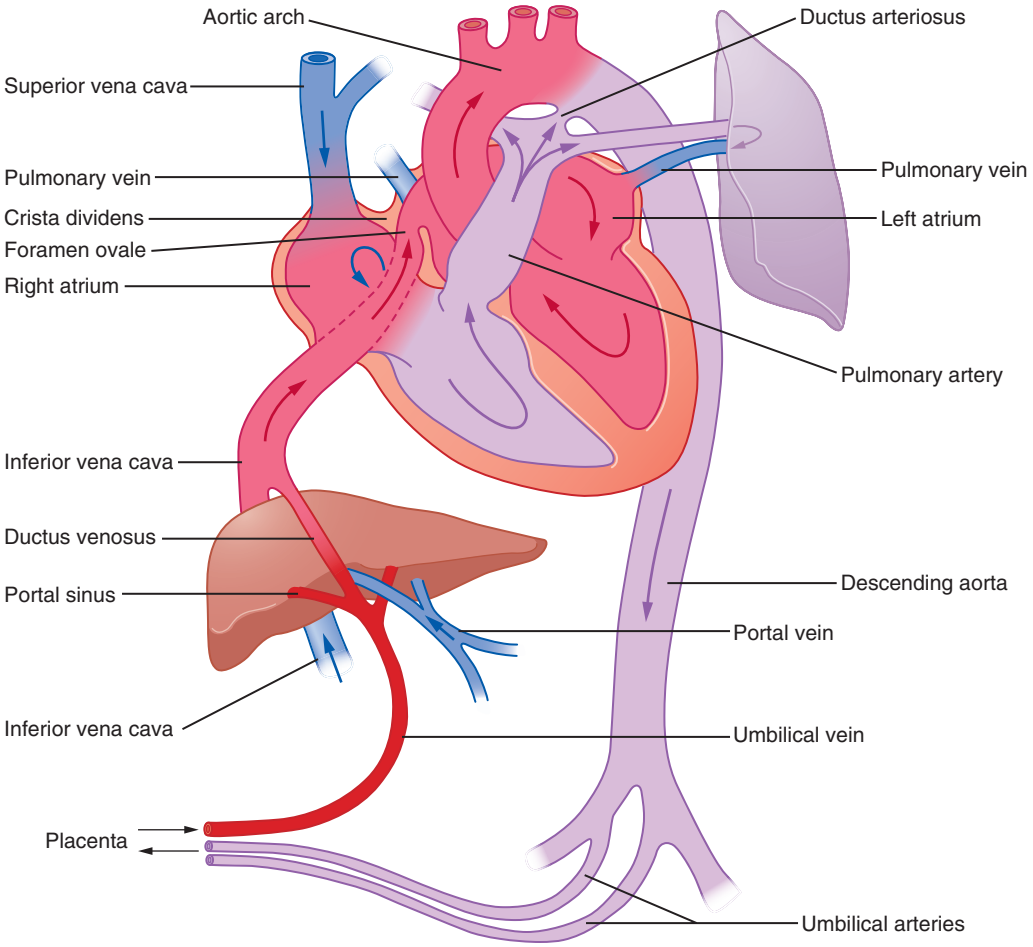
Drugs and other molecules in the maternal circulation smaller than approximately 1000 Da are primarily exchanged with the fetus by diffusion. The rate of transfer depends on maternal-to-fetal concentration gradients, maternal protein binding, molecular weight, lipid solubility, and ionization. The degree of fetal transfer for a specific drug is typically presented as a ratio of concentration in the umbilical vein to the maternal artery. Although all drugs transfer across the placenta to some degree, a few are significantly limited. Nondeloparizing neuromuscular blockers have high molecular weights and are poorly lipid-soluble, thus limiting their capacity for crossing the placenta and reaching the fetus. Succinylcholine has a low molecular weight but is also highly ionized and poorly lipid-soluble, which limits its ability to cross the placenta unless given in large doses. Similarly, unfractionated heparin, low-molecular-weight heparins, and glycopyrrolate are highly ionized and do not cross the placenta in significant amounts. In contrast, volatile anesthetic agents, benzodiazepines, local anesthetics, and opioids all have relatively low molecular weights and readily cross the placenta.

Fetal blood has a lower pH than maternal blood. When weakly basic drugs, such as local anesthetics and certain opioids, cross the placenta in a non-ionized state, they can become ionized in the relatively acidic fetal circulation. These newly ionized molecules are unable to readily diffuse back to the maternal circulation via the placenta, thus accumulating in the fetal circulation and potentially reaching levels higher than the maternal concentration. This is called "ion trapping" and can be more extreme during fetal distress, when the fetal pH is lower than normal. Unintended intravascular injection of local anesthetics can cause extremely high fetal concentrations of these drugs, which may result in bradycardia, ventricular arrhythmias, acidosis, and severe cardiac depression. The upcoming sections "Labor Analgesia" and "Anesthesia for Cesarean Delivery" further discuss placental transfer and fetal uptake considerations of specific agents.

Fetal Circulation and Physiology

Fetal circulation is significantly different from that of a newborn (Fig. 37.4).[15] Oxygen-rich blood from the placenta passes through the umbilical vein directly to the fetal liver, where the circulation splits and flows into both the ductus venosus (20%–30% of flow) and portal sinus circulation. It then passes into the inferior vena cava and enters the right atrium. The majority of this blood flows through the foramen ovale, into the left atrium, then the left ventricle, and empties into the aorta (a small portion travels through the pulmonary arteries to perfuse lung tissue). This shunted portion traveling through the foramen ovale has the highest oxygen levels and directly perfuses the brain (carotid arteries) and heart (coronary arteries). Fetal deoxygenated blood returning from the superior vena cava and lower extremities is directed toward the right ventricle and pulmonary trunk. The majority of this blood flow passes through the ductus arteriosus, into the descending aorta, and perfuses the lower extremities and hypogastric arteries. Deoxygenated fetal blood returns to the placenta via two umbilical arteries.

Two-thirds of fetal blood volume is within the placenta. During the second and third trimesters, the fetal blood volume is approximately 110 to 160 mL/kg, and after midgestation can be estimated



• **Fig. 37.4** The fetal circulation is arranged to allow oxygen-rich blood from the placenta to initially flow to the liver, where it divides to either the portal sinus or ductus venosus and then enters the right atrium via the inferior vena cava. The bulk of this blood passes through the foramen ovale, into the left atrium, then the left ventricle, and empties into the aorta (directly perfusing the brain and heart). Although this majority of flow bypasses the fetal lungs, a small portion does perfuse the lung tissue via the pulmonary arteries. Deoxygenated blood from the superior vena cava and lower extremities is directed toward the right ventricle and pulmonary trunk. The majority of this blood flow passes through the ductus arteriosus, into the descending aorta, and perfuses the lower circulation. See text for additional detail. *RUQ,* Right upper quadrant. (Modified from Murphy JP. The fetal circulation. *Continuing Education in Anaesthesia Critical Care & Pain,* 2005;5:107–112.)

from GA: Estimated fetal blood volume (mL) = 11.2 × GA − 209.4.[30,31] Hemoglobin F (HbF) is the primary oxygen carrier in the developing fetus, with a gradual shift from HbF to adult Hb (HbA) production starting at 32 weeks' gestation.[32] Hb levels in the fetus typically increase from 11 g/dL (17 weeks GA) to about 18 g/dL in a term newborn.[33,34]

The fetal heart rate is the primary determinant of fetal cardiac output, as the fetal myocardium is less compliant than adult myocardium, operating near the upper end of the Frank-Starling curve and less responsive to changes in preload.[35] Normal fetal cardiac output is 425 to 550 mL/kg/min throughout gestation.

The fluid-filled lungs of the fetus may potentially impair ventricular filling, thus preventing an increase in cardiac output after an increase in preload.[36] Fetal lung epithelium produces more than 100 mL/kg per day of fluid that facilitates pulmonary development. This pulmonary fluid leaves via the trachea and is either swallowed by the fetus or becomes part of the amniotic fluid.

The immature fetal liver is able to synthesize coagulation factors, the concentration of which increases with GA. These coagulation factors do not cross the placenta into maternal circulation, and are not as effective at clot formation compared with those factors found in adults. About 75% of umbilical venous blood initially passes through the fetal liver. Drugs in the umbilical blood thus undergo initial hepatic metabolism (first-pass metabolism) before these substances reach the fetal brain or heart. Although these fetal metabolic enzymes are less functional that those of adults, most drugs are still significantly metabolized. Additionally, drugs entering the fetal circulation enter the inferior vena cava via the ductus venosus. This blood is mixed with the venous blood returning from the lower extremities and pelvic viscera of the fetus, thus further diluting any concentrations of drugs passed through the placenta.

By 18 weeks' gestation, the fetus exhibits a neuroendocrine stress response to noxious stimuli.[37] This response occurs at the level of the spinal cord and brainstem, as thalamocortical connections necessary for the perception of pain are not present until after 24 to 26 weeks' gestation.[38,39] During fetal surgery, opioids are directly administered to the fetus to decrease the physiologic stress from the procedure.

Preeclampsia

Preeclampsia is a pathophysiologic disease specific to pregnancy that affects approximately 5% of pregnant women in the United States. Although the exact underlying cause remains unknown, it is characterized by endothelial dysfunction and an upregulation of cytokines. These changes affect the physiology of all organ systems and is associated with numerous maternal and fetal complications. Diagnostic criteria for preeclampsia with and without severe features are shown in Fig. 37.5.

Anesthetic management of preeclampsia centers on minimizing end-organ dysfunction, preparing for potential deterioration of the mother's condition, and optimizing fetal delivery. Two primary areas of intervention for women with preeclampsia with severe features include blood pressure control and seizure prophylaxis. Current guidelines recommend urgent treatment for systolic blood pressure above 160 mm Hg to prevent hemorrhagic stroke.[40] Medications for acute blood pressure control include intravenous (IV) labetalol, IV hydralazine, and oral nifedipine.[41]

Other critical components of preeclampsia management includes seizure prophylaxis with magnesium sulfate. Data and cost-effectiveness research support magnesium sulfate for seizure prophylaxis in patients with a diagnosis of preeclampsia with severe features (see Fig. 37.5).[40] Magnesium sulfate is administered by loading 4 to 6 g IV over 20 to 30 minutes with a continued infusion of 1 to 2 g/hr. Magnesium sulfate should be continued intrapartum, including during cesarean delivery, and until 24 hours postpartum. Prophylactic magnesium sulfate decreases rates of eclampsia by more than half, but it is associated with a wide range of side effects, including nausea/vomiting, slurred speech, muscle weakness, hypotension, dizziness, drowsiness, and headache. Magnesium can also potentiate both depolarizing and nondepolarizing muscle relaxants and augments uterine and smooth muscle relaxation. Serum plasma levels should be monitored when a patient is receiving magnesium sulfate therapy (Table 37.5). Treatment of magnesium toxicity includes discontinuation of the infusion and administration of IV calcium gluconate (1 g). Although not related to preeclampsia, administration of magnesium sulfate can reduce the risk of cerebral palsy if there is a concern for preterm delivery.[42]

TABLE 37.5 Magnesium Sulfate Effects

MAGNESIUM LEVEL (MG/DL)	
1.7–2.4	Normal range
5–9	Therapeutic range
12	Patellar reflexes lost
15–20	Respiratory arrest
>25	Cardiac arrest

Pharmacology

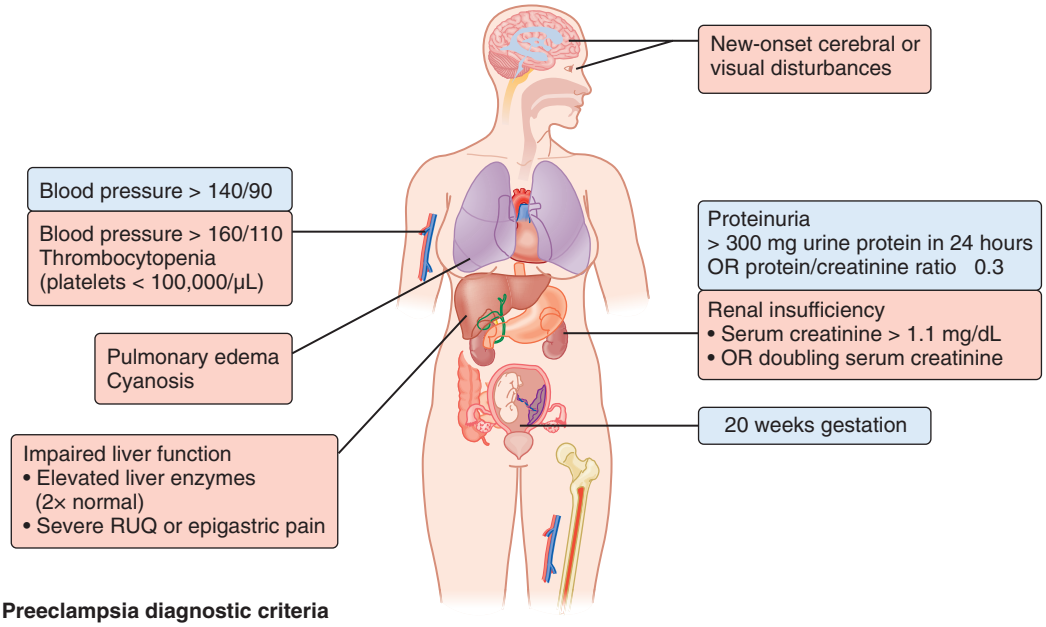
Labor Analgesia

Pain arising during labor is carried by somatic and visceral afferent sensory fibers to the spinal cord. During the first stage of labor (the period of cervical dilation), pain arises from afferent nerve fibers within the lower uterine segment and cervix and travels to the dorsal root ganglia of levels T10 to L1. As labor progresses to the second stage (pushing through delivery of the fetus), the pudendal nerve carries afferent pain signals from the vagina and perineum to the dorsal root ganglia of S2 to S4. Consequently, neuraxial labor analgesia must be effective from the T10 to L1 levels during the first stage of labor and also include the S2 to S4 levels during the second stage of labor.

Neuraxial Labor Analgesia

Neuraxial Local Anesthetics

Local anesthetics reversibly impede action potential conduction by blocking voltage-gated sodium channels. When administered neuraxially, they vary in their onset time, peak plasma concentrations, potency, and duration of action based on their lipid solubility, protein binding, and concentration. Many local anesthetics can be used for epidural analgesia, but the most common include bupivacaine and ropivacaine. These are selected because of a longer duration of action and favorable ratio of sensory to motor blockade. Lidocaine and 2-chloroprocaine are typically used for surgical obstetric anesthesia instead of labor analgesia. Dilute concentrations



Preeclampsia diagnostic criteria

Hypertension		Proteinuria
• 140 mmHg systolic or 90 mmHg diastolic on at least two occasions at least 4 hours apart after 20 weeks' gestation		• 300 mg per 24-hour urine collection • Protein/creatinine ratio 0.3 mg/dL • Dipstick reading of 1+ (if other quantitative methods unavailable)
		OR
Severe feature • 160 mm Hg systolic or 110 mm Hg diastolic, confirmed within short interval	**AND**	**Severe features** • Thrombocytopenia (platelets < 100 × 10^9/L) • Renal insufficiency (serum creatinine > 1.1 mg/dL or 2× serum creatinine concentration in the absence of other renal disease) • Impaired liver function (2× normal liver transaminase concentration and/or severe persistent right upper quadrant/epigastric pain that does not improve without medication and has no other etiology) • Pulmonary edema • Cerebral/visual symptoms/changes

• **Fig. 37.5** Preeclampsia features and diagnostic criteria. Preeclampsia results in significant changes in every organ system and is diagnosed when new-onset hypertension after 20 weeks' gestation (element of left column) and either proteinuria or a severe feature (noted in *red*) in the left column are present. If the patient has preeclampsia and displays any red criteria listed in a shaded area of the figure, the patient has preeclampsia with severe features. (Adapted from Hypertension in Pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol.* 2013;122:1122–1131.)

of bupivacaine (0.04%–0.125%) and ropivacaine (0.0625%–0.2%) are used for labor analgesia to allow larger volumes of administration, reduce motor block, and minimize the dose-dependent hypotension secondary to sympathetic blockade. Epidural veins, engorged secondary to impaired lower extremity venous return, are more vulnerable to unintentional epidural catheter placement, which may lead to accidental intravascular local anesthetic delivery. This systemic delivery of local anesthetic could lead to local anesthetic systemic toxicity (LAST), which can result in hemodynamic collapse, seizures, and death. In an attempt to prevent this, a small, nontoxic "test dose" of local anesthetic and epinephrine is administered before bolus dosing of an epidural, with the aim to detect unintended intravascular placement of an epidural catheter. Fortunately, the doses of bupivacaine and ropivacaine typically used for labor analgesia are small enough that cardiotoxicity is a rare event. If maternal blood concentrations of local anesthetic become substantially elevated, such as from an intravascular injection, significant fetal toxicity may also result, causing fetal bradycardia and cardiac depression.

Local Anesthetic Systemic Toxicity (LAST)

If LAST occurs, immediate implementation of Advanced Cardiac Life Support (ACLS) measures and administration of lipid emulsion is critical to increasing the chances of a favorable outcome.[43] The hypothetical mechanism of action for lipid emulsion therapy includes both the creation of a "lipid sink" that extracts the

circulating lipophilic toxin (e.g., bupivacaine) and reduces the unbound free toxin that binds to the myocardium, as well as direct cardiotonic effects.[44] It is administered as an initial IV bolus of 20% lipid emulsion 1.5 mL/kg over 1 minute while an infusion of 0.25 mL/kg/min is simultaneously initiated. Up to two repeat boluses of the same initial dose may be administered, and the infusion may be increased to 0.5 mL/kg/min if the patient remains hemodynamically unstable or adequate circulation deteriorates.[45] The dosing limit is 12 mL/kg. To optimize the efficacy of the lipid emulsion and tissue perfusion during treatment of LAST, the American Society of Regional Anesthesia and Pain Medicine guidelines recommend modifications to ACLS protocols that include avoidance of vasopressin, calcium channel blockers, β blockers, lidocaine, and incremental bolus dosing of epinephrine starting at 1 μg/kg or less.[45]

In addition to epidural administration via catheter throughout labor, local anesthetics can also be administered intrathecally, either as a single injection using a spinal needle or, less frequently, via an intrathecal catheter. A single injection of local anesthetic may be administered before epidural catheter placement in a combined spinal epidural technique. During this procedure, a small dose of local anesthetic (e.g., 2.5 mg bupivacaine) and/or opioid (e.g., 15 μg fentanyl) are administered via a spinal needle that has been inserted into the cerebrospinal fluid through the epidural needle. This technique is associated with a more rapid onset of pain relief, a lower rate of epidural catheter failure, and an increased rate of nonreassuring fetal heart rate tracings.[46–48] However, the technique is not associated with an increase in the rate of post-dural puncture headaches, and the dural puncture itself without injection of intrathecal medications improves the quality of the labor analgesia.[49]

Neuraxial Opioids

The analgesic effect secondary to epidural administration of lipid-soluble opioids, such as fentanyl or sufentanil, is not as profound as that seen with local anesthetics. However, when opioids are epidurally administered in conjunction with local anesthetics, the total local anesthetic dose required and the minimum local anesthetic concentration needed to attain adequate labor analgesia are significantly reduced. Common side effects of neuraxial opioids are dose-dependent and include pruritus, nausea, and sedation. These side effects are generally mild in standard doses for labor analgesia (e.g., fentanyl 2 μg/mL local anesthetic) and do not adversely affect the fetus.

Intrathecal opioids are more potent than epidural or systemic opioids and are most often administered during placement of a combined spinal epidural. They are typically combined with small doses of local anesthetic, thus decreasing the necessary dose as well as the side effects of the opioid.[50] Use of large doses of intrathecal opioids (e.g., 7.5 μg sufentanil) as a sole agent is associated with higher rates of maternal pruritus and fetal bradycardia, even without maternal hypotension.[51] The cause of the fetal bradycardia is unknown but may be related to uterine hyperactivity.

Neuraxial Adjuncts

Agents other than opioids can be administered epidurally to help with labor pain management. Low-dose **epinephrine** (2–5 μg/mL) when added to bupivacaine results in lower pain scores when compared with bupivacaine or ropivacaine alone. Similarly, low-dose **clonidine** (2 μg/mL) improves labor analgesia but also results in lower maternal blood pressures, the clinical significance of which is unclear.[52,53] Importantly, the U.S. Food and Drug Administration (FDA) has issued a "black box" warning regarding the concern of maternal hypotension secondary to neuraxial clonidine administration for labor pain relief. Studies have examined neuraxial neostigmine and dexmedetomidine as possible adjunctive agents, but these are not in regular use at this time in the United States. Epidural and intrathecal neostigmine reduce the amount of bupivacaine and ropivacaine needed for labor and postoperative analgesia after cesarean section, but intrathecal neostigmine increases the rates of maternal nausea.[54] **Dexmedetomidine** (0.5 μg/kg) when bolused with ropivacaine in labor epidurals results in significantly lower maternal pain scores, as well as lower maternal blood pressure and heart rate, when compared with ropivacaine alone, but it is also not currently in regular clinical use.[55]

Parenteral Opioid Labor Analgesia

More than half of laboring women in the United States receive systemic opioids at some point during their labor, making this mode of analgesia quite common. Despite moderate maternal satisfaction, systemic opioids are associated with adverse effects such as nausea, itching, drowsiness, and respiratory depression. Of note, all systemic opioids cross the placenta. Therefore smaller doses of opioids with minimal active metabolites are preferred, whereas higher doses or longer-acting opioids can cause negative fetal and neonatal side effects, especially if given close to the time of delivery.[56] Typically, labor and delivery units use regimented dosing schedules that limit the amount, frequency, and timing of opioid dosing in an attempt to limit these negative fetal effects.

Numerous opioids have been used for labor analgesia, including meperidine (pethidine), morphine, fentanyl, sufentanil, remifentanil, butorphanol, and nalbuphine. These medications vary widely with regard to the pharmacokinetics, pharmacodynamics, method of elimination, and metabolism. In addition, maternal and fetal effects vary greatly secondary to dosing.

The most commonly used opioid worldwide during labor is **meperidine**, which is metabolized to normeperidine, an active metabolite. The maternal half-life of normeperidine is 2 to 3 hours, and the fetal half-life is more than 12 hours. Repeated administration of meperidine in labor places the fetus at increased risk for decreased Apgar scores, depressed respiratory effort, lower oxygen saturation, abnormal neurobehavior, and difficulty breastfeeding after delivery.[57]

Fentanyl is frequently used in the United States secondary to its short duration of action and lack of active metabolites. When administered in small divided IV doses (50–100 μg in an hour), there are no significant effects on newborn assessment measures or breastfeeding compared with mothers who did not receive fentanyl in labor. In addition, fentanyl is associated with less neonatal respiratory compromise compared with the use of meperidine in labor.[56,58] Although inferior to epidural anesthesia, patient-controlled analgesia (PCA) dosing of IV fentanyl is occasionally used for patients with contraindications to epidural catheter placement. A retrospective examination of neonatal effects of PCA fentanyl for labor analgesia noted a positive correlation between total maternal fentanyl dose and neonatal depression, despite termination of fentanyl administration approximately 20 minutes before delivery.[59]

Use of a **remifentanil** PCA in labor provides another systemic opioid analgesic option for labor analgesia. Its ultrashort period of action has the potential to allow a greater level of analgesia while minimizing neonatal opioid side effects. However, remifentanil levels that create satisfactory labor analgesia are associated with increased risk of maternal respiratory depression, and its use requires a higher level of maternal monitoring and nursing supervision.[60] A small retrospective study comparing PCA remifentanil and PCA

fentanyl for labor analgesia demonstrated a greater rate of maternal desaturation (oxygen saturation by pulse oximetry <90%) with remifentanil (13% vs. 2%), but all desaturation episodes were transient and reversed with supplemental oxygen or patient arousal.[61] Use of PCA fentanyl created a greater need for either neonatal ventilation or neonatal supplemental oxygen. Although clinically effective, use of PCA remifentanil for labor analgesia provided inferior pain and satisfaction scores compared with epidural analgesia.[62] In most centers, its use is reserved for patients with contraindications to epidural labor analgesia.

Inhaled Nitrous Oxide for Labor Analgesia

Nitrous oxide is an odorless, colorless inhalational agent with low blood solubility. It undergoes minimal (<1%) metabolism, with 99% being exhaled unchanged. These characteristics make nitrous oxide a reasonable option for management of labor pain, as it reaches peak effect quickly, is rapidly eliminated through respiration, and its effects are predictable regardless of most other medical comorbidities. It has a desirable safety profile when the following conditions are met: it is used at a 50% concentration and blended with oxygen, it is self-administered by the laboring patient without the mask fastened to her face or held by another individual, and it is not used in combination with other sedating medications, such as benzodiazepines, opioids, barbiturates, or scopolamine.[56]

The mechanism by which nitrous oxide reduces labor pain is not thoroughly understood, but some data suggest that endogenous endorphins, corticotrophins, and dopamine are released from the midbrain and dorsal horn with administration of nitrous oxide. A substantial portion of the benefit from nitrous oxide comes from its ability to relieve anxiety, decrease awareness of pain, improve labor tolerance, and provide a sense of control through self-administration, as opposed to direct analgesia.[63] Peak effect occurs approximately 45 seconds after initiation (5 or 6 breaths), so patients should be instructed to begin nitrous oxide inhalation before the anticipated contraction. Alternatively, they may breathe it for continuous periods of time, which has been shown to provide more effective labor pain relief than intermittent use with contractions. Because of its rapid respiratory elimination, the effects of nitrous are quickly diminished after the mask is removed. Its use may be continued into the second stage of labor.

Side effects are generally mild and include nausea (5% to 13%), dizziness (3% to 5%), dysphoria (5% to 10%), and drowsiness (4%).[64] When used at 50% concentration, fewer than 0.5% of patients experience a temporary loss of consciousness. However, if the nitrous concentration is increased to greater than 75% and administered in combination with other sedatives, this rate can increase to more than 75% and poses a risk for hypoxia and aspiration.

Nitrous oxide has only a few notable contraindications to administration: (1) patients with impaired consciousness or who are otherwise unable to hold the face mask; (2) those with vitamin B_{12} deficiency or decreased cobalamin function; (3) those who have prior dysphoric reactions to nitrous oxide; and (4) patients with areas of potential gas space (unrecognized pneumothorax, recent craniotomy, bowel obstruction, recent middle ear surgery).

Anesthesia for Cesarean Delivery

Cesarean deliveries are routinely performed with neuraxial anesthesia when there are no contraindications. Advantages over general anesthesia include avoidance of aspiration and difficult intubation risks associated with maternal airway management, maternal participation in the birth of the fetus, minimization of anesthetic exposure to the fetus, and administration of neuraxial opioids for postoperative pain management. In an emergent setting, such as fetal bradycardia or uterine rupture, general anesthesia is used because of its rapidity and reliability. Similarly, when neuraxial anesthesia is contraindicated, such as with bleeding disorders, general anesthesia is used. This is a safe option for cesarean delivery and provides the benefits of a secure airway, controlled ventilation, and the potential for less hemodynamic instability.

Neuraxial Anesthesia for Cesarean Delivery

Spinal Anesthesia for Cesarean Delivery

Spinal anesthesia is typically used for planned elective cesarean delivery or for cesarean delivery in a stable laboring patient without an epidural. A typical spinal anesthetic consists of hyperbaric bupivacaine (10–15 mg) with preservative-free morphine (50–200 μg) for postoperative pain control, but a wide range of other local anesthetics, opioids, and adjuncts can be used. This small dose of local anesthetic does not carry the risk of systemic toxicity, has a rapid onset, and provides reliable surgical anesthesia from the midthoracic level to the sacrum for 90 minutes. Although maternal hypotension is more likely with spinal rather than epidural anesthesia because of the rapid sympathectomy, this method may still be used in patients with preeclampsia. Importantly, administration of a crystalloid co-load or colloid bolus, left uterine displacement, and vasopressors can minimize this spinal-induced hypotension.[65] Ephedrine had been used as the primary vasopressor for treatment of neuraxial sympathectomy–induced maternal hypotension based on sheep studies, but recent human data have suggested that phenylephrine for treatment or prevention of neuraxial-induced hypotension is effective and associated with less fetal acidosis and base deficit than ephedrine.[66] Most recently, norepinephrine has been demonstrated to provide effective prevention of hypotension during cesarean delivery with neuraxial anesthesia with less maternal bradycardia and improved cardiac output.[67,68]

Epidural Anesthesia for Cesarean Delivery

Epidural anesthesia for cesarean section is frequently used when a laboring patient already has an epidural in place for labor pain management. This technique is also selected in patients who are unlikely to tolerate the rapid sympathectomy associated with spinal anesthesia because of an underlying comorbidity. Use of an epidural catheter allows the gradual titration of neuraxial anesthesia. Additionally, if the procedure is likely to take longer than the predicted duration of a spinal anesthetic, an epidural can be redosed intraoperatively to extend the period of anesthesia. Although achieving a surgical block is slower with an epidural versus a spinal, it is possible to extend a T10 block for labor analgesia to a T4 surgical block in about 5 to 7 minutes using alkalinized 3% 2-chloroprocaine or alkalinized 2% lidocaine. If the epidural catheter was previously unused, it will take closer to 10 to 15 minutes to achieve a surgical block. Volumes of local anesthetic typically needed range from 10 to 20 mL. Unfortunately, the rate of failure to convert a labor epidural to use in a cesarean delivery is not insignificant, with an average rate of 7.7% in a literature meta-analysis.[69] Epidural adjuncts can be used to significantly improve block quality, such as epinephrine (5 μg/mL), fentanyl (50–100 μg), or sufentanil (10–20 μg). Epidural morphine (1.5–3 mg) is often administered for postoperative pain control.

General Anesthesia for Cesarean Delivery

General anesthesia is an appropriate choice for cesarean delivery in certain circumstances, such as when emergent delivery is required

or there are contraindications to neuraxial anesthesia. Although it is still a safe option for providing anesthesia, the relative risk of general anesthesia is 1.7 times that of neuraxial anesthesia, with two-thirds of the mortality from general anesthesia associated with intubation failure or induction difficulties.[70]

After preoxygenation and denitrogenation of the lungs, rapid sequence induction of general anesthesia using an IV induction agent as well as a rapidly acting muscle relaxant is carried out. Volatile anesthetics are frequently used to maintain general anesthesia before delivery, but then are reduced or eliminated after delivery to minimize uterine atony from inhaled anesthetic agents. Other agents that do not affect uterine tone (e.g., propofol, opioids, benzodiazepines, and muscle relaxants) are then frequently administered after delivery to prevent newborn depressive effects and obtain a more balanced anesthetic.

Induction Agents

Propofol has a rapid onset and is highly lipid and crosses the placenta with an umbilical vein/maternal artery ratio of 0.7 at delivery. However, at maternal induction does of 2.5 mg/kg or less, propofol has no significant effect on neonatal behavior scores, which may be attributable to maternal redistribution, fetal first-pass metabolism, or dilution by the fetal circulation and higher fetal brain water content. Larger or repeated dosing before delivery (e.g., 9 mg/kg) is associated with neonatal depression.

Etomidate also provides a quick onset of anesthesia because of its high lipid solubility. Although it easily crosses the placenta, its rapid hydrolysis and redistribution result in a short duration of action. Etomidate has minimal effects on the cardiovascular system, can cause involuntary muscle spasms, can increase the risk of seizures in patients at risk, and increases the incidence of nausea and vomiting. Notably, induction doses of etomidate (0.3 mg/kg) can result in decreased neonatal cortisol production, but the clinical significance of this is unknown.

Ketamine functions as an amnestic, hypnotic, and analgesic. It has minimal respiratory depressant effects and acts as a sympathomimetic, thus increasing arterial pressure, heart rate, and cardiac output. Because of these characteristics, ketamine, similarly to etomidate, is an appropriate choice for a patient with hemodynamic compromise. Standard induction doses (e.g., 1.5 mg/kg) do not cause neonatal depression. However, large doses can cause uterine hypertonia, which may result in decreased uterine perfusion.

Inhaled Anesthetics

Nitrous oxide is often used as a component of maintenance for general anesthesia, as it has minimal effects on maternal hemodynamics or uterine tone. It rapidly crosses the placenta, but the effects of nitrous oxide on neonates is negligible.

Isoflurane, sevoflurane, and desflurane are all non-ionized agents, lipid-soluble, have a low molecular weight, and therefore easily cross the placenta. Fetal concentration depends on maternal concentration and duration of exposure. Although general anesthesia is typically used when an emergent cesarean delivery is required (e.g., profound fetal bradycardia), neonatal depression after delivery is more likely due to compromised fetal status as opposed to exposure to inhalational anesthetics. If the depressed status of a neonate is secondary to anesthetic medications, the newborn should rapidly improve with basic ventilation and standard resuscitation measures. If no improvement is noted, other causes of their depressed status should be investigated.

A Cochrane review examined fetal outcomes after uncomplicated cesarean delivery with neuraxial or general anesthesia. "No significant difference was seen in terms of neonatal Apgar scores of six or less and of four or less at five minutes and need for neonatal resuscitation."[71] See "Emerging Developments" for further discussion of the potential impact of general anesthesia during pregnancy.

Muscle Relaxants

Succinylcholine is frequently used with general anesthesia in obstetric patients, as it has a rapid onset and short duration. Intubating conditions can be achieved with doses of 1 to 1.5 mg/kg with minimal medication crossing the placenta, as succinylcholine is highly ionized and hydrophilic. Larger doses of 2 to 3 mg/kg may result in detectable levels of succinylcholine in the umbilical cord. Although levels of Butyrylcholinesterase (pseudocholinesterase), the enzyme that hydrolyzes succinylcholine, are decreased during pregnancy, neuromuscular blockade is not significantly prolonged. Side effects are the same as those seen in the nonpregnant population and include increased maternal potassium levels and myalgia. Like halogenated anesthetic gases, succinylcholine is a known triggering agent for malignant hyperthermia.

Rocuronium is a potential induction alternative to succinylcholine. This fast-acting nondepolarizing agent achieves intubating conditions in 60 to 90 seconds when used at doses of 1.2 mg/kg. However, the duration of action of rocuronium is much longer than that of succinylcholine, which can be a safety concern if one is unable to ventilate or intubate the patient.

Maintenance of muscular relaxation is normally not required for cesarean delivery but can be achieved using a variety of nondepolarizing neuromuscular blockers, such as rocuronium, vecuronium, *cis*-atracurium, and so on. As a class, these medications are highly ionized and poorly lipid-soluble, and therefore they do not cross the placenta in significant amounts when given within normal dosing parameters. When extremely large and repeated doses are used, neonatal neuromuscular blockade may be seen secondary to these medications crossing the placenta.

Reversal Agents

Reversal of a nondepolarizing muscle relaxant should be considered at the end of every cesarean delivery performed with general anesthesia and muscular relaxation. Standard options include coadministration of **glycopyrrolate** and **neostigmine** for reversal of neuromuscular blockade. If administered at the completion of a cesarean delivery, placental transfer of these drugs is irrelevant. If these medications are administered to a pregnant patient undergoing nonobstetric surgery, however, placental transfer must be considered. Glycopyrrolate, an ionized quaternary ammonium compound, is poorly transferred across the placenta. Neostigmine is also an ionized quaternary ammonium compound, but it is smaller than glycopyrrolate and more capable of crossing the placenta. Although this combination is frequently administered to pregnant women for reversal without adverse effect, there have been case reports of profound fetal bradycardia when glycopyrrolate and neostigmine were coadministered.[72] Consequently, it has been suggested that neostigmine be administered with atropine to pregnant women.

Sugammadex has been used safely for reversal of neuromuscular blockade with rocuronium after completion of cesarean deliveries.[73] There have been no studies regarding the placental transfer or safety of sugammadex during pregnancy in humans. According to the pharmaceutical package insert, nonpregnant women using oral contraceptives containing estrogen or progestogen who receive sugammadex should be instructed to use an additional, nonhormonal method of contraception for 7 days after sugammadex administration. Sugammadex binds to

progestogen, which decreases progestogen exposure, thus making a dose of sugammadex equivalent to missing a dose of oral contraceptive.

Antiemetics

Nausea is an extremely common symptom, affecting about 80% of pregnant women. It is often worst in the first trimester and managed in an outpatient setting. First-line medications include ginger, pyridoxine (vitamin B_6), or antihistamines for mild symptoms. For moderate symptoms, options include pyridoxine/doxylamine combinations, dopamine antagonists such as metoclopramide, or serotonin antagonists such as ondansetron. For severe symptoms, corticosteroids or transdermal clonidine may be of benefit but the data are sparse.[74] Despite widespread use, there has recently been some concern regarding ondansetron and birth defects; however, animal studies have not demonstrated this nor any other adverse reproductive outcomes. Most human data are retrospective and often include exposures occurring after organogenesis, thus making interpretation difficult. A recent review of the topic has suggested avoiding ondansetron as first-line treatment, using ondansetron after 10 weeks of gestation to minimize risk of teratogenicity, and careful consideration regarding risk factors for serotonin syndrome and QT interval prolongation.[75]

Antibiotic Prophylaxis

Prophylactic antibiotics are recommended before incision during a cesarean delivery. Specifically, a single dose of a first-generation cephalosporin is the first-line choice. If a significant penicillin or cephalosporin allergy is of concern, a combination of clindamycin with an aminoglycoside is the recommended alternative option.[76] A recent randomized controlled trial demonstrated significantly decreased rates of endometritis, wound infection, and serious maternal adverse events when 500 mg of IV azithromycin was administered in addition to the standard recommended prophylaxis to women undergoing cesarean delivery during labor or after membrane rupture.[77] Azithromycin should be administered slowly over an hour rather than given as a bolus because of concern for ototoxicity.

Postoperative Analgesia

Neuraxial Opioids for Postoperative Analgesia

Neuraxial morphine, administered intrathecally at the time of spinal placement or via an epidural catheter, is generally used for postoperative pain management as it provides approximately 24 hours of analgesia. Common side effects include pruritus as well as nausea and vomiting. There is concern for delayed respiratory depression, and administration of neuraxial morphine warrants respiratory monitoring, although rates of clinically significant respiratory depression are less than 0.1% with current intrathecal dosing (≤250 μg). In general, higher intrathecal doses (150–250 μg) prolong analgesia but have increased rates of unwanted side effects compared with lower intrathecal doses (50–100 μg).[78]

A recent randomized controlled trial examined 3 doses (50, 100, and 150 μg) of intrathecal morphine administered to women undergoing elective cesarean delivery who also received postoperative ketorolac. There were no differences between groups in postoperative IV opioid supplementation or satisfaction with pain relief. Pruritus was decreased in the 50-μg group for the first 12 hours.[79]

Regarding epidural morphine, a noninferiority study examined 1.5 or 3 mg of epidural morphine administered in addition to systemic ketorolac and acetaminophen in patients undergoing cesarean delivery.[80] Pain scores, overall pain relief, satisfaction, and opioid consumption were not statistically different between the dosing regimens, but there was a decreased rate of pruritus and nausea and vomiting in the 1.5-mg group.

Systemic Opioid and Non-Opioid Analgesics

With routine use of neuraxial opioids and scheduled non-opioid analgesics, the amount of post-cesarean delivery systemic opioids needed to achieve postcesarean delivery pain control is declining.[78,81] Non-opioid analgesics play an important role in post–cesarean delivery analgesia by improving pain control, decreasing opioid requirements, and minimizing unwanted side effects. **Systemic opioids** should be provided on an as-needed basis to treat breakthrough pain after cesarean delivery, with patients receiving scheduled doses of nonsteroidal antiinflammatory drugs and acetaminophen in addition to analgesia from intrathecal morphine. Oral opioids (e.g., oxycodone 5–10 mg) are preferred in most patients as there is no evidence IV opioids provide analgesic benefit. It is safe for mothers to breastfeed with standard prescribed doses of opioids used for treatment of postoperative pain after cesarean section. However, caution and appropriate consultation are recommended for mothers requiring larger doses of opioids. Codeine is best avoided in breastfeeding mothers, as there is significant transfer to the breast milk and infants with specific genetic polymorphisms are at increased risk of significant respiratory depression.[82]

Ketorolac decreases pain scores and opioid use after cesarean delivery when administered in scheduled doses (e.g., 30 mg IV every 6 hours) during the first 24 hours after delivery. The patient should be transitioned to scheduled oral **ibuprofen** for continuation of the benefits from a nonsteroidal antiinflammatory pain regimen (e.g., 600 mg ibuprofen every 6 hours) when accepting oral intake.[78]

Acetaminophen has been shown to be advantageous when administered either before or after cesarean delivery to decrease pain and opioid use. A study examining the role of scheduled acetaminophen with as-needed opioids versus as-needed acetaminophen/opioid combination tablets found that scheduled acetaminophen resulted is less total opioid consumption.[81] In 2009, the FDA decreased the recommended maximum daily dose of acetaminophen from 4000 mg to 3250 mg,[83] and so a scheduled dosing of 1 g oral acetaminophen every 8 hours is reasonable after cesarean delivery once the patient can take oral medication. Avoiding opioid/acetaminophen combination medication reduces unnecessary opioid use and helps to avoid exceeding recommended maximum doses of acetaminophen.[78]

Gabapentin has been studied as a component of multimodal analgesia for cesarean delivery. When given as a single preoperative dose, the data are conflicting. There is some evidence to suggest improved pain scores as well as maternal satisfaction with a single 600-mg preoperative dose, but these findings have been inconsistent and there is a high level of fetal transfer.[78] When administered both preoperatively and postoperatively, slight reductions in pain scores and better patient satisfaction are demonstrated, as well as increased sedation, visual disturbances, and concern regarding breast milk transfer. Consequently, gabapentin is not commonly used for post–cesarean delivery pain unless the patient has a history of chronic pain.

Additional Peripartum Medications and Considerations

Vasopressors

Ephedrine was the standard treatment for spinal-induced hypotension until a 2009 human study revealed that ephedrine crosses the placenta to a greater extent than **phenylephrine** and is associated with fetal acidosis.[66] Although phenylephrine is now perferred to

ephedrine, both are safe options in pregnancy when reasonable dosing parameters are used and close attention and intervention is also focused on maternal heart rate. Interest in **norepinephrine** to treat spinal-induced hypotension during cesarean delivery has recently increased, as the combined alpha and beta activity of norepinephrine may theoretically prevent the reflex bradycardia often seen with phenylephrine administration. Studies comparing phenylephrine versus norepinephrine infusions suggest that use of norepinephrine in pregnancy is reasonable and may result in a relatively higher heart rate and cardiac output compared with phenylephrine, although the clinical significance is unknown, as neonatal outcomes are similar between groups.[67,68] Norepinephrine is the vasopressor of choice for patients with sepsis and may also be used during pregnancy in the intensive care setting. **Epinephrine** use during pregnancy is typically reserved for acute or emergency settings, such as anaphylaxis, cardiac arrest, or in the intensive care unit. There is concern for reduced uterine blood flow after administration of epinephrine to the pregnant patient because of the potent uterine vasoconstriction that may occur, theoretically resulting in fetal hypoxia.[84] However, in a decompensating pregnant patient, the best fetal resuscitation is maternal resuscitation, and this may require use of epinephrine. **Vasopressin** is a second-line vasopressor option for management of hypotension in patients with sepsis.[85] There are theoretical concerns for vasopressin activating uterine $V1_a$ receptors and resulting in uterine contractions. Although it has been used successfully during pregnancy, use of vasopressin warrants fetal and uterine contraction monitoring.

Uterotonics

Postpartum uterine atony can occur immediately after delivery or several hours later. If the atony persists, risk of significant postpartum hemorrhage and maternal morbidity are both increased. Initial prevention of uterine atony includes bimanual uterine massage and administration of oxytocin as either a continuous IV infusion or in small (e.g., 3 Units) repeated doses (Table 37.6). Rapid IV bolus administration is associated with vasodilation, hypotension, and tachycardia. Consequently, even small doses should be administered over at least 30 seconds.[86] Frequent communication between the anesthesiologist and obstetric provider in the postpartum period is critical to determining if additional uterotonics are required. Each uterotonic agent has unique side effects and considerations that may pose a contraindication when certain patient comorbidities exist.

Tocolytics

Tocolytics are typically used to delay delivery in the setting of preterm labor or to create a period of uterine relaxation to improve the fetal condition or optimize delivery. Specific dosing, mechanisms of action, and side effects are detailed in Table 37.7.

Anticoagulation

Antepartum Anticoagulation

The National Partnership for Maternal Safety (NPMS), which represents all major women's health care professional organizations, has recently created a safety bundle that reviews guidelines and recommendations for venous thromboembolism (VTE) prophylaxis.[87] The NPMS recommends that VTE risk assessment occur at the first prenatal visit, and that patients receive outpatient pharmacologic prophylaxis as appropriate (Table 37.8). For pregnant patients requiring anticoagulation for VTE prophylaxis with either unfractionated heparin or low-molecular-weight heparin (LMWH), the required doses may be greater than typical in nonpregnant patients secondary to changes in plasma volume and lower levels of antithrombin III. Given contraindications and delays to placement of neuraxial blockade specific to each drug and dosing regime, a detailed multidisciplinary discussion, including anesthesia, obstetrics, and other specialty physicians such as hematology and cardiology, is critical to determining an optimal anticoagulation plan with appropriate risk and benefit considerations. For example, in planning for delivery, a patient receiving prophylactic or therapeutic LMWH may: (1) continue current dosing, (2) be transitioned to doses of unfractionated subcutaneous heparin, or (3) be transitioned to an IV heparin infusion (allowing for possible anticoagulation reversal with protamine), depending on the underlying patient condition requiring anticoagulation.

Currently the new set of preliminary guidelines from the American Society for Regional Anesthesia and Pain Medicine on venous thromboembolism prophylaxis and neuraxial anesthesia is available only as an electronic device application (app).[88] These guidelines suggest neuraxial procedures be delayed at least 4 to 6 hours after a 5,000 U dose of subcutaneous unfractionated heparin, 10 to 12 hours after a prophylactic dose of enoxaparin, and at least 24 hours for treatment doses of enoxaparin (e.g.,1 mg/kg every 12 hours). The time interval between a dose of 7,500 and 10,000 U of subcutaneous unfractionated heparin (often used during pregnancy) and neuraxial anesthesia initiation is uncertain. If IV heparin is used, in addition to obtaining laboratory studies

TABLE 37.6 Uterotonic Therapy

Medication	Dose	Side Effects and Considerations
Oxytocin	10–40 Units/L IV infusion or Boluses ≤ 3 Units IV	Vasodilation, hypotension, tachycardia. Consider alternate agent if significant hemodynamic compromise.
Methylergonovine	0.2 mg IM	Vasoconstriction and hypertension. Relatively contraindicated with preeclampsia, pulmonary hypertension, or ischemic cardiac disease.
$PGF_{2\alpha}$-carboprost	0.25 mg IM	Diarrhea, hypertension, nausea, vomiting, bronchoconstriction, pulmonary vasoconstriction. Contraindicated in patients with asthma and those with pulmonary hypertension.
PGE_1-misoprostol	600–1000 μg PR, sublingual, or buccal	Maternal fever, shivering

IM, Intramuscular; *IV,* intravenous; *PG,* prostaglandin; *PR,* per rectum.

TABLE 37.7 Tocolytics

Medication	Initiation Dose	Maintenance Dose	Mechanism of Action	Side Effects	Anesthetic Interactions
Nifedipine	20–30 mg PO	10–20 mg q4–6h	Calcium channel blocker, prevents release of calcium from sarcoplasmic reticulum. Overall decreased actin-myosin interaction→relaxation of smooth muscle.	Hypotension, headache, flushing, dizziness, nausea.	May see vasodilation, hypotension, myocardial depression, and conduction delays when used with volatile anesthetics.
Indomethacin	50–100 mg PO or PR	25–50 mg q4h	Cyclooxygenase inhibitor, prevents synthesis of prostaglandins, which stimulate uterine contractions.	Nausea, heartburn, transiently abnormal platelet aggregation. Greater than 32 weeks' gestation may cause fetal ductal closure, transient fetal oligohydramnios.	None. Safe for neuraxial placement.
Terbutaline	0.25 mg SQ	0.25 mg q20min to 3h	Relatively selective for β_2 receptors; stimulating these receptors causes relaxation of uterine smooth muscle.	Vasodilation/hypotension, tachycardia, pulmonary edema, hyperglycemia, hypokalemia.	Consider waiting 15 minutes after administration before induction of general anesthesia, avoid agents that may cause tachycardia.
Magnesium sulfate	4–6 g IV bolus over 20 min	2–4 g/h IV infusion	Competitive antagonist of calcium. Also decreases release of acetylcholine at neuromuscular junction and sensitivity of motor endplate to acetylcholine.	Chest pain/tightness, palpitations, nausea, transient hypotension, burry vision, sedation, pulmonary edema.	Renal excretion (monitor levels closely in patients with renal dysfunction), potentiates action of depolarizing and nondepolarizing muscle relaxants, decreased MAC.
Nitroglycerin	100–400 μg IV bolus	Repeat boluses q2min. Onset 30–45 seconds, effect lasts for 2 min	Increases cGMP, which dephosphorylates myosin light chains and results in smooth muscle relaxation.	Maternal hypotension, headache.	Vasodilation, hypotension. Concurrent administration of phenylephrine recommended.

cGMP, Cyclic guanosine monophosphate; *IV,* intravenous; *MAC,* minimum alveolar concentration; *PO,* per oral; *PR,* per rectum; *SQ,* subcutaneous.
Adapted from Walton JR, Grobman WA. Preterm labor and delivery. In: Chestnut DH, Wong CA, Tsen LC, et al. *Chestnut's Obstetric Anesthesia: Principles and Practice.* 5th ed. Philadelphia: Elsevier; 2014:787–808.

TABLE 37.8 Antepartum Anticoagulation Therapy

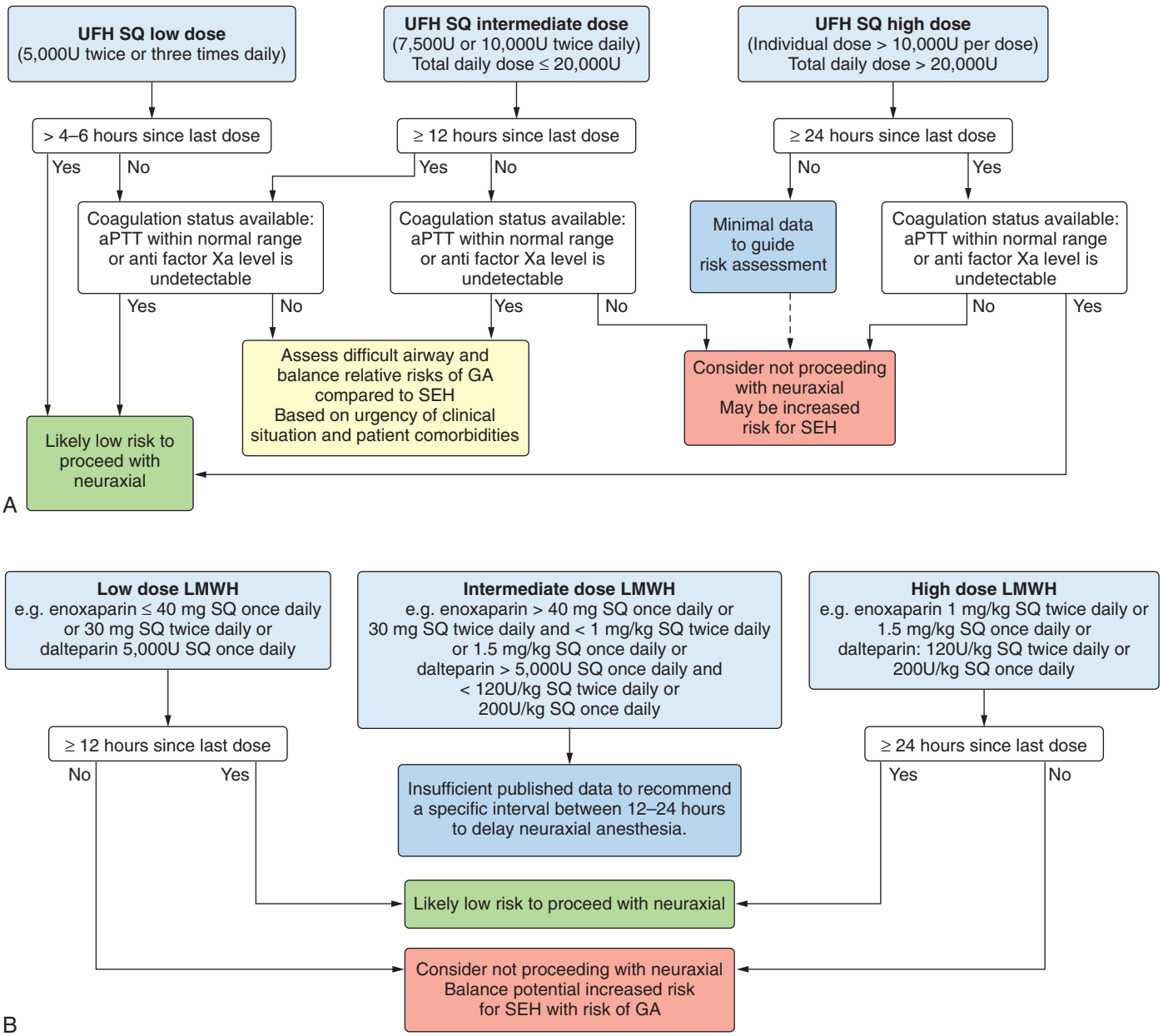
Clinical History	Anticoagulation
Multiple prior venous thromboembolism episodes Prior venous thromboembolism with high-risk thrombophilia[a] Prior venous thromboembolism with acquired thrombophilia[b]	Treatment dose low-molecular weight heparin or unfractionated heparin
Idiopathic prior venous thromboembolism Prior venous thromboembolism with pregnancy or oral contraceptive Prior venous thromboembolism with low-risk thrombophilia[c] Family history of venous thromboembolism with high-risk thrombophilia[a] High-risk thrombophilia (including acquired)[a,b]	Prophylactic-dose low-molecular weight heparin or unfractionated heparin
Low-risk thrombophilia[c]	No treatment

[a]High-risk thrombophilias include factor V Leiden homozygosity; prothrombin gene mutation homozygosity; factor V Leiden, prothrombin gene mutation compound heterozygosity; and antithrombin III deficiency.
[b]The primary acquired thrombophilia is antiphospholipid antibody syndrome.
[c]Low-risk thrombophilias include factor V Leiden or prothrombin gene mutation heterozygosity and protein C or S deficiency.
Adapted from D'Alton ME, Friedman AM, Smiley RM, et al. National Partnership for Maternal Safety: Consensus Bundle on Venous Thromboembolism. *Anesth Analg.* 2016;123:942–949.

demonstrating return to normal coagulation status, a platelet count should be determined for any patient receiving heparin for more than 4 days to screen for heparin-induced thrombocytopenia. For patients beginning a new course of subcutaneous prophylactic LMWH, a platelet level should be obtained after a week of treatment to screen for heparin-induced thrombocytopenia. A recent consensus statement by the Society for Obstetric Anesthesia and Perinatology regarding thromboprophylaxis during pregnancy provides decision aids for use of neuraxial anesthesia (Fig. 37.6).[89]

Postpartum Deep Vein Thrombosis Prophylaxis

After a vaginal birth, the NPMS recommends use of LMWH or unfractionated heparin for women with a history of VTE or thrombophilia (Table 37.9). For all women who have undergone cesarean delivery and are at "low risk" for VTE, pneumatic compression devices are recommended until the patient is fully ambulatory. For women who have additional risk factors for VTE, recommendations suggest use of both pneumatic compression devices as well as pharmacologic prophylaxis.



• **Fig. 37.6** Thromboprophylaxis and neuraxial anesthesia during pregnancy. A flowchart to assist with the decision to use a neuraxial procedure in an obstetric patient receiving anticoagulation with either unfractionated heparin (A) or LMWH (B). *aPTT,* Activated partial thromboplastin time; *GA,* general anesthesia; *SEH,* spinal epidural anesthesia; *SQ,* subcutaneous; *UFH,* unfractionated heparin. (Adapted from Leffert L, Butwick A, Carvalho B, et al. The Society for Obstetric Anesthesia and Perinatology Consensus Statement on the anesthetic management of pregnant and postpartum women receiving thromboprophylaxis or higher dose anticoagulants. *Anesth Analg.* 2018;126:928–944.)

TABLE 37.9 Venous Thromboembolism Prophylaxis

Clinical History	Anticoagulation
Multiple prior venous thromboembolism episodes Prior venous thromboembolism with high-risk thrombophilia[a] Prior venous thromboembolism with acquired thrombophilia[b]	6 weeks of treatment dose of low-molecular weight heparin or unfractionated heparin
Idiopathic prior venous thromboembolism Prior venous thromboembolism with pregnancy or oral contraceptive Prior venous thromboembolism with low-risk thrombophilia[c] Family history of venous thromboembolism with high-risk thrombophilia[a] High-risk thrombophilia (including acquired)[a,b] Prior venous thromboembolism provoked Low-risk thrombophilia and family history of venous thromboembolism[c]	6 weeks of prophylactic dose of low-molecular weight heparin or unfractionated heparin
Low-risk thrombophilia[c]	No treatment

[a]High-risk thrombophilias include factor V Leiden homozygosity; prothrombin gene mutation homozygosity; factor V Leiden, prothrombin gene mutation compound heterozygosity; and antithrombin III deficiency.
[b]The primary acquired thrombophilia is antiphospholipid antibody syndrome.
[c]Low-risk thrombophilias include factor V Leiden or prothrombin gene mutation heterozygosity and protein C or S deficiency.
Adapted from D'Alton ME, Friedman AM, Smiley RM, et al. National Partnership for Maternal Safety: Consensus Bundle on Venous Thromboembolism. *Anesth Analg.* 2016;123:942–949.

Emerging Developments

In Utero Anesthetic Exposure and Brain Development

Evidence for neuronal apoptosis in the developing brain after exposure to a wide range of anesthetic agents, such as halogenated agents, propofol, and benzodiazepines, has been demonstrated in animal studies. Clinical implications for the fetus and newborn related to the extremely limited anesthetic exposure during a cesarean delivery with general anesthesia are unknown, as there is a lack of human studies as well as difficulty extrapolating animal studies to humans regarding exposure in utero. Currently no specific anesthetic agent (e.g., volatiles, propofol, ketamine, benzodiazepines) has been demonstrated to be safer than another. In December 2016 the FDA issued a communication warning that "repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in **pregnant women during their third trimester** may affect the development of children's brains."[90] A consensus statement in response to this FDA warning was released by a group of medical organizations that care for children and pregnant women, including the American Society of Anesthesiologists and the Society for Obstetric Anesthesia and Perinatology. This statement notes that it is unknown if anesthetic drugs or other patient or clinical factors are responsible for these findings, and cautions clinicians and parents against delaying necessary surgical or diagnostic procedures that require anesthesia.[91] Current research efforts are ongoing to better understand long term effects of anesthetics on the developing brain.

Key Points

- Pregnancy, labor, and delivery are each associated with significant changes in anatomy and physiology affecting all maternal organ systems. These changes alter the pharmacokinetics and pharmacodynamics of many anesthetics and analgesics and have significant implications for anesthetic management.
- In addition to maternal anesthetic considerations, obstetric anesthesia requires an understanding of uteroplacental physiology and consideration of fetal well-being when determining an optimal patient management plan.
- Maternal-fetal transfer of most medications occurs primarily by diffusion. Fetal peak drug levels depend on maternal/fetal concentration gradients, molecular weight and ionization of the drug, and lipid solubility.
- Preeclampsia is associated with significant maternal and fetal mortality. Preeclamptic patients have an elevated risk of cerebral hemorrhage, seizure, pulmonary edema, and coagulopathy. Antihypertensives should be administered to treat systolic blood pressure greater than 160 mm Hg for prevention of intracerebral hemorrhage. Magnesium sulfate should be administered for seizure prophylaxis in patients with preeclampsia with severe features.
- Neuraxial analgesia is the most effective option for managing labor pain. To obtain optimal analgesia, blockade of the T10 to L1 levels is required during the first stage of labor and must also include the S2 to S4 levels during the second stage of labor.
- Use of scheduled acetaminophen and nonsteroidal antiinflammatory drugs in the treatment of postoperative pain after cesarean delivery significantly decreases opioid use and improves pain scores and maternal satisfaction.
- Venous thromboembolism is a significant cause of maternal morbidity and mortality during pregnancy, labor, and the peripartum period. Current guidelines highlight the need for risk assessment early in pregnancy and appropriate prophylaxis in the postpartum period.
- A multidisciplinary approach with open communication is essential to successful management of the obstetric patient in the peripartum period.

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38

Chemotherapy, Immunosuppression, and Anesthesia

BEN CHORTKOFF AND DAVID STENEHJEM

CHAPTER OUTLINE

Chemotherapy
- Drugs That Cause DNA/RNA Damage
- Drugs That Suppress Proliferation: Microtubule-Binding Agents
- Molecular Therapies, Growth Inhibitors, and Targeted Therapies

Monoclonal Antibodies

Antimetastasis Therapy

Immunotherapy

How Anesthetics Might Affect Cancer
- Opioids
- Volatile Anesthetics
- Propofol
- Local Anesthetics
- Other Factors

The concept of "immunosurveillance" describes a homeostatic balance whereby cells that undergo transformation into cancer cells are normally eliminated or kept in check by the immune system.[1,2] In 1985 an autopsy study found that 36% of "normal" thyroid glands showed occult carcinomas, even though the incidence of clinically diagnosed thyroid cancer is one-thousandth of that rate in the same population.[3] In 1987 another group found in situ breast carcinoma in 20% of autopsy examinations of women 20 to 54 years of age who died of unrelated causes.[4] The expected incidence of clinically diagnosed breast cancer is on the order of about 0.1%. These studies found cancer cells 10^2 to 10^3 more frequently than cancer is manifest clinically. Malignant transformation of cells within the body is relatively common but clinical cases of cancer rarely result. The transformed cells are typically kept in check by immunosurveillance.

Once cancer is identified in a patient, treatment may include chemotherapy and radiation therapy aimed at killing the cancer cells, surgery to excise solid tumors, and immune therapy aimed at helping the immune system eliminate or at least modulate cancer cells. Surgical excision remains the best therapy for control of solid tumors (either with or without adjuvant therapies) and is what most often brings patients under the care of the anesthesiologist. Patients with nonsolid tumors (e.g., leukemias) may come to the operating room for biopsy or diagnostic staging. Patients also present for unrelated surgery regardless of the type of cancer and regardless of the stage of cancer therapy. Given the prevalence of newly diagnosed cancers each year (approximately 1,700,000 among a total population in the United States of 320,000,000 [0.5%]), along with the ever-increasing rate of survival of patients with a history of cancer (14,500,000 [4.5% of the population]),[5] it is clear that anesthetists will frequently encounter patients in all stages of cancer and cancer treatment (Table 38.1). They therefore have a responsibility to understand how cancer therapies might influence anesthetic management. In addition, researchers are exploring how anesthetic management might influence cancer. This chapter highlights end-organ effects of common chemotherapies and reviews current concepts about anesthetic effects on cancer. Both may prove important in determining the best possible anesthetic plan for the individual patient with cancer.

Chemotherapy

Using systemic medications to poison a cancer cell often results in collateral damage. The majority of chemotherapies target the cancer cell's most distinctive feature, its rapid division and proliferation. However, cell division is not unique to the cancer cell. Disrupting cell division also affects normal functioning cells in involved and uninvolved internal organs, causing both acute and chronic injury after prior and/or cumulative exposures.

Understanding the mechanisms by which the different chemotherapeutics inflict injury on the target cancer cells helps predict and elucidate what injuries might occur in the rest of the body. For example, agents that interfere with DNA replication are effective against rapidly proliferating tumors but also harm areas where rapid cellular turnover is the norm (e.g., the intestinal mucosa and bone marrow). Agents that affect the activity of microtubules within the cell will affect microtubule function not only during cellular division, but also in the performance of other microtubule activities (e.g., the preparation and delivery of synaptic vesicles at the neuromuscular junction). Disrupting synaptic vesicles causes peripheral neuropathies. Finally, agents that kill rapidly dividing cells by generating oxygen free radicals also injure cells with high metabolic activity such as cardiac myocytes, leading to cardiomyopathies.

Conventional cancer drugs have a very narrow therapeutic index. They are highly toxic to both the targeted cancer cells and non-targeted cells. The "maximum tolerated dose" has the highest probability of decreasing tumor burden and is usually the prescribed

Abstract

In the United States, nearly 5% of the population has or has had cancer. Anesthetists frequently encounter patients in all stages of cancer and cancer treatment. This chapter highlights the short term and long term end-organ effects of common chemotherapeutics relevant to the anesthetist and reviews current concepts about how anesthetics may impact cancer and cancer survival.

Keywords

cardiotoxicity
pulmonary fibrosis
oxygen free radicals
malignancy
metastasis
monoclonal antibodies
immunotherapy
angiogenesis

TABLE 38.1 The 12 Most Frequent Cancers in the United States

Primary Cancer	New Diagnoses[a]	Survivors[b]
Breast	249,000	3,131,440
Lung	224,000	430,000
Prostate	181,000	2,975,970
Colorectal	134,000	1,245,800
Bladder	77,000	455,520
Melanoma	76,000	528,860
Non-Hodgkin lymphoma	73,000	569,800
Thyroid	64,000	470,020
Kidney	63,000	389,000
Leukemia	60,000	177,940
Endometrial	60,000	624,890
Pancreatic	53,000	
All sites	1,685,210	14,483,830 (4.5% of people in the United States)

[a]Estimated number of patients with a new diagnosis of each cancer in 2016.
[b]Estimated number of patients living with a diagnosis of the specific cancer as of January 2014 (American Cancer Society, 2016). Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2016/cancer-facts-and-figures-2016.pdf.

dose. Anesthetists should therefore anticipate that their patients who have received chemotherapy have received near-toxic doses at which organ injury may occur.

In relation to surgery, chemotherapy can be administered (1) before surgical excision, as neoadjuvant therapy, to facilitate surgery by reducing tumor burden, killing micrometastases, and potentially decreasing the survivability of tumor cells liberated during surgical manipulation; (2) after surgical excision, as adjuvant therapy, in an attempt to eradicate clinically undetectable residual tumor burden; or (3) unrelated to surgical timing, as palliative therapy, to ameliorate patient symptoms.

Medications used to kill cancer cells can be divided into three broad categories. The first category directly damages DNA and/or ribonucleic acid (RNA), and includes alkylating agents, antimetabolites, antineoplastic antibiotics, and topoisomerase inhibitors. The second category suppresses proliferation of dividing cells by interfering with microtubule function. The third category includes targeted therapies, also known as precision medicine therapies. Targeted therapies are molecules that hinder specific cellular enzymes unique to or overexpressed in malignant cells. Targeted therapies can also be molecules made to attach to specific cell membrane antigens to mark the cell and facilitate recognition of the cancer by the immune system.

Drugs That Cause DNA/RNA Damage

Alkylating Agents

The prototypical alkylating agent, mechlorethamine (an analog of the chemical warfare agent mustard gas) is a simple molecule composed of an electrophilic backbone carrying an alkyl side chain (Fig. 38.1). As an agent of war, mustard gas was a potent vesicant or blistering agent causing initial injury to exposed surfaces, including skin, eyes, and when inhaled, the lungs. Absorption would then lead to a drastic reduction in cell production in bone marrow and lymphatic tissue. During DNA replication, the alkyl group becomes covalently bonded to a DNA nucleotide (usually guanine) and physically interferes with subsequent transcription and cell division. On a molecular level this may be considered analogous to placing a set of handcuffs on rapidly dividing DNA (Fig. 38.2). The alkylating agents are toxic in all phases of the cell cycle but are most lethal to rapidly proliferating tissues. Subcategories of alkylating agents (Table 38.2) include nitrogen mustards (e.g., cyclophosphamide), nitrosureas (e.g., carmustine), alkyl sulfonates (e.g., busulfan), and platinum drugs (e.g., cisplatin).

The alkylating agents are used to treat Hodgkin lymphoma, lymphosarcoma, leukemias, and bronchogenic sarcomas. Normal rapidly dividing cells—for example, bone marrow, intestinal mucosa, and hair follicles—are also killed along with the targeted tumor. The platinum-based chemotherapeutic agents are listed with the alkylating agents although they do not "alkylate" DNA (they do not have an alkyl group). They do act in the same manner by permanently binding to (hand-cuffing) guanine residues in DNA. Their main use is with testicular and ovarian cancers, bladder cancer, head and neck cancer, and small cell lung cancer. Oxaliplatin is used in metastatic colorectal cancer. The platinum-based agents additionally cause peripheral neuropathies and acute and chronic nephrotoxicity.

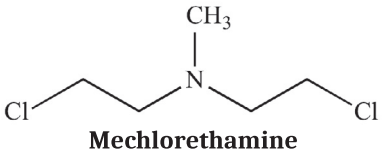
The alkylating agents have side effects mostly limited to bone marrow suppression and gastrointestinal tract effects, although late-onset pulmonary fibrosis is associated with long-term therapy (especially cyclophosphamide, busulfan, and the nitrosureas). Platinum-containing agents uniquely cause neuropathies and nephrotoxicity. Cyclophosphamide uniquely inhibits plasma pseudocholinesterase activity and can prolong the effect of succinylcholine.[6–8] (Remifentanil, unlike succinylcholine, has an ester group that is metabolized by nonspecific blood and tissue esterases. Cyclophosphamide would not be expected to alter its metabolism.)[9]

Antimetabolites

The antimetabolites are analogs of normal metabolites and inhibit cell growth and division (Table 38.3). Methotrexate is a folic acid analog, 5-fluorouracil is an analog of uracil (Fig. 38.3), and 6-mercaptopurine is a guanine analog. The analogs inhibit enzymes or cause them to synthesize aberrant molecules. They are frequently used in the treatment of colorectal, bladder, and pancreatic cancers as well as for leukemia. The antimetabolites affect all proliferating cells, causing side effects of immunosuppression, severe nausea and vomiting, ulcerative stomatitis and diarrhea, hemorrhagic enteritis, and potentially intestinal perforation, but there are few recognized long-term end-organ effects that alter anesthetic management.

Antineoplastic Antibiotics

The antineoplastic antibiotics are almost wholly produced by *Streptomyces* bacteria. The *Streptomyces* are a genus of soil bacteria from which scientists harvest antibiotics (e.g., streptomycin, neomycin, tetracycline, chloramphenicol), antifungals (e.g., nystatin, amphotericin B), antiparasitics (ivermectin), and antitumor compounds (e.g., actinomycin D, bleomycin, and the anthracyclines). The antitumor compounds can be classified based on the



Mechlorethamine

• **Fig. 38.1** Mechlorethamine (structure shown in top panel) is the first chemotherapeutic alkylating agent and is an analog of the WWI chemical warfare agent mustard gas. The picture (shown in the bottom panel) is a sobering illustration of the toxicity of these compounds, depicting British soldiers suffering the effects of mustard gas. It initially causes blistering to exposed surfaces (e.g., skin, eyes, lungs) and subsequently produces profound bone marrow and lymphatic cell suppression. (Photo: Military.com by Joseph V. Micallef.)

primary mechanism by which they damage DNA. One group causes DNA alkylation, and another damages DNA by inhibiting topoisomerase II and by generating oxygen free radicals (Fig. 38.4). The boundaries are not sharp and some crossover exists—for example the aminoquinones alkylate but also produce oxygen free radicals. The importance in the distinction lies in the cardiotoxicity of the agents that produce free radicals. The antitumor antibiotics that alkylate DNA show few long-term end-organ effects, whereas those that generate oxygen free radicals (e.g., the anthracyclines) are probably the most frequently cited and well-studied class of cardiotoxic anticancer agents.[10] (Table 38.4)

Antineoplastic antibiotics are often used to treat breast and bladder cancers as well as leukemias and lymphomas. Many cause acute cardiotoxicity (arrhythmias, hypotension, decreased contractility) within a week of initiation of therapy as well as chronic cardiotoxicity that can develop late. The mechanism of the late cardiotoxicity is cardiomyocyte apoptosis largely owing to oxidative stress induced by reactive oxygen species (free radicals) generated intracellularly. Oxygen free radicals are generated within mitochondria and by a second pathway involving intracellular iron complexes. The heart is rich in mitochondria and has relatively poor ability to rid itself of oxygen free radicals. Cardiotoxicity is further amplified by topoisomerase inhibition in the cardiomyocyte that alters calcium channel activity.[10] Acute cardiomyocyte injury from anthracyclines (e.g., doxorubicin (Adriamycin and daunorubicin) is associated with elevated serum troponin levels.

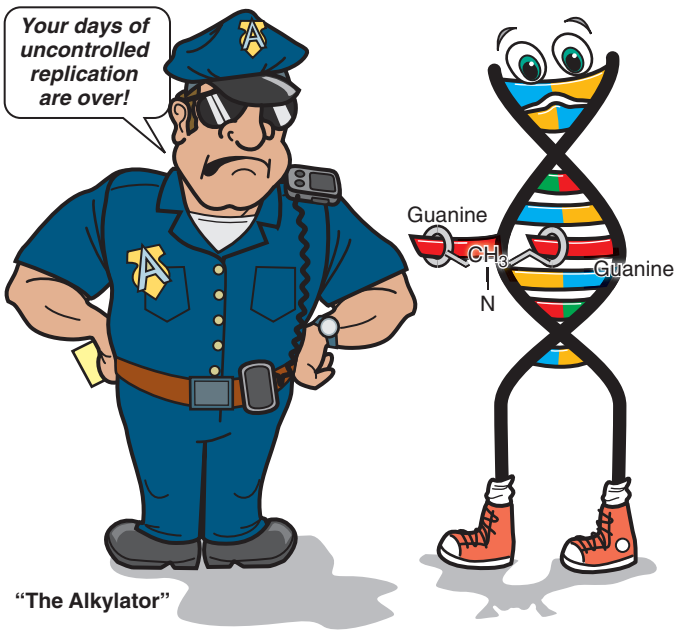
Acute doxorubicin toxicity is reversible, whereas subacute or chronic injury is irreversible. Acute, subacute, and chronic toxicity are related to the cumulative dose administered. The incidence of cardiomyopathy is about 4% when the cumulative dose is 500 to 550 mg/m^2, 18% at 550 to 600 mg/m^2, and 36% at greater than 600 mg/m^2.[11] Toxicity peaks at about 1 to 3 months after treatment and presents as biventricular congestive heart failure. Chest or mediastinal radiation, a previous history of cardiac injury, hypertension, and coadministration of other cardiotoxic chemotherapeutics (e.g., trastuzumab) increase the incidence of chronic cardiomyopathy. Late-onset dilated or restrictive cardiomyopathy can present years or decades after anthracycline treatment and can be first revealed during exposure to the myocardial-depressant effects of anesthetics.[12,13] In addition, the biventricular failure has been shown to be poorly responsive to inotropes in animal models.[14]

Analogs of the polycyclic aromatic antibiotics have been developed with the goal of decreasing the cardiotoxicity associated with anthracyclines (Table 38.5). Other important antineoplastic antibiotics include the enediynes, actinomycin D (dactinomycin), and bleomycin. The enediynes include antibiotics that are produced by species other than *Streptomyces*. They damage DNA by oxidation (binding the DNA backbone and removing hydrogens), cleaving the DNA strands. They are highly toxic and their poor selectivity for cancer cells limits their current use. This might be overcome

TABLE 38.2 Alkylating Agents by Subclass

Nitrogen Mustards	Nitrosureas	Triazines and Hydrazines	Ethyleneimines	Alkyl Sulfonates	Platinum Drugs[a]
Mechlorethamine	Arabinopyranosyl-N-methyl-N-nitrosourea (Aranose)	Dacarbazine	Thiotepa (Thioplex)	Busulfan	Cisplatin
Chlorambucil	Carmustine (BCNU, BiCNU)	Temozolomide	Hexamethyl-melamine (HMM, altretamine, Hexalen)	Treosulfan	Carboplatin
Cyclophosphamide (Cytoxan)	Chlorozotocin	Procarbazine		Mannosulfan	Oxaliplatin
Melphalan (Alkeran)	Ethylnitrosourea (ENU)				Nedaplatin
Ifosfamide (Ifex)	Fotemustine				Satraplatin
Trofosfamide	Lomustine (CCNU)				Triplatin tetranitrate
Estramustine	Nimustine N-nitroso-N-methylurea (NMU) Ranimustine (MCNU) Semustine Streptozocin				

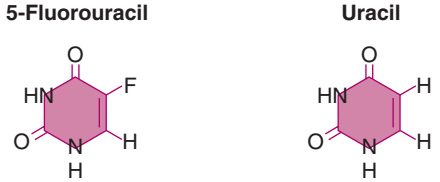
[a]Platinum-based agents do not literally alkylate but act like the other agents by binding to the guanine residue in DNA.



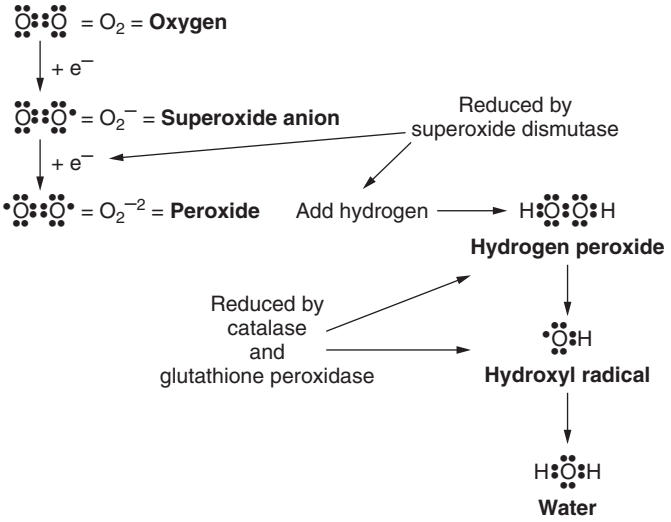
• **Fig. 38.2** Alkylating agents can bind to a single nucleotide leading to DNA fragmentation or can crosslink two nucleotides halting replication by essentially "hand-cuffing" the DNA. The cartoon shows DNA "hand-cuffed" when an alkylating molecule crosslinks its guanine nucleotides. To simplify the cartoon, the hand-cuffs are shown crosslinking two opposing guanine nucleotides. In actual DNA molecules, guanine pairs with cytosine. The guanine nucleotides crosslinked by alkylating agents are in the same strand of DNA, not directly opposed.

TABLE 38.3 Antimetabolites

Folate Analog	Pyrimidine Analogs	Purine Analogs
Methotrexate	5-Fluorouracil Floxuridine Capecitabine Gemcitabine Cytarabine (Ara-C)	6-Mercaptopurine Azathioprine 6-Thioguanine



• **Fig. 38.3** Antimetabolites are molecular analogs similar enough to be incorporated into enzymatic pathways but different enough to disrupt the outcome. 5-fluorouracil is an analog of uracil and differs from it by a single fluorine atom. It inhibits thymidylate synthetase, thereby interfering with DNA synthesis; it also is incorporated into ribonucleic acid (RNA), which damages RNA's ability to synthetize proteins.



• **Fig. 38.4** Oxygen free radicals. A free radical is "an especially reactive atom or group of atoms that has one or more unpaired electrons." Oxygen free radicals, also known as reactive oxygen species (ROS), occur when oxygen is used in a cell but is incompletely reduced to water. Oxygen free radicals, like peroxide, have an unpaired electron in their outer orbit that can destructively interact with lipid membranes, causing lipid peroxidation, or can similarly harm proteins and DNA. Cellular defenses against ROS include the enzymes superoxide dismutase, which catalyzes the reduction of the superoxide radical to oxygen and hydrogen peroxide; catalase, which catalyzes the reduction of hydrogen peroxide; and glutathione peroxidase, which catalyzes the reduction of hydrogen peroxide and the hydroxyl radical to water. Cardiomyoctes are rich in mitochondria (key cellular sites for the production of hydrogen peroxide) and are relatively lacking in catalase.[50] This makes them particularly susceptible to injury by oxygen free radicals. ("Free Radical" Merriam-Webster.com Merriam-Webster, n.d. Web. 28 July 2018.)

TABLE 38.4 Antineoplastic Antibiotics

Alkylate DNA	Alkylate and Produce Oxygen Radicals	Inhibit Topoisomerase Type II and Produce Oxygen Radicals[a]	Other Antineoplastic Antibiotics
Adozelesin	Mitomycin C	Anthracyclines[b]	Actinomycin D (Dactinomycin)
Bizelesin	Streptonigrin	Anthracenediones[c]	Fostriecin
Brostallicin		Anthrapyrazoles	Bleomycin
Carzelsin		Enediynes[d]	
CC-1065		Miscellaneous	
Duocarmycins			
Mithramycin A			
Tallimustine			

[a]The underscored text represents subcategories of the antineoplastic antibiotics as listed in Table 38.5.
[b]Acute cardiotoxicity includes arrhythmias, hypotension, and depression of contractility. Chronic toxicity results in cardiomyocyte apoptosis and can manifest a year or longer after exposure as congestive heart failure refractory to inotrope therapy.
[c]Developed to have less cardiotoxicity
[d]Produced by species other than *Streptomyces*. They are toxic but poorly selective for cancer cells, so current efforts are underway to conjugate these compounds with tumor-targeting molecules such as monoclonal antibodies.

in the future by conjugating these compounds to tumor-targeting entities such as monoclonal antibodies (MAbs). Actinomycin D disrupts DNA transcription by binding to DNA at transcription initiation sites and preventing elongation by RNA polymerase. It can cause liver toxicity, specifically hepatic veno-occlusive disease and clotting disorders, that might not manifest for days after treatment ends.

Bleomycin interacts with iron to produce oxygen free radicals. It is inactivated by the enzyme aminohydrolase (bleomycin hydrolase) that is found throughout the body except in the skin and lungs. Because of the scarcity of aminohydrolase in the skin, approximately 20% of patients receiving bleomycin therapy develop painless flagellate hyperpigmentation in their skin.[15] In the lungs, where aminohydrolase activity is particularly low, alveolar epithelial cells accumulate bleomycin. Bleomycin injures the pulmonary endothelium, causing increased capillary permeability and edema, and the edema leads to even greater accumulation of bleomycin. Necrosis of the type I alveolar epithelium stimulates increased migration of macrophages, which recruit additional inflammatory cells that release oxygen radicals and stimulate fibroblast activity.[16]

Exposure to high oxygen concentrations as part of operative anesthesia has been associated with potentiation of bleomycin pneumotoxicity and acute respiratory distress syndrome. A report of the deaths of five patients with acute respiratory distress syndrome–like symptoms after surgical procedures involving exposure to approximately 40% inspired oxygen concentrations 6 to 12 months after bleomycin treatment led to this association.[17] This led to a recommendation to limit supplemental oxygen to <30%, or as necessary to maintain oxygen saturation as measured by pulse oximetry (SpO_2) at 90% or above. Subsequent studies have identified other risk factors, including excessive intraoperative intravenous (IV) fluids and transfusions,[18] preexisting renal failure, preexisting pulmonary disease, and tobacco use.[18,19] Proximity to bleomycin infusion might be more important than high inspired oxygen concentrations, but minimizing inspired oxygen (<30% if possible) remains an important anesthetic guideline for reducing postoperative pulmonary complications.[20]

When anesthetizing patients who have been exposed to antineoplastic antibiotics, four points should be considered:

1. Subclinical asymptomatic cardiomyopathies can exist despite normal resting cardiac function.[13] These can be unmasked by anesthesia.
2. If congestive heart failure manifests, it is often refractory to inotrope therapy.[14]
3. Actinomycin D can cause hepatotoxicity and coagulation abnormalities.
4. Bleomycin pulmonary fibrosis can be potentiated by exposure to elevated inspired oxygen, by excessive IV fluids, and by blood transfusions.[18]

Topoisomerase Inhibitors

Topoisomerase enzymes are important for the proper activity of RNA and DNA polymerase. Polymerases separate DNA strands to transcribe base codes (whether to produce messenger RNA [mRNA] and proteins or to duplicate DNA in preparation for cellular division). As the polymerase separates segments of DNA, the remaining portion of the strands becomes more densely coiled (Fig. 38.5). Topoisomerase enzymes cleave the hypercoiled segments

TABLE 38.5 Antineoplastic Antibiotics That Inhibit Topoisomerase Type II and Produce Oxygen Radicals

Anthracyclines	Anthracenediones	Anthrapyrazoles	Enediynes
Doxorubicin (Adriamycin, Doxil, Myocet)	Mitoxantrone	Losoxantrone	Calicheamicin
Daunorubicin	Ametantrone	Teloxantrone	Esperamicin
Idarubicin	Pixantrone	Piroxantrone	Dynemicin
Amrubicin			Kedarcidin
Epirubicin			Maduropeptin
Valrubicin			Neocarzinostatin
Pirarubicin			Lidamycin
Berubicin			
Carubicin			
Esorubicin			
Detorubicin			
Duborimycin			
Zorubicin			
Aclarubicin			

of DNA, relax the DNA strands, and then reattach the cleaved ends, thereby allowing the transcription to progress. There are two classes of topoisomerase enzymes separated by whether they cleave one strand of the DNA (topoisomerase type I) or both strands (topoisomerase type II) as they relieve the hypercoiled state of the native DNA. Inhibitors of topoisomerase are specific to type I or type II.

The two most common topoisomerase type I inhibitors are the camptothecin derivatives topotecan and irinotecan. Topotecan is used in the treatment of ovarian cancer, small cell lung cancer, cervical and renal cell cancers, as well as leukemias and lymphomas. Irinotecan is used for colorectal cancers. The major adverse effects include immunosuppression and, especially with irinotecan, diarrhea. Diarrhea from irinotecan can be severe, and anesthetists might anticipate hypovolemia, metabolic acidosis, and hypokalemia after recent treatments.

Among the most common topoisomerase II inhibitors are the epipodophyllotoxins (extracted from the mandrake plant, the most common example being etoposide), and the group of antineoplastic antibiotics mentioned earlier (e.g., Adriamycin). The major risk of the type II topoisomerase inhibitors is related to the fact that they also produce oxygen free radicals, as previously described for the anthracycline antibiotics, leading to cardiotoxicity (Table 38.6).

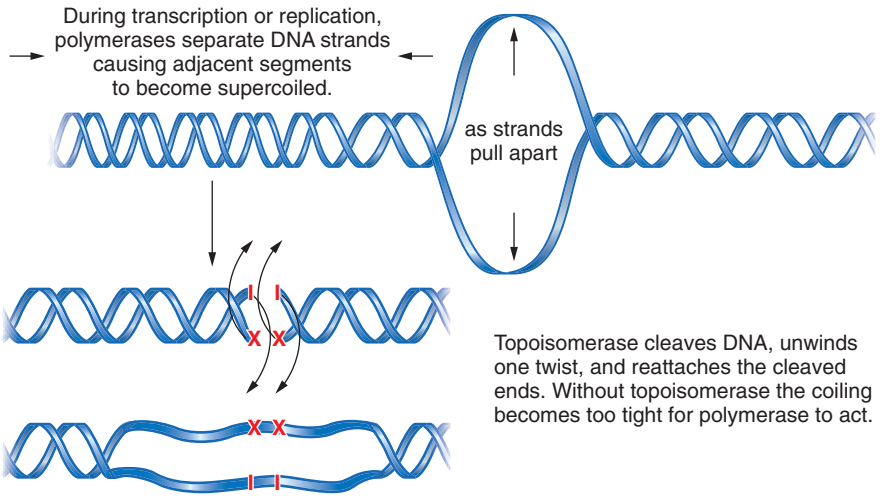
Drugs That Suppress Proliferation: Microtubule-Binding Agents

Microtubules are part of the cytoskeleton of cells. They are filamentous proteins that form long polymers, composed of α- and β-tubulin heterodimers. They provide basic organization of the cytoplasm, including the positioning of organelles, the moving of vesicles and granules, and packaging work within the mitochondria (Fig. 38.6). Their activity is critical in actively dividing cells as they create the mitotic spindle that helps segregate chromosomes during cellular division. Disruption of microtubule function prevents cellular proliferation.

The microtubule-binding agents do not distinguish between tubulin activity in mitosis and tubulin activity that transports synaptic vesicles (packages of neurotransmitter prepared for release in neurons) or tubulin activity within the Golgi apparatus involved in packaging proteins into vesicles. Thus the disruption of microtubule dynamics can diminish neurotransmitter preparation and delivery in nonproliferating cells; this often manifests as neurotoxicity. Microtubule activity is also important in cell migration. Inhibition of tubule activity suppresses cell migration by vascular endothelial cells. This produces a favorable antiangiogenic side effect, starving potential metastases of needed blood supply.

Medications that affect the microtubules are classified into two major groups based on whether they disrupt function by stabilizing or destabilizing the microtubule apparatus within cells (Table 38.7). The taxanes (e.g., paclitaxel [Taxol]), originally isolated from the bark of the Pacific yew tree, stabilize microtubules and act principally by binding to guanosine diphosphate–bound tubulin. This impedes dynamic polymerization and depolymerization and halts the conveyer-like activity that the cell depends on for cytoplasmic transport and cell division. In addition, paclitaxel induces apoptosis by binding to the apoptosis inhibitor protein Bcl-2 (B-cell lymphoma 2).

Docetaxel is a second-generation partially synthetic taxane that not only stabilizes tubulin, but also inhibits vascular endothelial growth factor (VEGF). It also displays immunomodulatory and proinflammatory activity. The tubulin stabilizers cause dividing cells to stall in the most radiosensitive phase (G_2/M) of the cell cycle, and therefore may be used as adjuncts for radiation therapy.[21]



• **Fig. 38.5** During transcription or replication, polymerases separate DNA strands causing adjacent segments to become tightly supercoiled. The drawing depicts the action of topoisomerase, which cleaves tightly coiled DNA, then reattaches the ends with one twist removed. The cartoon shows topoisomerase working hard to relax a tight DNA. When a topoisomerase inhibitor like adriamycin enters the scene, the DNA supercoiling cannot be relaxed thereby blocking transcription and replication.

The vinca alkaloids, originally extracted from leaves of the Madagascar periwinkle plant, destabilize microtubules and cause depolymerization. *Vinca* is the Latin name for the periwinkle genus. Alkaloids are secondary metabolites (organic compounds, often with a defense role, not directly involved in the normal growth, development or reproduction of plants, bacteria, and fungi) and are so named because of the alkalinity of the extracted compounds. Similar to the taxanes, exposure to the vinca alkaloids leads to significant neuronal dysfunction and subsequent peripheral neuropathies, loss of deep tendon reflexes, cranial nerve paralysis (especially cranial nerve VI, the abducens nerve). They cause wasting and paresis of extensor muscles, depression, convulsions, and hallucinatory psychoses. Generalized sensory and motor dysfunction can persist indefinitely after termination of therapy.

For patients who have received microtubule inhibitors, anesthetists should be aware of potential motor and sensory neuropathies, and the role they may play in the use and monitoring of depolarizing and nondepolarizing muscle relaxants. Wasting and paresis of extensor muscles may increase fall risk. In addition, partial palsy of the cranial nerves may lead to double vision, disconjugate gaze, hoarseness, facial palsies, or other symptoms that might be misinterpreted as cerebral ischemia. Previously unnoticed neuropathies may be unmasked in the postoperative period owing to residual anesthetic or neuromuscular blockade effects.

Molecular Therapies, Growth Inhibitors, and Targeted Therapies

The classical approach to fighting cancer has focused on poisoning rapidly dividing cells, an effective but nonspecific attack against dysfunctional cellular proliferation, one of the hallmarks of malignancy. Chemotherapeutics that damage rapidly dividing DNA, interfere with RNA synthesis, or interrupt cell division by hindering microtubule function are limited by (1) the collateral damage they cause to normal cells and (2) cancer cell mutations that defeat the effectiveness of the poison. Other hallmarks of malignant cells

TABLE 38.6 Topoisomerase Inhibitors

Type I	Type II
Camptothecan (causes severe cystitis)	Podophyllotoxins 1. Etoposide 2. Teniposide
Topotecan (FDA approved for ovarian cancer)	Amsacrine
Gimatecan	Antineoplastic antibiotics: Anthracyclines 1. Daunomycin (Daunorubicin) 2. Doxorubicin (Adriamycin) 3. Epirubicin 4. Detorubicin 5. Carubicin 6. Idarubicin 7. RTA 744 Anthracenediones (mitoxantrone) Anthrapyrazoles 1. Teloxantrone 2. Piroxantrone Dactinomycin Fostriecin Streptonigrin
Irinotecan (nausea/vomiting, severe diarrhea)	Quinoxalines 1. Chloroquinoxaline 2. XK469
Second-generation camptothecan derivatives 1. Lurtotecan 2. Exatecan 3. Rubitecan	Asulacrine isethionate
Third-generation camptothecan derivatives 1. Diflomotecan	Razoxane
Stealth-CKD602	Elliptinium
Karenitecin	Amonafide
Indolocarbazoles 1. Rebeccamycin 2. NB-506 3. Edotecarin 4. AT2433 5. Lamellarins	Batracylin
Indenoisoquinoline	

TABLE 38.7 Microtubule Binding Agents

Tubulin Stabilizers

1. Taxanes
   a. Taxol
   b. Docetaxel
   c. Larotaxel
   d. Ortataxel
   e. TPI 287
2. Epothilones
3. Rhazinilam
4. Eleutherobin
5. Peloruside A
6. Laulimalide

Tubulin Destabilizers

1. Alkaloids
   a. Indoles
      i. Vinca alkaloids
         1. Vinblastine
         2. Vincristine
         3. Vindesine
         4. Vinorelbine
         5. Vinflunine
      ii. Colchicine alkaloids
         1. Colchicine
         2. Demecolcine
         3. Trimethylcolchicinic acid
   b. Quinolones and isoquinolones
   c. Pyrrolidines
   d. Pyridines and piperidines
   e. Pyrrolizidines and quinolizidines
   f. Purines
   g. Terpenoids
2. Benzoylphenylureas

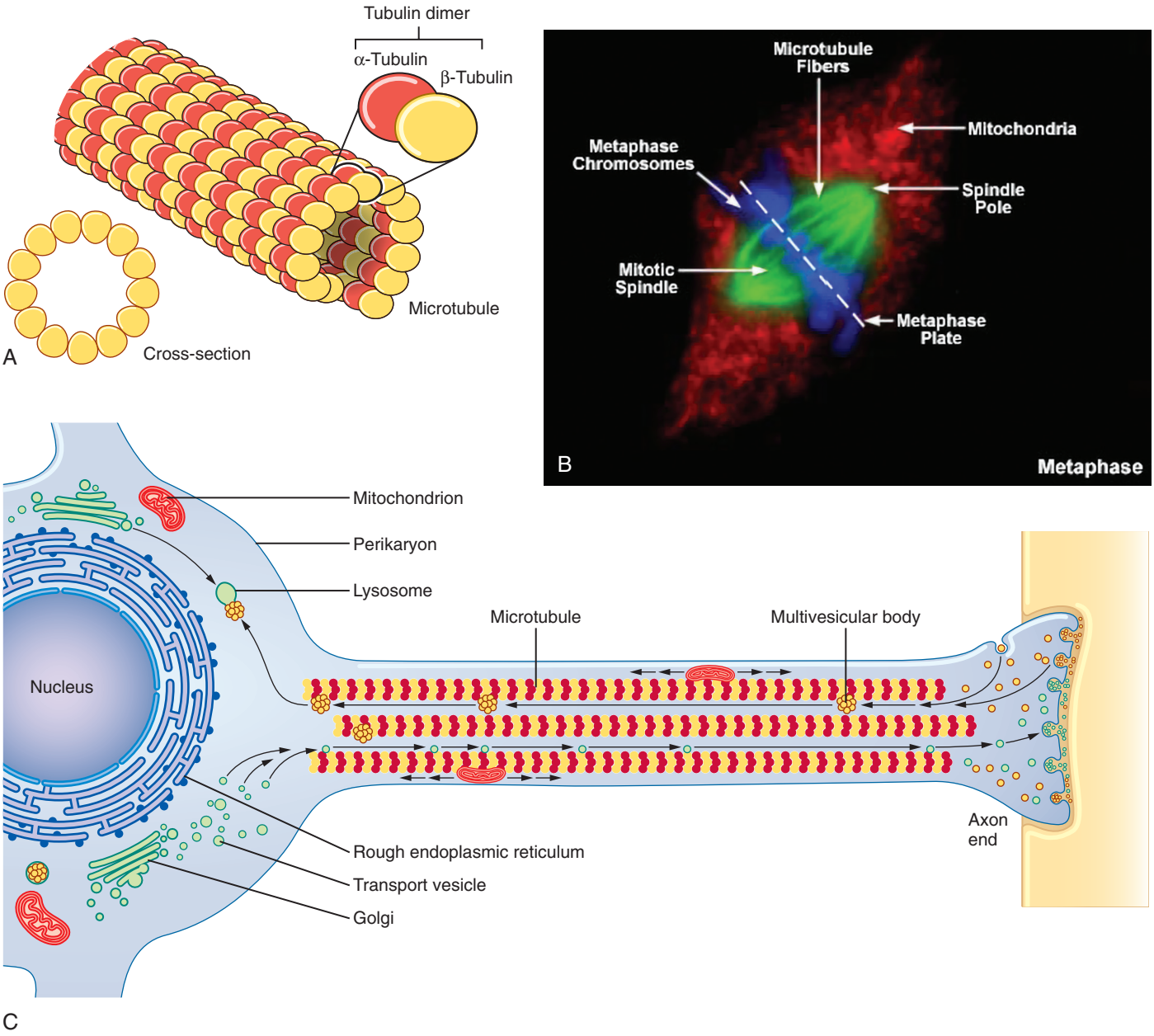
include robust survival (self-sufficiency in growth signals and insensitivity to anti-growth signals), ability to invade and metastasize, initiate and sustain angiogenesis, and evade normal apoptosis pathways.[22]

Targeted therapies focus on molecular level functioning (or malfunctioning) of intracellular regulatory processes that activate or inactivate proteins involved in controlling these hallmarks of malignancy. Given the rapid expansion of medications in this category, including monoclonal antibodies (mAb), kinase inhibitors, and other enzymatic pathway blockers, these drugs are considered broadly by mechanism of action.

Although these molecules are considered "targeted therapies" and are more specific in their action on proteins identified with cancer cells, it is important to be aware that the proteins that are targeted may also have roles in normal cells. For instance, kinase inhibitors and mAbs can damage cardiac myocytes. They can cause prolongation of the QT interval resulting in arrhythmias, and cause myocyte apoptosis resulting in cardiomyopathies and congestive heart failure.

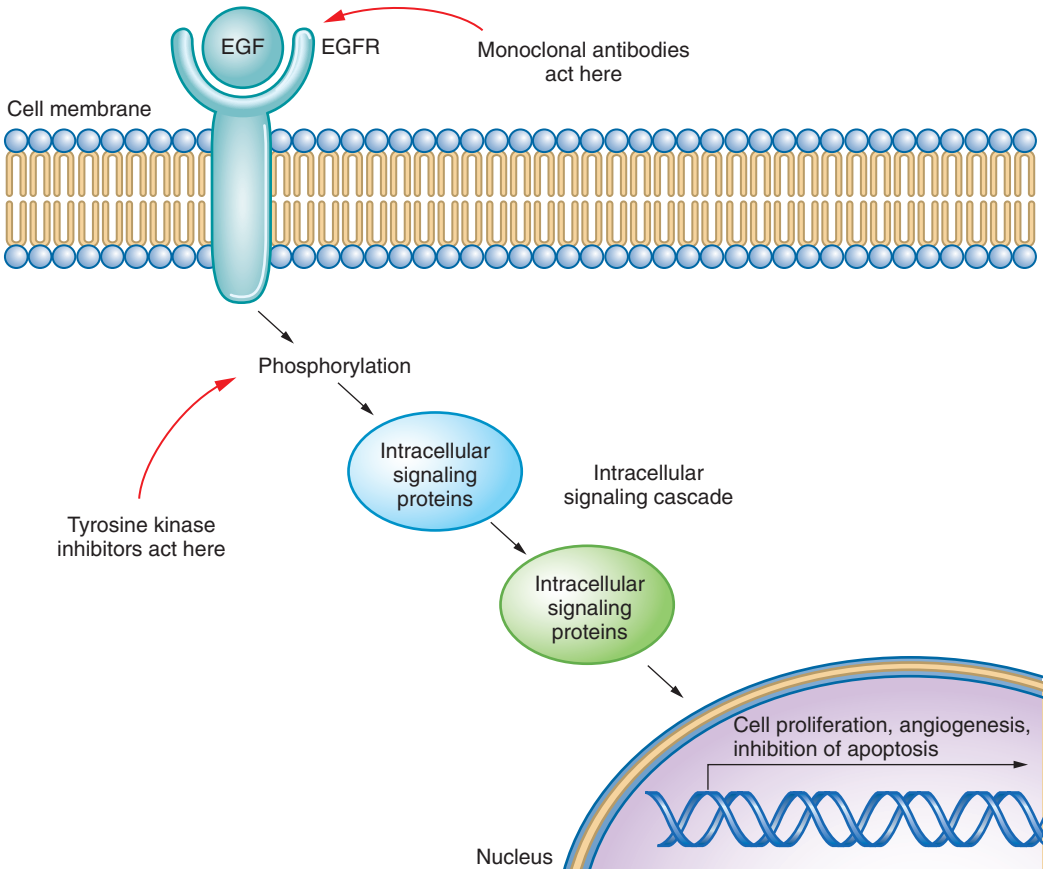
The targeting of epidermal growth factor receptor (EGFR, a transmembrane tyrosine kinase) serves as an example of how mAbs and tyrosine kinase inhibitors (TKIs) can be used to disrupt malignant activity. Other growth factor receptors have also been identified as protein targets where inhibition can similarly suppress malignant activity. These growth factor receptors are vascular endothelial growth factor (VEGF, which controls blood vessel development); platelet-derived endothelial growth factor (PDGF, which controls blood vessel development and cell growth); insulin-like growth factor (IGF, which activates signaling pathways that ultimately result in cell proliferation and resistance to apoptosis); and fibroblast growth factor (FGF, which controls cell growth).

In humans, the epidermal growth factor receptor (EGFR) is known as the human epidermal receptor (HER) and is homologous to a viral oncogene first identified in the late 1970s called erythroblastic



• **Fig. 38.6** Microtubules are part of the cytoskeleton of cells and are involved in organizing and separating chromosomes during cell division, moving vesicles and granules within the cell, and promoting cellular migration. Panel A is a simplified diagram of the microtubule built by the polymerization of alpha and beta tubulin dimers; Panel B is a flourescence microscopy image (Michael Davidson, Florida State University, 2015) showing the role of the mirotubules (stained green) in a dividing cell. Panel C illustrates another critical function of microtubules, the delivery of neurotransmitter packed vesicles to the axonal synapse. Microtubule binding agents like the vinca alkaloids indiscriminately disrupt all of the microtubule activities and result in toxicities such as peripheral neuropathies, loss of deep tendon reflexes, cranial nerve (VI) paralysis, and neuromuscular wasting.

leukemia viral oncogene (ErbB). There are four closely related members in this receptor family and they are named by convention EGFR/ErbB-1 (or just EGFR), HER2/ErbB-2 (or just HER2), HER3/ErbB-3, and HER4/ErbB-4. These receptors sit in the cell wall with an extracellular binding area that responds to ligands such as epidermal growth factor, transforming growth factor-α, and neuroregulin (Fig. 38.7). Following the protein inward, there is a hydrophobic transmembrane section, and then, within the cell, an intracellular portion that catalyzes the phosphorylation of tyrosine residues in proteins (i.e., tyrosine kinase). Adding phosphate to a tyrosine residue in a protein acts to turn on (or turn off) that protein's activity that then affects a multitude of basic cellular activities, including growth, survival, proliferation, adhesion, migration, differentiation, and apoptosis.[23] Preclinical studies showed that artificially activating EGFR promotes multiple tumorigenic processes, including stimulating proliferation, angiogenesis, and metastasis, as well as protecting cells from apoptosis.[24] These receptors are normally present in all eukaryotic cells, but many types of solid tumors exhibit



• **Fig. 38.7** Epidermal growth factor receptor (EGFR) is one of a family of closely related receptor tyrosine kinases. EGFR is a transmembrane protein that has an extracellular binding area, a hydrophobic transmembrane section, and an intracellular portion where its tyrosine kinase activity turns on or shuts down various cellular activities through phosphorylation mediated intracellular signaling. Epidermal growth factor (EGF) is the natural ligand that activates the receptor. Chemotherapeutic agents can target the ligand or any portion of the receptor. Monoclonal antibodies are typically aimed at the extracellular portion while the tyrosine kinase inhibitors interfere with the intracellular kinase signaling domain.

elevated levels of EGFR, elevated activity of EGFR, and/or elevated presence of EGFR ligands. Cancers that overexpress EGFR are often aggressive and are associated with poor patient outcomes.

Anticancer strategies focused on EGFR may target the extracellular portion or the intracellular portion of the kinase. Extracellular inhibitors bind either to the ligands of the receptors or to the receptor itself. Binding the receptor itself not only creates a blockade, but also initiates endocytosis of the receptor, bringing the receptor and antibody into the cell, and eliminating the receptor's presence and activity. In addition, receptor endocytosis creates an opportunity to design a "poison pill" or "magic bullet." Toxic substances (e.g., chemotherapy or radioactive particles) can be attached to an antibody designed to bind to an extracellular receptor. The toxic substance is taken into the cell (along with the receptor) by endocytosis, killing the targeted cell.

Tyrosine kinase inhibitors (by convention given names ending in "-nib") target the intracellular portion of the kinase and block EGFR from adding phosphoryl groups from adenosine triphosphate ATP to proteins (specifically to tyrosine residues) (Table 38.8). The TKIs produce significantly less severe adverse effects compared with conventional chemotherapy drugs. Side effects include fatigue, diarrhea, rashes, anorexia, and anemia. Interstitial lung disease is a rare complication with gefitinib and erlotinib, but when it occurs about one-third of the cases are fatal.[25] Lapatinib may rarely cause cardiotoxicity or liver damage manifesting as late as several months after treatment. Some kinase inhibitors (e.g., pazopanib, vandetanib, and nilotinib) cause QT prolongation and elevate risk for torsades de pointes. Patients receiving these kinase inhibitors will likely be monitored with serial electrocardiograms by their oncology teams. Perioperative medications known to prolong QT intervals should be used judiciously.

Other small molecule enzyme pathway inhibitors and examples of each include proteasome inhibitors (bortezomib), mechanistic target of rapamycin (mTOR) inhibitors (temsirolimus and everolimus), phosphoinositide 3-kinase inhibitors (idelalisib), histone deacetylase inhibitors (vorinostat, belinostat, panobinostat), and hedgehog pathway blockers (vismodegib).

Monoclonal Antibodies

MABs are laboratory-produced antibodies that bind to specific cellular antigens, such as a protein present on the surface of cancer cells but absent from (or expressed at lower levels by) normal cells. MABs are made by injecting a mouse with a specific human antigen of interest, harvesting from the mouse's spleen the B cells producing the antibody to the antigen, and then fusing those cells with immortal myeloma cells in vitro. The resulting hybridoma (fused B-cell and myeloma cell) undergoes repeated mitosis and is cultured

into a community of identical cells (clones), all producing the single desired antibody. The resulting mouse antibodies are made less immunogenic (less foreign) by grafting the important portions onto human antibody segments. The antibody is classified differently depending on how much of the mouse antibody has been substituted with human antibody (Fig. 38.8). If the constant region (Fc) is human and the antigen-binding region (Fab) is mouse, the antibody is classified as "chimeric." If in addition, part of the variable region is human, the antibody is classified as "humanized." By convention, the names given to the resulting antibodies identify the antibodies as monoclonal, describe their status as "mouse," "chimeric," "humanized," or "fully human," and identify their target tumor site. The naming convention works from the back of the name to the front. Monoclonal antibody names all end with "-mab". Preceding "mab" is either "o" for mouse, "xi" for chimeric, "zu" for humanized, or "u" for human. The letters immediate preceding o, xi, zu, or u identify the target of the antibody. For example, "-ci-" is used for an antibody targeting the circulation, "-li-" for lymphocyte (immune system), "-ne-" for nervous system, "-mul-" for musculoskeletal, and a "-tu-" for multiple tumor types. The manufacturer selects the first few letters to individualize the final name. So, cetuximab (ce-tu-xi-mab) (reading from the back of the name) is a monoclonal antibody, chimeric, attacking multiple tumor types. Bevacizumab (beva-ci-zu-mab) is a monoclonal antibody, humanized, attacking circulation (antiangiogenic) (Table 38.9). The World Health Organization passed a revised nomenclature scheme dropping the source component of the name for monoclonal antibodies named after 2017. The intent is to simplify the names and allow more distinctive, less same-sounding, names. (World Health Organization International Nonpropriietary Names Programme, INN Working Doc.17.416, May 2017.)

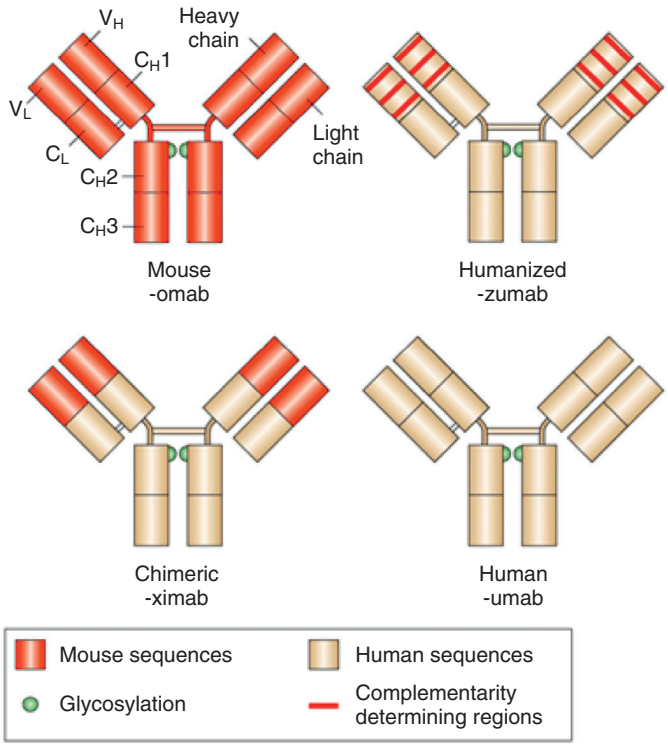
MAbs have been made to target (bind to) ligands (the molecular messenger) that stimulate tyrosine kinase receptors—for example, bevacizumab (Avastin) binds to vascular endothelial growth factor A (VEGF-A). Other MAbs target the extracellular receptor portions of transmembrane kinases—for example, trastuzumab (Herceptin) and pertuzumab (Perjeta) bind to the extracellular receptor portion of HER2, which is overexpressed in 25% to 30% of breast cancers. In another example, cetuximab (Erbitux) and panitumumab (Vectibix) bind to the receptor portion of EGFR. Binding the receptor decreases the aberrant activity of these kinases and leads to endocytotic removal of the protein from the cellular surface.

Other MAbs are designed to target protein antigens uniquely expressed, or overexpressed, on the surface of malignant cells. For example, rituximab (Rituxan) binds to the protein antigen CD20 primarily found on the surface of B cells. Once bound, it

TABLE 38.8 Tyrosine Kinase Inhibitors

Generic Name	Proprietary Name	Tyrosine Kinase Targets
Afatinib	Gilotrif	*EGFR, HER2*
Axitinib	Inlyta	*VEGFR, C-KIT, PDGFR, BCR-ABL*
Bosutinib	Bosulif	*BCR-ABL, SRC*
Cabozantinib	Cabometyx	*VEGFR2, C-MET*
Crizotinib	Xalkori	*C-MET, ROS1*
Dasatinib	Sprycel	*BCR-ABL, SRC*
Erlotinib	Tarceva	*EGFR*
Gefitinib	Iressa	*EGFR*
Imatinib	Glivec	*BCR-ABL, C-KIT, PDGFR*
Lapatinib	Tyverb	*EGFR, HER2/NEU*
Nilotinib	Tasigna	*BCR-ABL, KIT, PDGFR, DDR,* and others
Pazopanib	Votrient	*FGFR, PDGFR, VEGFR, C-KIT* and others
Regorafenib	Stivarga	*VEGFR2-TIE2,* and others
Sorafenib	Nexavar	*VEGFR, PDGFR, C-RAF*
Sunitinib	Sutent	*PDGFR, VEGFR, C-KIT,* and others

BCR-ABL, Fusion gene also known as the Philadelphia chromosome; *C-KIT,* also known as CD117 and stem cell growth factor receptor; *C-MET,* mesenchymal epithelial transition factor. also known as hepatocyte growth factor receptor, *C-RAF,* proto-oncogene, serine/threonine kinase; *DDR,* DNA damage responsive; *EGFR,* epidermal growth factor receptor; *HER2,* human epidermal growth factor receptor 2; *HGFR,* hepatocyte growth factor receptor; *PDGFR,* platelet-derived growth factor receptor; *ROS1,* c-ros oncogene 1; *SRC,* a nonreceptor tyrosine kinase first identified as causing sarcomas in chickens; *TIE2,* tyrosine kinase with immunoglobulin-like and EGF-like domains (also called TEK: tyrosine kinase, endothelial); *VEGFR,* vascular endothelial growth factor receptor.



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• **Fig. 38.8** Drawing of simplified mouse monoclonal antibodies with the substitutions that would change antibodies to chimeric, humanized, or human. C_H, constant domain of heavy chain of immunoglobulin M; C_L, constant domain of light chain of immunoglobulin M; V_H, variable domain of heavy chain; V_L, variable domain of light chain.

TABLE 38.9 Monoclonal Antibodies

Generic Name	Brand Name	Site of Action
Bevacizumab	Avastin	*VEGF-A*
Cetuximab	Erbitux	*EGFR-1*
Panitumumab	Vectibix	*EGFR-1*
Trastuzumab	Herceptin	*HER-2*
Pertuzumab	Perjeta	*HER-2*
Nimotuzumab	BIOMAb *EGFR*, Theracim, Theralo, Taixinsheng	*EGFR-1*
Rituximab	Rituxan	*CD20* on B cells
Ofatumumab	Arzerra	*CD20*
Others		*CD22*, *CD33* (myelomonocytes), *CD2* (T lymphocytes), *CD52* *IGF-1R* *GD2*
Oregovomab	OvaRex	*CA125*

CA125, Cancer antigen 125; *CD,* cluster of differentiation; *EGFR,* epidermal growth factor receptor; *GD2,* ganglioside G2; *HER-2,* human epidermal growth factor receptor 2; *IGF-1R,* insulin-like growth factor 1 receptor; *VEGF,* vascular endotheliat growth factor.

TABLE 38.10 Derivations of Names of Monoclonal Antibodies

Prefix	Target			Source			Suffix
Choice	anibi		angiogenesis inhibitor	a	=	rat	-mab
	b(a)	=	bacterial	axo	=	rat/mouse hybrid	
	c(i)	=	cardiovascular	e	=	hamster	
	f(u)	=	fungal	i	=	primate	
	gr(o)	=	growth factor	o	=	mouse	
	k(i)	=	interleukins	u		human	
	l(i)		immuno-modulating	xi		chimeric	
	mul		musculoskeletal	xizu		chimeric/humanized hybrid	
	n(e)		neural	zu		humanized	
	s(o)		bone				
	tox(a)		toxin				
	t(u)		tumors				
	v(i)		virus				

Example: Avastin is bevacizumab (beva-ci-zu-mab), an angiogenesis inhibitor

beva	ci	(cardiovascular)	zu	(humanized)	mab

General Pollicies for Monoclonal Antibodies. World Health Organization. INN Working Document 09.251 Distr.: Public English Only 24/06/2009 website: www.who.int/medicines/services/inn/generalpoliciesformonoclonalantibodies2009.pdf.

induces antibody-mediated and complement-mediated cytotoxicity and marks the cells for attack by the T lymphocytes (Table 38.10).

The infusion of MAbs can be expected to result in immediate flulike symptoms (that can be attenuated by pretreatment with steroids and antihistamines) and occasional anaphylaxis. MAbs can also cause long-term effects in the lungs (pulmonary fibrosis), in the liver as immune-mediated hepatitis (inhibitors of cytotoxic T-lymphocyte antigen 4 [CTLA4] and programmed cell death protein 1/programmed death ligand 1 [PD-1/PD-L1]), in the kidney as proteinuria from VEGF agents such as bevacizumab, and rarely, the heart by HER-2–directed therapies such as trastuzumab, pertuzumab, and ado-trastuzumab emtansine. The mechanisms of organ injury are poorly understood.

Antimetastasis Therapy

Additional new strategies for minimizing cancer spread include targeting cellular mechanisms upon which the cell depends for successful metastasis. Targets include receptor proteins and messaging ligands that direct the cell to migrate, adhere, break down the surrounding matrix in its new home, and grow new blood vessels to feed and nurture the new tumor location. Specific inhibitors at each of these steps represent new opportunities to foil cancer spread. Currently under investigation are peptide inhibitors and MAbs that targets integrin, a transmembrane receptor that plays a major role in the migration and adhesion of cells; matrix metalloproteinase, which encourages angiogenesis; or chemokine receptors, which are responsible for cellular migration. Inhibiting these cellular mechanisms suppresses cell-cell interactions, cell-matrix interactions, migration, and angiogenesis.

Immunotherapy

MAbs targeted to cell surface antigens can act to help the host immune system. Specifically, T cells and natural killer (NK) cells recognize and attack the targeted malignant cell. Reawakening this part of the immune system is beneficial to survival in immunogenic cancers (e.g., melanoma, lung, renal, and head and neck cancers). Targeted therapies as well as nonspecific antiinflammatories can act to suppress other aspects of the immunoresponse, quieting the part of the immune system that facilitates cellular adhesion and angiogenesis, thereby decreasing metastatic risk. These and other methods of manipulating the host immune response to cancer are termed *immunotherapy.* Suppressing one part of the immune system, the interleukins and other cytokines (i.e., the messaging portion of the inflammatory process), may help decrease tumor metastasis, whereas stimulating a different part of the immune system, the cellular portion of the immune system (i.e., T cells and NK cells) facilitates killing malignant cells.

Adding surgery to the mix further increases the complexity. Surgical manipulation of the tumor during excision can release tumor cells into the circulation. Growth hormone, epinephrine, serotonin, cytokines, and other neurohumeral substances secreted in response to stress are all important in healing, but they may also promote the survival of metastatic tumor cells. Meanwhile, stress and anesthetics have been shown to suppress the cellular component of immunity, potentially impeding the body's ability to handle and eliminate liberated cancer cells. Manipulating the immune system to improve patients' chances for a disease-free outcome is a complex and often conflicting challenge, but could also be an opportunity for anesthesiologists to influence outcome.

How Anesthetics Might Affect Cancer

In 1959 Bernard and Edwin Fisher injected carcinosarcoma cells intraperitoneally into rats and then examined the rats 5 months later. They found no evidence of tumor growth unless they subjected the rats to laparotomy 3 months after the injection. All of the rats that underwent laparotomy developed tumors within weeks of the surgery.[26] Several consequences of surgery may promote metastasis including: shedding of cancer cells during surgical manipulation, a decrease in antiangiogenesis factors, an increase in growth factors, and immunosuppression.[27]

In humans, additional interventions associated with surgery might also affect cancer spread at the time of surgical excision. For example, perioperative blood transfusions cause a degree of immunosuppression that might increase the risk of cancer recurrence. In contrast, the intraoperative administration of corticosteroids, also expected to suppress the immune system, was associated with improved survival in a retrospective study of Whipple procedures for pancreatic cancer.[28] Anesthetics, stress, opiates, pain, hypothermia, hyperglycemia, and other factors within the control of the anesthesiologist are immune modulators and may have a role in increasing or decreasing the recurrence rate of cancer immediately after surgical excision. Tumor excision surgery might not be the only time the homeostatic balance between tumor growth and the immune system's ability to suppress tumor growth is at risk for disruption. Subclinical concentrations of tumor cells may be present long after a cancer has been excised. Circulating tumor cells were detected in one-third of breast cancer patients after mastectomy without evidence of disease for up to 22 years.[29] Thus control over residual circulating tumor cells or subclinical micrometastases (minimum residual disease in patients after surgical excision) could, in theory, be influenced by subsequent and unrelated surgeries and anesthetics.

Multiple authors suggest that anesthesia may contribute to the recurrence of cancer,[30,31] that technique and drug choice can interact with the cellular immune system and affect long-term outcome,[32] and that the type of anesthesia could indirectly promote malignant cell development.[33] Patients who present for surgical excision of their cancer often have potentially curable solid tumors Yet, metastatic recurrence after perceived complete resection is the major cause of death. The identification of anesthetic techniques that decrease the risk of metastatic and/or recurrent disease after surgery might positively affect disease-free survival. Evidence is accumulating that suggests certain anesthetic techniques might be beneficial to patients undergoing cancer excision operations. In the future, it may be possible to enumerate specific directives on how the perioperative period and the medications used may influence the reemergence or the suppression of residual cancer cells.

Opioids

Pain has been shown to suppress immune function and to promote metastasis in rats, and analgesic treatment with morphine prevented this effect.[34] However, morphine has also been shown to (1) suppress immune function (NK T-cell activity, phagocytosis, cytokine activity); (2) stimulate angiogenesis; (3) increase prostaglandins, (4) activate mu receptors on breast and lung cancer cells as well as on NK cells, and (5) activate non-mu norepinephrine transporter (NET)-1 receptors found on breast and gastric cancer cells. Morphine stimulates endothelial proliferation, cell cycle progression, and angiogenesis in vitro and in vivo, leading to enhanced tumor neovascularization in breast cancer. The morphine antagonist naltrexone has been shown in tissue culture to suppress ovarian cancer cell proliferation equivalently to Taxol or cisplatin with short-term exposure, but to stimulate growth after long-term exposure (possibly as a result of upregulation of mu receptors over time).[35]

Clinical studies support the possibility that opioids (endogenous or administered) might influence the progression of cancer. More than 2000 women with breast cancer were categorized by the genetic makeup of their mu receptors—specifically, by the presence or absence of a polymorphism in the mu-receptor gene known as A118G. The mutation results in a less responsive receptor; that is, individuals with the A118G mutation experience less analgesia from opioids. Women with the less responsive mu receptor (A118G) were significantly less likely to die from their breast cancer within 10 years of their diagnoses.[36] Studies comparing survival in cancer patients who received standard versus narcotic-sparing anesthetic regimens (e.g., regional blockade for analgesia) have yielded provocative yet inconsistent results. In a retrospective study, 50 patients who received paravertebral blocks had one-quarter the recurrence rate of breast cancer compared with 79 patients whose pain was treated with morphine patient-controlled analgesia.[37] In another study 102 patients undergoing open radical prostatectomy received combined epidural-general anesthetics and were compared with 123 patients whose analgesic requirements were treated with opiates. The patients receiving opiates had twice the recurrence rate using prostate-specific antigen serum concentrations as a surrogate for recurrence.[38] Reviewing medical records for postoperative opioid use in 99 patients who had undergone video-assisted thoracic surgical lobectomy for non–small cell lung cancer, investigators found a strong association between the dose of opioid and the rate of recurrence.[39] Other retrospective studies have not found a difference,[40] and studies yielding an association between improved outcomes and decreased opioid have not been replicated.

Volatile Anesthetics

Volatile anesthetics have long been known to moderately suppress the immune system. Studies from as early as the 1970s investigated whether this suppression increased the risk of postoperative wound infection, and no correlation was identified. Whether or not this low-level immune suppression hinders the host's ability to kill malignant cells liberated during surgical manipulation has become a question of contemporary interest. There have been mixed results in rat models. In one study melanoma tumor cells were injected into the tail veins of mice receiving either oxygen alone, or 1.3 MAC of halothane or isoflurane. Twenty-one days later the lungs were examined for metastatic nodules. The mice receiving isoflurane had over twice and the halothane group had three times the number of nodules as controls.[41] In a similar study design using a different tumor cell line, rats exposed to halothane showed a nonsignificant increase in the number of lung metastases compared to controls.[42] In a third study, the halothane group did not differ from controls, but when a sham surgical procedure was added the number of metastases more than doubled in the lungs of the rats.[43]

Propofol

Propofol seems to have less or no immunosuppression effects. In a study on rats receiving 1 hour of propofol, halothane, ketamine, or thiopental anesthesia, only propofol did not suppress NK T-cell activity, and this correlated with a lower count of retained tumor cells in the lungs of rats receiving propofol compared with the other anesthetics.[42] Mice inoculated with thymoma tumor cells

were given subanesthetic concentrations of intraperitoneal propofol daily for 3 weeks and their cytotoxic T cells were harvested and tested for activity level. T-cell activity was enhanced compared with saline solution controls, and the tumor growth was suppressed during the study period.[44] One study compared the effects of preoperative and postoperative blood serum on the growth of breast cancer cells in culture. Half of the women had been randomly assigned to receive a propofol infusion with paravertebral blocks for their breast cancer surgery; the other half received sevoflurane and morphine. The highest concentration of serum tested against the cultured breast cancer cells showed the postoperative serum suppressed cancer cell proliferation only for the patients who had received propofol. This finding was only at the highest concentration tested and did not extend to inhibiting migration or other cellular activity. Other differences between patients that might have contributed to an effect included lower pain scores, less opioid use, the addition of local anesthetic, and the absence of volatile anesthetic exposure in the propofol group.[45]

Local Anesthetics

In vitro and animal data demonstrate direct tumoricidal activity and decreased metastatic risk with local anesthetics, and some retrospective human studies support the hypothesis that perioperative local anesthetic administration—whether subcutaneous, intravenous, or epidural— decreases the risk of tumor recurrence. Local anesthetics block voltage-gated sodium channels (VGSCs) in excitable cells. Tumor cells have been found to express an array of ion channels (including VGSCs) with subunit variants unique to the tumor. In vitro studies have shown the tumor variants of VGSCs are often more sensitive to lidocaine than those found on differentiated normal cells. Inhibiting the activity of VGSCs may decrease cellular metastatic behaviors like adhesion and migration, as well as impair proliferation.[46] Independent of the VGSCs, local anesthetics appear to inhibit kinesin motor machinery and microtubule activity, inhibit inflammatory Src signaling, directly induce apoptosis in some tumor cells, and potentially inhibit potassium and calcium channels in tumor cells.[47] Rats injected intraperitoneally with breast adenocarcinoma cells showed significantly fewer metastases after surgical intervention when they received spinal bupivacaine before the surgery.[43] Some retrospective studies in humans have supported improved survival when, for melanoma excision, local anesthetic was infiltrated into the skin[48]; for mastectomy local anesthetic was used to provide paravertebral blocks[37]; and for prostate surgery local anesthetic was administered epidurally.[38] Attempts to reproduce these findings in humans have been inconclusive.

If local anesthetics provide a survival benefit, it could be from direct effects on the cancer cells or indirect effects related to decreasing the stress response associated with otherwise painful stimuli, by decreasing perioperative opioid use, or by modulating inflammatory cytokines and shifting interleukin balances away from tumorigenic and toward tumoricidal.[49]

Other Factors

Other factors within the control or manipulation of the anesthesiologist that influence stress response, perfusion, inflammatory response, and the immune system include β agonists, cyclooxygenase-2 (COX-2) inhibitors, ketamine, benzodiazepines, hypotension, hypovolemia, hypoxia, hypothermia, and allogenic blood transfusions. All of these factors in addition to ones previously mentioned are likely contributors to the complex milieu that either promotes tumor growth and survival, or inhibits tumor survival and proliferation. One day in the future the anesthesiologist may follow a protocol avoiding certain anesthetics and attending to the emotional and physical stress response with anxiolytics, steroids, COX-2 inhibitors, statins, β blockers, and peripheral or regional nerve blockade. The anesthesiologist might administer interleukins and other cytokines to stimulate NK cell activity, administer continuous systemic infusions of local anesthetic, and administer targeted angiostatins. Maintaining patient normothermia, avoiding hypotension, and avoiding hypoxia and hyperoxia may be shown to have as significant import on long-term tumor recurrence as on acute patient outcomes.

Key Points

- Terminology reflecting chemotherapy timing in relation to surgical excision is as follows:
  a. Neoadjuvant: before surgical excision
  b. Adjuvant: after surgical excision
  c. Palliative: unrelated to timing of surgery
- Alkylating agents suppress bone marrow and cause nausea, vomiting, and diarrhea. Additionally, the platinums cause neuropathies and cyclophosphamide may inhibit plasma pseudocholinesterase activity.
- The anthracycline class of antineoplastic antibiotics is probably the most frequently cited and well-studied class of cardiotoxic anticancer agents. Oxygen free radicals are generated in the mitochondria. Cardiomyocytes are rich in mitochondria and are relatively susceptible to the toxic effects of reactive oxygen species. Cardiotoxicity is further amplified when topoisomerases are used with anthracyclines.
- Cardiomyopathy from anthracyclines can present years or decades after exposure and may be poorly responsive to inotropes.
- Bleomycin is inactivated by an enzyme that is scarce in alveolar epithelial cells. Thus bleomycin accumulates in alveolar cells and via oxygen free radical generation causes injury, increased capillary permeability and edema, necrosis of type I alveolar cells, and pulmonary fibrosis. Exposure to high oxygen concentrations may potentiate this toxicity. Current recommendations are to limit supplemental oxygen to 30% or as necessary to maintain SpO_2 of at least 90%. Judicious use of intravenous fluids, avoidance of blood transfusions, lung-protective ventilator management, and shorter surgical duration may also lower the risk of pulmonary fibrosis.
- The microtubule inhibitors may cause motor and sensory neuropathies.
- TKIs are small molecules that block the intracellular phosphorylation of proteins, the on/off switch for specific protein activity. TKIs cause significantly fewer side effects than conventional chemotherapy drugs. However, a subset can produce QT prolongation (e.g., pazopanib, vandetanib, and nilotinib). Patients are typically monitored with serial electrocardiograms by their oncology teams. Perioperative medications known to prolong QT intervals should be used judiciously.

- Monoclonal antibodies are laboratory-produced antibodies that bind to specific cellular antigens, such as a protein present on the surface of cancer cells but absent from (or expressed at lower levels by) normal cells, extracellular receptors overexpressed in cancer cells, and/or the ligands that stimulate those receptors.
- Anesthetics, stress, opiates, pain, hypothermia, hyperglycemia, and other factors within the control of the anesthesiologist are immune modulators and may have a role in increasing or decreasing the recurrence rate of cancer after surgical excision. Future investigations are likely to define best anesthetic plans for specific cancers.

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Infection, Antimicrobial Drugs, and Anesthesia

KHALED J. ZAZA AND HARRIET W. HOPF

CHAPTER OUTLINE

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Introduction

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- Monobactams (Aztreonam)
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***Clostridium Difficile* Infection**

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Historical Perspective

After antibiotics came into widespread use in the 1940s and 1950s, the possibility that giving antibiotics perioperatively might prevent surgical site infection (SSI) became a matter of debate. Miles and colleagues[1] used a guinea pig model to demonstrate that appropriate antibiotics were effective in preventing invasive infection and necrosis only when given within 2 hours before or after intradermal injection. This gave rise to the concept of a "decisive period" during which antibiotics are effective, which remains a guiding principle of antibiotic prophylaxis. Miles and colleagues also established the crucial role of local perfusion in delivering antibiotics when they showed that intradermal injection of epinephrine prior to antibiotic administration led to antibiotic failure.[1]

Knighton and colleagues,[2] using the same model, demonstrated that increased inspired oxygen was equally as effective as antibiotics in preventing infection by *Escherichia coli* and that the two effects were additive. He also concluded that the decisive period for oxygen is considerably longer (up to 6 hours) than that of antibiotics.[3]

The first controlled clinical trial of the efficacy of antibiotic prophylaxis in 1964 demonstrated a benefit in abdominal operations.[4] Thereafter, numerous clinical trials were performed with somewhat variable results, likely due to the wide range of approaches to antibiotic prophylaxis in terms of dosage, antibiotic selection, and timing of administration, among other factors. Eventually, in terms of timing, the use of antibiotic prophylaxis immediately prior to incision was demonstrated to be most effective.[5]

By the 1970s, antibiotic prophylaxis for high-risk surgery—meaning clean contaminated and contaminated cases—was becoming well accepted and widely used. In 1985, DiPiro and colleagues[6] showed that higher serum and tissue cephalosporin concentrations were better achieved when the drugs were given at the time of anesthesia induction compared with administration later in the operating room. Classen and colleagues[5] published a prospective series of 2,847 patients in 1992 and introduced the 0- to 60-minute interval that subsequently became the clinical standard. While the decisive period for human (as opposed to guinea pig) SSI extends about 60 minutes both *before* and *after* incision, dosing before incision was chosen as the standard. Resident bacteria become enmeshed in fibrin clot that forms after incision, while antibiotics generally do not penetrate the fibrin clot. Thus, it is important that antibiotics are present at adequate levels in the wound at the time of incision so that they are incorporated into the fibrin clot as it forms.

Introduction

Between 2006 and 2009, SSIs complicated approximately 1.9% of surgical procedures in the United States.[7] Rates vary widely, however, depending on site of surgery, surgical technique, patient comorbidities, and other factors. Moreover, the number of SSIs is likely underestimated given that approximately 50% of SSIs become evident after discharge from the hospital.[8]

The United States Centers for Disease Control and Prevention (CDC) define SSI as an infection related to operative procedures that occurs near or at the surgical incision (incisional or organ/

Abstract

Prevention of surgical site infection (SSI) remains a high priority, particularly as the number of surgical procedures performed continues to increase. Surgical antibiotic prophylaxis is cost-effective in reducing SSI. The ideal prophylactic agent should prevent SSI, prevent SSI-related morbidity and mortality, be cost-effective, avoid adverse effects, and have no adverse consequences on the microbial flora of the patient or the hospital. Cefazolin remains the drug of choice for prophylaxis in most procedures because it is safe and has proven efficacy. Anesthesiologists play a major role in preventing SSI and should contribute to the development of local guidelines based on national guidelines, local patterns of resistance, cost, and surgeon preference.

Keywords

surgical antibiotic prophylaxis
infection control
antibiotics
surgical site infection

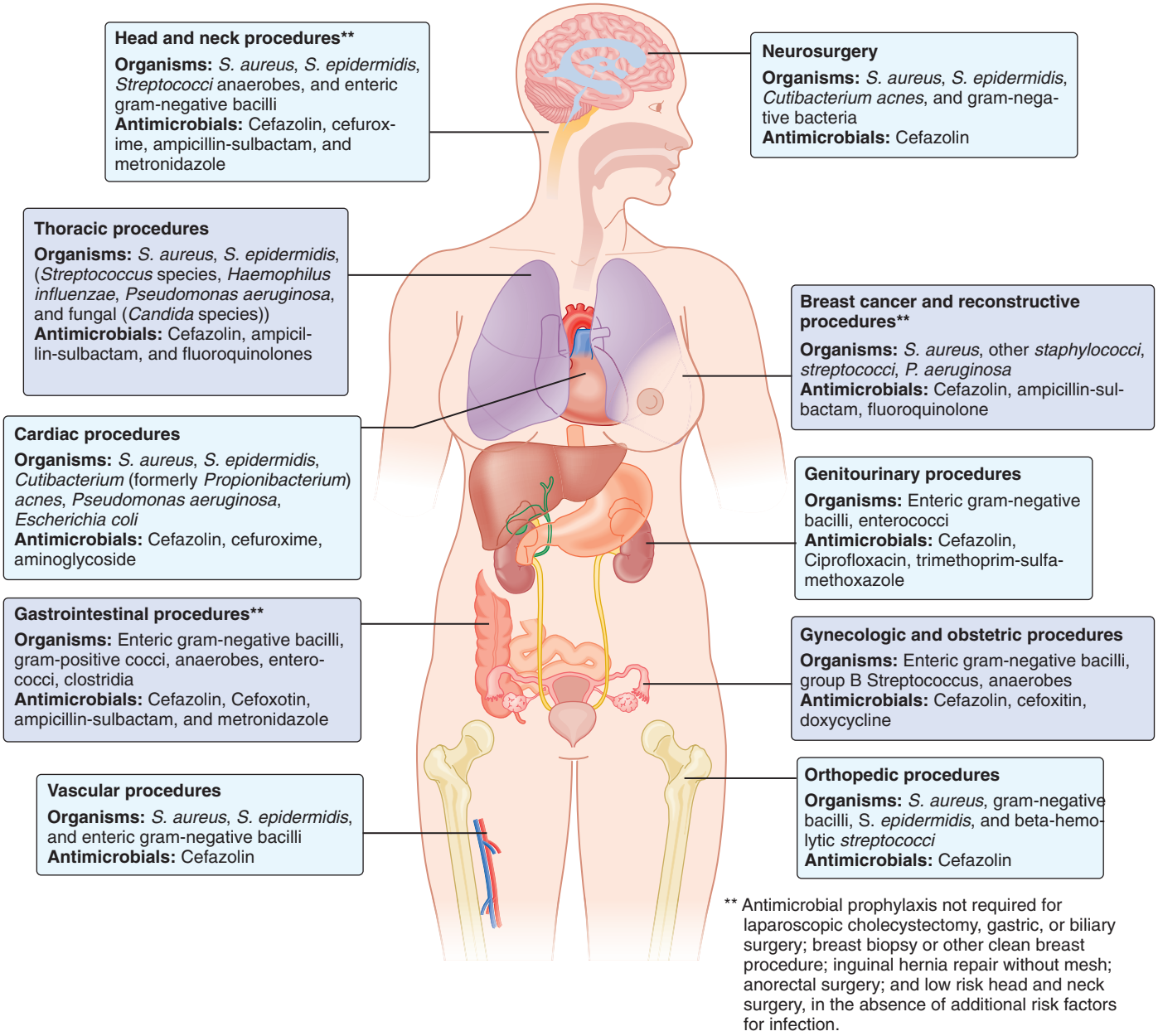
space) within 30 days of the procedure or within 90 days if a prosthetic implant was left after surgery.[9]

The prevention of SSI remains a national priority,[10] particularly as the number of surgical procedures performed in the United States continues to increase.[11,12] SSIs are a major cause of morbidity, mortality, patient suffering, intensive care unit admissions, prolonged length of stay, hospital readmission, and increased health care cost.[13–16] It has been estimated that approximately half of SSIs are preventable by application of evidence-based strategies.[17]

National quality-improvement initiatives have been established as joint efforts by professional organizations and government agencies to further improve the safety and outcomes of surgery and health care.[18–21] These efforts have identified antibiotic prophylaxis before surgery as the standard of care and a keystone for the prevention of SSI.[13,22]

Surgical Antibiotic Prophylaxis

Ideally, the antimicrobial of choice for prophylaxis should prevent SSI, prevent SSI-related morbidity and mortality, be cost-effective, avoid adverse effects, and have no adverse consequences on the microbial flora of the patient or the hospital.[21] The agent for antibiotic prophylaxis must therefore cover the most likely spectrum of bacteria present in the surgical field, and ensure adequate serum and tissue concentrations during the period of potential contamination when the surgical site is open. See Fig. 39.1 for antibiotic choice by site of surgery.



• **Fig. 39.1** Common surgical microbial organisms and antibiotic prophylaxis. Alternatives may be used when there is a patient history of hypersensitivity, contraindications, or resistance, as outlined in reference 21; note that use of alternatives should be avoided when possible, as alternatives are often less effective.[41] (Information incorporated from Bratzler DW, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Surg Infect (Larchmt)*. 2013;14:73. Antimicrobial prophylaxis for surgery. Med Lett Drugs Ther 2016; 58:63)

Wounds are divided into four classes according to the degree of expected microbial contamination during surgery (Table 39.1).[23] The most common surgical-site pathogens in clean procedures are skin flora, including *Staphylococcus aureus* and coagulase-negative staphylococci (e.g., *Staphylococcus epidermidis*).[24] In clean-contaminated procedures, the most common pathogens include gram-negative rods and enterococci in addition to skin flora. Data from the National Nosocomial Infections Surveillance (NNIS) system for 2006 to 2007 indicated that the proportion of SSI caused by *S. aureus* has increased to 30%, with about half of those caused by methicillin-resistant *S. aureus* (MRSA), although there is considerable local variability.[21] Colonization with *S. aureus*, primarily in the nares, occurs in roughly 1 in 4 persons and increases the risk of SSI by 2- to 14-fold.[25,26] MRSA infections are associated with higher mortality rates, longer hospital stays, and higher hospital costs compared with other infections.[21]

Effective antibiotic prophylaxis requires therapeutic drug concentrations to be delivered to the operative site before contamination and to remain adequate until the end of surgery. Timing of prophylactic antibiotic administration for surgical procedures depends on the pharmacology and half-life of the drug.[13,21] The preoperative dose timing recommended by the American Society of Health-System Pharmacists (ASHP) involves administering doses within 60 minutes (120 minutes for vancomycin and fluoroquinolones) before surgical incision.[12,27] Timing is challenging, because both early and late antibiotic administration increase SSI rates.[27–29] The importance of having a standardized approach to antimicrobial prophylaxis involves institution-specific guidelines that emphasize timing and choice of appropriate agents according to the type of procedure, local sensitivity patterns, and allergy (Table 39.2).

TABLE 39.1 Classification of Surgical Wounds According to Bacterial Contamination

Classification	Description
1. Clean (Class I)	Uninfected operative wounds in which no inflammation is encountered and the wound is closed primarily. A systemic tract (respiratory, alimentary, genital, or urinary tract) is not entered.
2. Clean-Contaminated (Class II):	Operative wounds in which any of the systemic tracts (respiratory, alimentary, genital, or urinary tract) is entered under controlled conditions and without unusual contamination.
3. Contaminated (Class III):	Open, fresh, traumatic wounds. Operations with major breaks in sterile technique (open cardiac massage, spillage from the gastrointestinal tract, and so on) Incisions with acute, nonpurulent inflammation (dry gangrene)
4. Dirty or Infected (Class IV):	Old infected/traumatic wounds with retained devitalized tissue, foreign bodies, or perforated viscera, or abscesses.

Adapted from Ortega G et al. An evaluation of surgical site infections by wound classification system using the ACS-NSQIP. *J Surg Res.* 2012;174(1):33–38.

TABLE 39.2 General Recommendations for Antibiotic Prophylaxis

- Administer preoperative, prophylactic antimicrobial agents only when indicated based on published clinical practice guidelines[21] and timed such that an effective concentration of the agent is established in the serum and tissues at the time of surgical incision.
- Antibiotic prophylaxis choice, dose, and timing should be determined by a hospital committee based on national guidelines,[21] local patterns of antibiotic sensitivity, and other considerations.
- Always confirm the antibiotic selection with surgeons at the time-out or earlier.
  - The surgeon may wish to delay antibiotics until after culture.
  - Antibiotics may not be indicated (e.g., low risk, elective procedures such as laparoscopic cholecystectomy or breast biopsy in which implants will not be used).
  - Make sure to record the reason for not giving antibiotics on the record.

Beta-Lactam Allergies

  - Penicillin allergy is almost never a contraindication to cefazolin or other cephalosporin administration. A *documented* history of anaphylaxis or other serious reaction (angioedema, bronchospasm, Stevens-Johnson syndrome, or toxic epidermal necrolysis) is the exception. Determine the severity of a patient's beta-lactam allergy prior to choosing an alternative antimicrobial.
  - Lack of understanding of a true allergic reaction can lead to choosing an antimicrobial with reduced efficacy, increased cost, and greater risk of side effects.
- Ideally, an antibiotic infusion should be completed before incision, but Centers for Medicare and Medicaid guidelines consider starting the infusion before incision adequate. When possible, for drugs requiring slow (> 30 minutes) infusion, the infusion should be initiated in the preoperative holding area.
- Administer the appropriate parenteral prophylactic antimicrobial agents *before* skin incision for cesarean section, as this reduces the risk of SSI compared to the previous practice of administering the antibiotic after delivery of the baby and clamping of the umbilical cord.[30]
- When a tourniquet is used, the dose should be completed at least 5 minutes before the tourniquet is inflated.
- Dosing schedules for prophylactic antibiotics are more frequent than for therapeutic use to maintain wound tissue levels throughout surgery and ongoing contamination; usually, re-dosing is recommended after 2 half-lives. For cefazolin, 1 g is the recommended re-dose, regardless of initial dose. Renal insufficiency may delay re-dosing, although the initial dose is usually not affected.
- Additional intraoperative doses should be given when there is significant blood loss (~half to 1 blood volume). Use the recommended second dose for this purpose.
- In clean and clean-contaminated procedures, do not administer additional prophylactic antimicrobial agent doses after the surgical incision is closed in the operating room, even in the presence of a drain.[30] The duration of antimicrobial prophylaxis should be less than 24 hours for most procedures
- When *therapeutic* antibiotics are given preoperatively for an infection or presumed infection (e.g., acute appendicitis), prophylactic antibiotics are not required. Each situation should be examined individually. In some cases, coverage of skin flora may be appropriate prior to skin incision; often, however, continuation of the therapeutic antibiotics is all that is required.
- Patients should be treated on a case-by-case basis. While local guidelines are the starting point, other factors, such as colonization with resistant organisms, should inform the decision.

Modified with permission from University of Utah Health.

Clinical Pharmacology of Common Perioperative Antimicrobial Agents

Beta-Lactam Antibiotics

Beta-lactam antibiotics, defined by their shared structural β-lactam ring, are among the most common perioperatively prescribed drugs, including penicillin, cephalosporins, carbapenems, monobactams, and β-lactamase inhibitors. Beta-lactam antibiotics inhibit the transpeptidation reaction in sensitive bacteria and inactivate several enzymes known as penicillin-binding proteins (PBPs) that are involved in cross-linking cell wall peptidoglycans. This interferes with osmotic stability of the bacteria. Different β-lactam antibiotics inhibit different PBPs and have varying efficacies in inhibiting bacterial growth or killing the organism. Apart from a few agents, all are excreted renally and require dose adjustment in renal insufficiency.

Resistance to penicillins and other β-lactams can be caused by inactivation of the antibiotic, altered target PBPs, or impaired penetration/efflux. Hydrolysis of the β-lactam ring by certain bacterial β-lactamases yields penicilloic acid, which lacks antibacterial activity.[31] Beta-lactamase inhibitors (clavulanic acid, sulbactam, and tazobactam) resemble β-lactam molecules and extend the spectrum of other β-lactams when combined. Altered target PBPs are the basis of MRSA and the use of an efflux pump or altered drug entry are exhibited by gram-negative species.

Penicillins

Penicillins can be assigned to 1 of 3 groups: penicillins, antistaphylococcal penicillins, or extended-spectrum penicillins. These groups have varying activity against gram-positive organisms and gram-negative organisms.

Serum concentrations of penicillins after intravenous administration is determined by protein binding. Penicillins are widely distributed in body fluids and tissues with the exception of a few formulated to delay absorption, resulting in prolonged blood and tissue concentrations. Doses must be adjusted according to renal function except with nafcillin, oxacillin, and dicloxacillin, which are cleared by biliary excretion as well.[31]

Penicillins are generally well tolerated. The serious adverse effects are due to hypersensitivity or autoimmune reactions to a penicillin–protein complex. Patients with true allergy to penicillins can be treated with alternative drugs, although, as discussed earlier, this increases the risk of SSI and thus should be avoided when the risk of cross-reaction is low, as with a history of rash.

Cephalosporins

Cephalosporins have a broader spectrum of activity than penicillins but are not active against *Listeria monocytogenes* and strains of *E. coli* and *Klebsiella* species expressing extended-spectrum β-lactamases. They are classified into 4 generations according to their spectrum of antimicrobial activity.

- **First-generation cephalosporins (cephalexin, cefazolin).** Cefazolin (half-life, 1.5 hours) is the drug of choice for surgical prophylaxis and many streptococcal and staphylococcal infections.[31]
- **Second-generation cephalosporins (cefaclor, cefuroxime, cefprozil, and the cephamycins cefoxitin and cefotetan).** Members of this group have differences in pharmacokinetics: protein binding and toxicity. In addition to inhibiting organisms covered by first-generation drugs, they have extended gram-negative coverage against organisms such as *Haemophilus influenzae* and *Bacteroides fragilis*. Cefoxitin has an approximate 4-hour half-life and must be re-dosed every 2 hours intraoperatively. While cefoxitin is effective for antibiotic prophylaxis for clean-contaminated abdominal colorectal surgery, cefazolin and metronidazole are recommended because cefazolin only requires re-dosing every 4 hours.[31,32]
- **Third-generation cephalosporins (including cefotaxime, ceftazidime, and ceftriaxone).** Cephalosporins of this group also have extended gram-negative coverage and achieve therapeutic levels in the cerebrospinal fluid when given intravenously. Ceftazidime is the only agent with useful activity against *Pseudomonas aeruginosa*. Ceftriaxone requires no dose adjustment in renal insufficiency because it is excreted through the biliary tract.
- **Fourth-generation cephalosporins (cefepime).** Cefepime is active against *P. aeruginosa*, *Enterobacteriaceae*, methicillin-susceptible *S. aureus* (MSSA), *S. pneumoniae*, and *Haemophilus* and *Neisseria* sp. It penetrates well into cerebrospinal fluid. It has a half-life of only 2 hours, however.[31]
- **Cephalosporins active against methicillin-resistant staphylococci.** Ceftaroline is a distinct cephalosporin with increased binding to penicillin-binding protein 2a, which mediates methicillin resistance in staphylococci. It is therefore active against methicillin-resistant staphylococci, and gram-negative organisms, excluding *P. aeruginosa*.[31]

Despite an increased risk of hypersensitivity in patients with documented penicillin anaphylaxis, the frequency of cross-allergenicity between the two drugs is low. Cephalosporins that contain a methylthiotetrazole group, such as cefotetan, may cause hypoprothrombinemia and bleeding disorders as well as disulfiram-like reactions. Administration of vitamin K and the avoidance of alcohol-containing medications is required in patients with such sensitivity.[31]

Monobactams (Aztreonam)

Aztreonam is active against aerobic gram-negative organisms but not gram-positive bacteria or anaerobes. It penetrates well into the cerebrospinal fluid. It should be used with caution in patients with documented allergies to ceftazidime owing to structural similarity.

Carbapenems (Doripenem, Ertapenem, Imipenem, and Meropenem)

Carbapenems have a wide spectrum of activity against most gram-negative rods and gram-positive organisms. All but ertapenem penetrate body tissues and fluids well. *Enterococcus faecium*, methicillin-resistant strains of staphylococci, and *C. difficile* are resistant to the carbopenems. Imipenem, unlike doripenem and meropenem, is administered together with cilastatin, an inhibitor of renal dehydropeptidase, to prevent inactivation. Excessive levels of imipenem in patients with renal failure may lead to seizures.[31]

Aminoglycosides (Including Streptomycin, Neomycin, Kanamycin, Amikacin, Gentamicin, and Tobramycin)

Aminoglycosides diffuse across the bacterial cell membrane and irreversibly inhibit protein synthesis by binding to the 30S ribosomal protein subunits. In combination with β-lactam antibiotics and vancomycin, they exhibit synergistic killing against drug-resistant gram-positive and gram-negative bacteria. They are water soluble and more active at alkaline than at acid pH.[33]

Mechanisms of resistance to aminoglycosides include inactivation of the drug by adenylylation, acetylation, or phosphorylation as

well as impaired entry or deleted/altered target receptors. Aminoglycosides (half-life ~ 2–3 hours) exhibit concentration-dependent killing (higher concentrations kill a larger proportion of bacteria faster) and have a significant postantibiotic effect through which their antibacterial activity persists beyond the time during which measurable drug is present.[33]

Aminoglycosides are ototoxic and nephrotoxic. Slow administration, over 30 to 60 minutes, reduces the risk of toxicity. Toxicity increases with concurrent administration of loop diuretics (e.g., furosemide or ethacrynic acid) or other nephrotoxic antimicrobial agents (e.g., vancomycin or amphotericin). The administration of high doses with nondepolarizing neuromuscular blocking agents can result in prolonged neuromuscular blockade, which is usually reversible with calcium gluconate or neostigmine.[33]

Fluoroquinolones

The clinically administered fluoroquinolones are active against a variety of gram-positive and gram-negative bacteria, including *P. aeruginosa and Enterobacter*. They act by inhibiting bacterial DNA synthesis and replication. Resistance is through alteration in drug permeability and target enzymes.[34]

Most fluoroquinolones require dose adjustment in renal insufficiency, except for moxifloxacin, which is metabolized in the liver and should be used with caution in patients with hepatic dysfunction.

Fluoroquinolones are generally well tolerated. Use of fluoroquinolones is associated with a higher risk of *C. difficile* infection. Photosensitivity has been reported with lomefloxacin and pefloxacin. Gatifloxacin, levofloxacin, gemifloxacin, and moxifloxacin should be avoided or used with caution in patients with known QTc interval prolongation or uncorrected hypokalemia. Fluoroquinolones are not recommended as first-line agents for patients under 18 years of age owing to risks of growing cartilage damage and arthropathy. Fluoroquinolones also present a risk of tendinopathy. Fluoroquinolones should be reserved for patients in whom there are not equally effective alternative options.[34,35]

Vancomycin

Vancomycin is a glycopeptide antibiotic primarily active against gram-positive bacteria. It also inhibits cell wall synthesis by binding to the bacterial d-Ala-d-Ala peptidoglycan binding site, preventing cross-linking and causing lysis. Resistance is through the modification and replacement of the d-Ala-d-Ala terminus by d-lactate. Vancomycin is effective against methicillin-resistant staphylococci and is widely distributed in the body. However, penicillins are still more effective against methicillin-susceptible strains.[31]

The administration of vancomycin with other aminoglycosides increases the risk of ototoxicity and nephrotoxicity associated with the drug. Dose adjustment is required in renal insufficiency. Infusion-related flushing, known as "red man" syndrome, is also a common reaction attributed to the release of histamine. These adverse effects, along with hypotension, can be prevented by prolonging the infusion period (1–2 hours) or pretreating with an antihistamine, such as diphenhydramine.[31]

Clindamycin

Clindamycin inhibits protein synthesis by binding to the 50S bacterial ribosomal subunit and interfering with aminoacyl translocation reactions. It is active against streptococci, staphylococci, pneumococci, bacteroides species, and other anaerobes. Enterococci and gram-negative aerobic organisms are resistant because of poor permeability. Clindamycin is recommended for prophylaxis in patients with true penicillin allergies, although it is not as effective. It should be administered over 15 to 30 minutes to prevent hypotension.[36]

Resistance to clindamycin, which generally confers cross-resistance to macrolides, is through enzymatic inactivation or altered target receptor protein. Clindamycin penetrates well into abscesses (half-life ~ 2.5 hours) and is metabolized by the liver. No dosage adjustment is required for renal insufficiency. Impaired liver function can sometimes occur with the administration of clindamycin as well as increased risk for diarrhea and colitis due to *C. difficile*.[36]

Metronidazole

Metronidazole is an antiprotozoal drug with potent antibacterial activity against anaerobes, including *bacteroides* and *clostridium* species. It forms toxic metabolites intracellularly through absorption by anaerobic bacteria and sensitive protozoa. Metronidazole is widely distributed in tissues and is metabolized in the liver. Patients taking metronidazole should be instructed to avoid alcohol because of a disulfiram-like effect.[37]

Amphotericin B

Amphotericin B is a macrolide antifungal with the broadest spectrum of action, yet quite toxic. It is insoluble in water; therefore, it is administered either as a colloidal suspension with sodium deoxycholate or packaged in liposomal preparations to reduce toxicity.

Amphotericin B binds to ergosterol in fungal cell membranes and alters permeability through the formation of pores, leading to cell death. Resistance occurs through impaired binding or altered target sterols.

The drug is widely distributed in most tissues (half-life ~15 days); no dose adjustment is required in hepatic or renal dysfunction. Toxicity ranges from infusion-related chills, muscle spasms, and hypotension to renal tubular acidosis with severe potassium and magnesium wasting. Premedication with antihistamines or corticosteroids can be helpful, as can slow infusion rates. It is because of this that amphotericin B is usually replaced with the newer azole drugs later during treatment when the fungal burden is reduced.[38]

Selection of Antimicrobial Agents for SSI Prevention

A broad variety of agents are approved for use in surgical antimicrobial prophylaxis, including first- and second-generation cephalosporins, clindamycin, gentamicin, carbapenems, fluoroquinolones, and vancomycin.[21] Cefazolin remains the drug of choice for prophylaxis in most procedures. It is the most widely studied antimicrobial agent with proven efficacy. It has a desirable duration of action, favorable spectrum of activity against organisms commonly encountered in surgery, reasonable safety, and low cost.[21] The use of newer, broad-spectrum agents should be avoided to reduce the emergence of resistant bacterial strains.

Cephalosporins are also the antibiotics most commonly associated with allergic reactions. When a patient develops anaphylaxis intraoperatively, the offending agent is often difficult to identify and supportive care is indicated. In patients with a documented anaphylactic (immunoglobulin E [IgE]-mediated) or other serious reaction such as angioedema, bronchospasm, Stevens-Johnson

syndrome, or toxic epidermal necrolysis to a given antibiotic, the antibiotic should be avoided and replaced with antibiotics with a similar spectrum of coverage in subsequent surgeries.[21] Cephalosporins can, however, be used safely in patients with a history of non-IgE-mediated reactions, such as rash or nausea.[39,40]

The most commonly reported antibiotic allergy is to penicillin. In patients with an anaphylactic reaction to penicillin, there is a less than 1% cross-reactivity to cephalosporins. While this risk is low, it is recommended that cephalosporins be avoided in such patients and replaced with appropriate alternatives, such as vancomycin or clindamycin. Most reactions to penicillin, however, are not IgE mediated, including the development of a rash or hives, nausea, or gastrointestinal distress. For patients who report a non-IgE-mediated reaction or who do not know what their reaction was, there is no contraindication to cephalosporins, including cefazolin.[39,40] Alternatives to cefazolin have less efficacy, more side effects, and are usually more expensive. Vancomycin, while it kills most *S. aureus* (bactericidal), prevents the growth only of enterococcus (bacteriostatic), has poor bone penetration, and must be given slowly to prevent vasodilation and hypotension. Clindamycin can induce MRSA infections and cannot be administered as a bolus dose. Blumenthal et al.,[41] in a cohort of over 8000 patients who underwent surgery for which cefazolin is the recommended agent for antibiotic prophylaxis at Massachusetts General Hospital from 2010 to 2014, found a 50% increased risk of SSI in the 11% of patients who reported an allergy to penicillin, including those who report side effects, intolerance, and non-IgE-mediated hypersensitivity in addition to true allergy. The increased rate of SSI in these patients was completely attributable to the use of alternative antibiotics—including clindamycin, vancomycin, and gentamicin—for surgical antibiotic prophylaxis. Thus, it is important to use cefazolin whenever appropriate and to reserve the alternatives for patients in whom there is a true contraindication to cephalosporins.[42,43]

In the context of known or suspected MRSA colonization, vancomycin is generally the prophylactic antibiotic of choice. Screening for MRSA carriage in the general population remains controversial, but there is some evidence for cost-effectiveness in certain subgroups of patients, such as joint replacement and cardiac surgery.[44,45] Screening for *S. aureus* requires only a nasal swab, and decolonization is relatively easy and safe, requiring nasal mupirocin ointment and showering with chlorhexidine for 5 days.[46] Administration of vancomycin is complex, as it must be given slowly and usually requires 1 to 2 hours to infuse completely. In general, it is considered acceptable if the infusion is started within 120 minutes before incision. Because the infusion must be started preoperatively, the timing can be difficult to estimate. Therefore, it is recommended to give a dose of cefazolin, as well, in the operating room as a way to ensure adequate antibiotic levels at the time of incision while providing coverage for MRSA with vancomycin.[21]

Dosing and Administration of Prophylactic Antibiotics

Dosing guidelines are based on achieving and maintaining adequate tissue levels of the antibiotic throughout surgery, while the incision is open (see Tables 39.3 through 39.5 for full dosing recommendations). Dosing is usually by intervals of weight (e.g., 60–120 kg) in adults and by mg/kg basis in pediatric patients up to the standard adult dose.[47,48] Aminoglycosides are an exception, with weight-based dosages up to a maximum dose.[49] Fluoroquinolones should be avoided in pediatric patients because of the potential for serious toxicity, including arthropathy with erosions of the cartilage in weight-bearing joints and a higher risk of *C. difficile* infection.[34]

Intraoperative dosing of prophylactic antibiotics is generally more frequent than therapeutic dosing and is based on drug half-life, such that high tissue levels (above the minimum inhibitory concentration for that antibiotic) are maintained throughout surgery. Intraoperative re-dosing is recommended when the duration of the procedure exceeds 2 half-lives of the drug.[21] For example, cefazolin is dosed every 8 hours for therapeutic indications but repeated every 4 hours intraoperatively.[21] Antibiotics should also be re-dosed after loss of more than half of a patient's estimated blood volume during a procedure.

The route of administration of prophylactic antibiotics varies according to the type of surgical procedure, but for the majority of procedures, intravenous administration is preferred because it results in rapid and predictable serum and tissue concentrations. Oral antibiotics are appropriate for some outpatient urologic procedures, such as prostate biopsy or cystoscopy. In colorectal surgery, oral antibiotics can reduce SSI rate when given in addition to intravenous prophylactic antibiotics.[50–52]

Continuous infusion of perioperative antibiotics has been evaluated in cardiac surgical procedures as an alternative to intermittent dosing; there is some evidence of benefit.[53,54] During cardiopulmonary bypass, changes in effective circulating volume and total volume of distribution can occur, which can reduce tissue levels below minimum inhibitory concentrations with agents such as cefazolin, which exhibit time-dependent antimicrobial killing.[55–57]

Antimicrobial administration should be complete at least 5 minutes before procedures that restrict blood flow to the surgical site, such as cross-clamping of an artery or inflation of a tourniquet, to ensure adequate tissue levels of antibiotic prior to interruption of blood supply.

Patient-related factors associated with an increased risk of SSI include extremes of age; obesity; diabetes mellitus; tobacco use; colonization with pathogenic microorganisms, such as MRSA and enterococcus; coexistent remote infections; and impaired immunity.[21] Obese patients have an increased risk of SSI, which is multifactorial.[58,59] One recently identified factor is altered pharmacokinetics and inadequate antibiotic dosing.[60–63] Cefazolin doses should be adjusted for total body weight rather than lean body weight. While details are not fully evaluated, and recommendations vary somewhat, the recommended dose is 30 mg/kg up to a maximum of 1.5 g for patients weighing less than 60 kg, 1 to 2 g for patients weighing 60 to 80 kg, 2 g for patients weighing 80 to 120 kg, and 3 g for patients weighing greater than 120 kg. The repeat dose for all adult patients is 1 g, regardless of initial dose. Cefazolin has a low cost and favorable safety profile, so that most guidelines recommend erring on the side of higher doses.[21]

In general, prophylactic antibiotics should not be continued after the closure of the incision; when they are continued, they should be discontinued by 24 hours following surgery. Prolonging the course of prophylactic antibiotics does not reduce the risk of infection but does increase the risk of adverse consequences of antibiotic administration, including resistance, *C. difficile* infection, and sensitization.[21]

Clostridium Difficile Infection

Many of the antibiotics used perioperatively for prophylaxis—such as fluoroquinolones, clindamycin, and broad-spectrum penicillins

TABLE 39.3 Drugs and Doses Available Routinely for Antibiotic Prophylaxis to Be Given in Operating Room by Anesthesia Team

Drug	Initial dose (< 60 kg)	Initial Dose (60-120 kg)	Initial Dose (≥ 120 kg)	Timing[a]	Repeat Dose[b] (Interval)	Repeat Dose Interval for SCr > 3
Ampicillin[a]		2 g		Infuse over 10–15 min. Start 0–60 min before incision.	2 g (2 h)	6 h
Cefazolin[c]	1.5 g	2 g	3 g	Slow IV push 0–60 min before incision	1 g (4 h)	12 h
Cefoxitin		2 g		Slow IV push 0–60 min before incision	1 g (2 h)	12 h
Cefuroxime		1.5 g		Slow IV push 0–60 min before incision	1.5 g (4 h)	No re-dose
Ciprofloxacin (IV)[a]		400 mg		Infuse over 60 min. Start 0–60 min before incision.	400 mg at 6 h	12 h
Clindamycin[a]		900 mg		Infuse over 15–30 min. Start 0–60 min before incision	600 mg (6 h)	12 h
Ertapenem[a]		1 g		Infuse over 15–30 min, Start 0–60 min before incision	1 g (24 h)	24 h
Fluconazole[a]		400 mg		Infuse over 30–60 min. Start 0–60 min before incision.	400 mg (24 h)	24 h
Gentamicin[a]		5 mg/kg max 320 mg		Infuse over 30 min. Start 0–60 min before incision.	No re-dose	No re-dose
Levofloxacin[a]		500 mg		Infuse over 60 min, Start 0–120 min before incision	500 mg (12 h)	24 h
Metronidazole[a]		500 mg		Infuse over 30 min. Start 0–60 min before incision.	500 mg (6 h)	12 h
Aztreonam[a]		2 g		Infuse over 30 min. Start 0–60 min before incision.	1 g (4 h)	12 h
Meropenem[a]		500 mg		Infuse over 30 min, Start 0–60 min before incision.	500 mg (4 h)	12 h
Caspofungin		50 mg		Infuse over 60 min. Start 0–120 min before incision.	50 mg (24 h)	24 h
Ampicillin/Sulbactam (Unasyn)[a]		3 g		Infuse over 30 min, Start 0–60 min before incision	1.5 g (4 h)	12 h
Trimethoprim/Sulfamethoxazole		160 mg		PO: 0–60 min before biopsy	-	-

[a]Infusion must begin prior to incision (Centers for Medicare and Medicaid guidelines). Ideally, it should be completed before incision.
[b]Note that dosing schedule is more frequent than for therapeutic use to maintain wound tissue levels throughout surgery and ongoing contamination. Additional intraoperative doses should be given when there is significant blood loss (~ half to 1 blood volume). Use the recommended second dose for this purpose.
[c]. For orthopedic joint cases, based on recent American Academy of Orthopedic Surgeons recommendations, cefazolin should be dosed at 1 g for < 60 kg, 2 g for 60–120 kg, and 3 g for > 120 kg. The repeat dose remains the same: 1 g every 4 hours intraoperatively.
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and cephalosporins—increase the risk of *C. difficile* infection;[64–66] the spore-forming, toxin-producing, gram-positive anaerobe behind antibiotic-associated diarrhea and pseudomembranous colitis. *C. difficile* infection is one of the most common nosocomial infections and is a significant cause of morbidity and mortality, especially among older adult hospitalized patients.[67] The incidence of *C. difficile* infection among hospitalized adults in the United States nearly doubled between 2001 and 2010.[68]

Among the established risk factors (advanced age, hospitalization, and severe illness) antibiotic use is the most widely recognized and modifiable risk factor.[69–72] Though any antibiotic can predispose to colonization by *C. difficile*, the increased duration of therapy by multiple broad-spectrum antimicrobials significantly increases incidence.[73]

Antimicrobials disrupt the normal colonic flora and facilitate the growth and colonization of the gram-positive bacteria; exotoxins then bind to receptors on intestinal epithelial cells, leading to inflammation and diarrhea.

The management of *C. difficile*–induced diarrhea involves oral vancomycin/fidaxomicin, supportive care, and discontinuation of the inciting antibiotic as soon as possible; antimotility agents, such as loperamide and opiates, are also usually avoided. *C.*

TABLE 39.4 Drugs and Doses Available Routinely for Antibiotic Prophylaxis—Re-dose for Therapeutic Antibiotics Started Preoperatively[a]

Drug	Initial Dose (< 80 kg)	Initial Dose (≥ 80 kg)	Initial Dose (≥ 120 kg)	Timing	Repeat Dose[b] (Interval)	Repeat Dose Interval for SCr >3
Piperacillin/Tazobactam (Zosyn)	3.375 g	3.375 g		Infuse over 30 min[1]	Re-dose prior to incision if most recent dose > 2 h before incision; then re-dose at 2 h intervals.	12 h
Ampicillin/Sulbactam (Unasyn)	3 g	3 g		Infuse over 30 min[1]	Re-dose prior to incision if most recent dose > 2 h before incision; then re-dose at 4 h (1.5 g).	12 h
Meropenem	500 mg	500 mg		Infuse over 30 min[1]	Re-dose prior to incision if most recent dose > 2 h before incision; then re-dose at 4 h.	12 h
Cefazolin	1 g	2 g	3 g	Slow IV push 0–60 min before incision	Re-dose prior to incision if most recent dose > 2 h before incision; then re-dose 1 g at 4 h.	12 h
Cefepime	1 g	2 g		Infuse over 30 min[1]	Re-dose prior to incision if most recent dose > 2 h before incision; then re-dose 1 g at 4 h.	-

[a]Protocol used when therapeutic antibiotics are started preoperatively (e.g., in the emergency department) to treat actual or presumed infection, for example, appendicitis or acute cholecystitis. Either the same drug can be continued or the usual prophylactic antibiotic agent for that procedure may be used. Note that, procedurally, these cases are not counted in our compliance monitoring, because these are therapeutic rather than prophylactic guidelines. This table is created to provide guidance to providers in determining when to re-dose the antibiotics from the perspective of patient benefit.
[b]Note that dosing schedule is more frequent than for therapeutic use to maintain wound tissue levels throughout surgery and ongoing contamination. Additional intraoperative doses should be given when there is significant blood loss (~ half to 1 blood volume). Use the recommended second dose for this purpose.
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difficile is easily spread; thus, implementing infection-control policies to minimize cross-contamination is critical. Of note, *C. difficile* spores are not susceptible to alcohol; thus, hand-washing with soap and water is required to prevent cross-contamination from infected patients.

Cost Containment

Although antimicrobial prophylaxis plays an important role in reducing the rate of SSI, other factors—such as attention to basic infection-control strategies,[74] the surgeon's experience, duration of the procedure, operating room environments, instrument sterilization, perioperative temperature and glycemic control, and the underlying medical condition of the patient—all impact SSI rates.[75,76]

The costs of SSI are thousands of dollars per infection, especially those involving prosthetic joint implants[17,77] or antimicrobial-resistant organisms.[78] The cost of treatment in patients who develop MRSA infection is twice as high as in patients with methicillin-susceptible staphylococcal infections. Patients with MRSA infections also have double the mortality.[79]

Summary

The prevention of SSI remains a high priority, particularly as the number of patients at risk for SSI continues to increase. Anesthesiologists can make a major contribution to preventing SSI and should work in consultation with the surgical team to implement guidelines determined by the local infection-control committee. Surgical antibiotic prophylaxis is cost-effective in reducing SSI. The ideal prophylactic agent should prevent SSI, prevent SSI-related morbidity and mortality, be cost-effective, avoid adverse effects, and have no adverse consequences on the microbial flora of the patient or the hospital.[21] Cefazolin remains the drug of choice for prophylaxis in most procedures because it is safe and has proven efficacy. Anesthesiologists play a major role in preventing SSI and should contribute to the development of local guidelines based on national guidelines, local patterns of resistance, cost, and surgeon preference.

Emerging Developments

While the efficacy of perioperative prophylactic antibiotics is well established, a number of opportunities remain to optimize both antibiotic prophylaxis and other approaches to preventing SSIs. Development of standardized decision support systems within electronic health records to optimize antibiotic choice and provide recommended initial doses and considerations in administration would advance the quality of patient care delivered across all health care environments. Questions remain related to weight-based antibiotic administration, re-dosing schedule, and antimicrobial efficacy in pediatric populations, including dosing in newborns as well as antibiotic choice and dosing across all age groups.

Given the increasing prevalence of antibiotic-resistant organisms, the development of new antibiotics and antibiotic classes with enhanced spectrum of activity will become increasingly important. While preoperative MRSA and MSSA screening is increasingly used, particularly for cases such as joint replacement and cardiac surgery, further studies to evaluate the cost-effectiveness and rational use of such testing would provide evidence for better management of decontamination during the perioperative period. Recent studies have demonstrated that many antibiotics induce changes in bacterial metabolism that promote the formation of reactive oxygen species that lead to bacterial cell death.[80] Thus, antibiotics appear to require

TABLE 39.5 Drugs and Doses Available Routinely for Preoperative Antibiotic Prophylaxis

Drug	Initial Dose	Timing	Repeat Dose (Interval)
Ciprofloxacin IV	400 mg	Infuse over 60 min. Start 0–60 min prior to incision.	400 mg (6 h)
Levofloxacin	500 mg	Infuse over 60 min. Start 0–120 min prior to incision.	500 mg (12 h)
Vancomycin[a] (<70 kg)	1 g	Infuse at 1 g/h. Start 0–120 min prior to incision.[c]	Single re-dose at 8 h No repeat dose for serum creatinine>2
Vancomycin[a] (70–110 kg)	1.5 g	Infuse at 1 g/h. Start 0–120 min prior to incision.[c]	Single re-dose at 8 h No repeat dose for serum creatinine>2
Vancomycin[a] (≥ 110 kg)	2 g	Infuse at 1 g/h. Start 0–120 min prior to incision[c]	Single re-dose at 8 h No repeat dose for serum creatinine >2
Ciprofloxacin (oral)[b]	500 mg	Take PO 0–60 min prior to incision.	400 mg IV (6 h)

[a]Vancomycin is indicated only for patients per protocol undergoing cardiac, orthopedic, or abdominal wall reconstruction surgery and at high risk with a positive screen or no screen. These patients should be identified in the preoperative clinic. They should never be scheduled as the first case, and should be asked to come in 3–4 hours before surgery so that vancomycin can be initiated in preoperatively.

[b]Oral administration of ciprofloxacin is acceptable for urology cases, but IV is preferable when IV access is available.

[c]To avoid having a SCIP fallout when the infusion is started more than 120 minutes prior to incision (60 minutes for ciprofloxacin), patients should receive either cefazolin or clindamycin 0–60 minutes prior to incision in the operating room.

Notes

Penicillin allergy is almost never a contraindication to cefazolin or other cephalosporin administration. A *documented* history of anaphylaxis or other serious reaction (angioedema, hives, bronchospasm, Stevens-Johnson syndrome, or toxic epidermal necrolysis) is the only exception.

Always confirm the antibiotic plan with surgeons at the time-out or earlier.

The surgeon may wish to delay antibiotics until after culture.

Antibiotics may not be indicated.

Make sure to record the reason for not giving antibiotics on the record.

Ideally, an antibiotic infusion should be completed before incision, but Centers for Medicare and Medicaid guidelines consider starting the infusion before incision adequate. When possible, for drugs requiring slow (> 30 min) infusion, the infusion should be initiated in preop.

When a tourniquet is used, the dose must be completed at least 5 minutes before the tourniquet is inflated.

Additional intraoperative doses should be given when there is significant blood loss (~ half to 1 blood volume). Use the recommended second dose for this purpose.

When *therapeutic* antibiotics are given for an infection or presumed infection (e.g., acute appendicitis), prophylactic antibiotics are not required. Each situation should be examined individually: When was the antibiotic given? Which antibiotic was used? In some cases, coverage of skin flora may be appropriate prior to skin incision, but often continuation of the therapeutic antibiotics is all that is required.

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oxygen for optimal function; the dose-dependence of this relationship is an area for future research.

Developing technology to monitor antimicrobial serum and tissue concentrations could create the opportunity for personalized approaches to antibiotic prophylaxis. Similarly, identifying pharmacogenomic influences on antibiotic metabolism and efficacy—as well as rapid, accurate tests for a patient's resident flora—would allow personalization of perioperative prophylactic antibiotic selection and dosing.

While antibiotic prophylaxis is a critical component of current perioperative surgical management, other factors—including improved antisepsis, reduction of cross-transmission of pathogens, and enhancement of host defenses—are complementary. Improvements in all aspects of perioperative infection control are required to further reduce SSI rates. For example, recent studies have demonstrated that increasing the rate of hand hygiene by anesthesiologists from less than 1 to 7 times an hour reduces workspace contamination, intravenous stopcock contamination, and health care–associated infection rates.[81] Increasing compliance of anesthesiologists with the World Health Organization's Five Moments of Hand Hygiene[82] might increase the efficacy of antibiotic prophylaxis. Similarly, inattention to requirements for sterile compounding and handling of intravenous medications by anesthesiologists may lead to individual cases or outbreaks of infectious complications. For example, there have been documented outbreaks involving bupivacaine and steroids used for joint injections in pain clinics.[83] The lipid nature of propofol supports the growth of bacteria and provides an opportunity for both intrinsic and extrinsic contamination. Soon after its introduction, improper handling of propofol was associated with sepsis and even death; more recent reports of similar propofol-associated infections and sepsis suggest that manufacturer guidelines are not universally followed.[84]

Key Points

- Surgical antibiotic prophylaxis is indicated for most operations and is a keystone for the prevention of SSI.
- The antimicrobial of choice for prophylaxis should prevent SSI, prevent SSI-related morbidity and mortality, be cost-effective, avoid adverse effects, and be chosen based on the microbial flora of the patient or the hospital.
- The American Society of Health-System Pharmacists (ASHP) recommends administering doses within 60 minutes of surgical

incision for most antibiotics and within 120 minutes for vancomycin and fluoroquinolones.

- Anesthesiologists are in the best position to administer most prophylactic antibiotics; therefore, they make a major contribution to preventing SSI. Anesthesiologists should work in consultation with the surgical team and the local infection-control committee to implement guidelines for antibiotic prophylaxis.

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40 Renal Physiology

JOSEPH S. MELTZER

CHAPTER OUTLINE

Renal Blood Flow and Glomerular Filtration Rate
- Renal Blood Flow
- Renal Clearance
- Renal Plasma Flow
- Glomerular Filtration Rate

Age-Related Renal Changes

The Nephron

Water and the Kidney

Salt and the Kidney

Potassium and the Kidney

Toxin and Metabolite Excretion

Acid–Base Balance

Renal Hormone Production
- Defining Renal Failure

Risk of Perioperative Acute Kidney Injury

Acute Kidney Injury in Surgical Patients

Assessment and Management of Acute Kidney Injury
- Preoperative Approach

Intraoperative Management of Renal Function

Anesthetic Drugs and Impaired Renal Function

Common Perioperative Medications That Impair Renal Function

Perioperative Renal Replacement Therapy

Hepatorenal Syndrome

Emerging Developments
- Prevention and Biomarkers for Acute Kidney Injury

The kidney is a complex multifunctional organ that can be affected by anesthesia and the physiologic alterations of the perioperative period. The main functions of the kidney in the context of anesthesiology include (1) regulation of salt and water balance, (2) toxin and metabolite elimination (including drugs), (3) electrolyte homeostasis, (4) acid–base balance, and (5) hormone production. These functions must be understood and recognized for optimal patient care during and after surgery or intensive care. The anesthetist must understand the kidney's role in salt and water balance; otherwise, hypovolemia, volume overload, or acute renal failure can complicate surgery. The elimination of toxins and metabolites is important in the perioperative period; this function also includes the elimination of many anesthetic drugs, which can be viewed as exogenous toxins given their narrow therapeutic margin. Electrolyte balance is key for cardiovascular stability and prevention of dysrhythmias. Acid–base balance is vital for proper enzyme and cellular function. Hormones such as renin and erythropoietin play critical roles in blood pressure regulation and red blood cell production, critical concerns during the perioperative period. These many functions of the kidney help maintain homeostasis during periods of changing fluid and electrolyte intake and losses. Fig. 40.1 shows the anatomy and blood supply of the kidneys.

Renal Blood Flow and Glomerular Filtration Rate

Renal Blood Flow

The kidney is the most robustly perfused organ per gram of tissue in the human body, receiving 20% to 25% of cardiac output. Renal blood flow (RBF) is directly proportional to the *transrenal gradient*, the pressure difference between the renal artery and renal vein, and inversely proportional to the resistance of the renal vasculature. Autoregulation of RBF is accomplished by changing renal vascular resistance as arterial pressure changes, thereby maintaining constant blood flow across a range of mean arterial pressure from 50 to 150 mm Hg in normotensive people.[1]

While global RBF is relatively constant, its distribution within the kidney is quite heterogeneous. The renal cortex and renal cortical nephrons receive 90% of RBF while the renal medulla and its juxtamedullary nephrons receive only about 10%. This great disparity in regional blood flow makes the renal medulla sensitive to ischemic injury. RBF is calculated by determining both the clearance of a given substance from the plasma and the renal plasma flow (RPF).

Renal Clearance

The renal clearance of a substance is the volume of plasma completely cleared of the substance per unit time.

$$C = U \times V/P, \quad [1]$$

where C = clearance in mL/min, U = urine concentration in mg/mL, V = urine volume/time in mL/min, and P = plasma concentration in mg/mL.

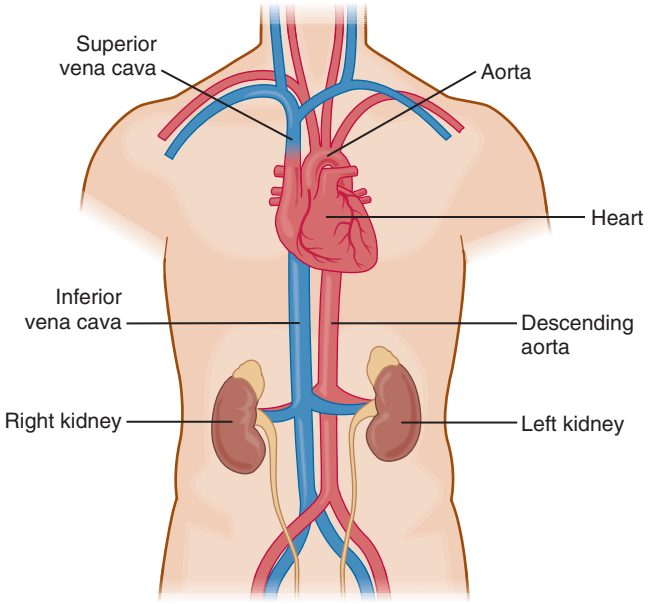
Abstract

The main functions of the kidney are (1) regulation of salt and water balance, (2) toxin and metabolite elimination, (3) electrolyte homeostasis, (4) acid–base balance, and (5) hormone production.

Renal blood flow is directly proportional to the transrenal gradient, the pressure difference between the renal artery and the renal vein. Autoregulation mechanisms maintain constant renal blood flow over a range of blood pressures.

Keywords

clearance
glomerular filtration rate
renin
acid-base balance
electrolyte homeostasis
acute kidney injury



• **Fig. 40.1** The anatomy of the kidneys. The kidneys are retroperitoneal organs attached to the abdominal aorta and inferior vena cava by the renal arteries and veins, respectively. The right kidney most often lies caudal to the left kidney, inferior to the liver.

Renal Plasma Flow

RPF is calculated by the clearance of para-aminohippuric acid (PAH), as at low concentrations this compound is completely cleared from the plasma by renal tubular filtration and secretion in a single pass.

[2]

$$RPF = C_{PAH} = U_{PAH} \times V/P_{PAH},$$

where RPF = renal plasma flow in mL/min, C_{PAH} = clearance of PAH in mL/min, U_{PAH} = urine concentration of PAH in mg/mL, V = urine flow rate in mL/min, and P_{PAH} = plasma concentration of PAH in mg/mL.

RBF (in mL/min) is determined via the following equation:

[3]

$$RBF = RPF/1 - \text{hematocrit}.$$

Glomerular Filtration Rate

Glomerular filtration rate (GFR) is measured by the clearance of inulin, a fructose polysaccharide that is readily filtered but not resorbed or secreted by the renal tubule, therefore being directly proportional to GFR.

[4]

$$GFR = U_{inulin} \times V/P_{inulin} = C_{inulin},$$

where GFR = glomerular filtration rate in mL/min, U_{inulin} = urine concentration of inulin in mg/mL, V = urine flow rate in mL/min, P_{inulin} = plasma concentration of inulin in mg/mL, and C_{inulin} = clearance of inulin in mL/min.

Normal GFR is about 120 mL/min in men and 100 mL/min in women. GFR can also be estimated with blood urea nitrogen (BUN) and plasma creatinine. BUN and plasma creatinine increase as GFR decreases. Notably, GFR decreases with age although plasma creatinine remains relatively constant owing to a decrease in muscle mass. Creatinine clearance is less accurate than inulin clearance but much more practical to measure.

[5]

$$GFR \approx U_{creatinine} \times V/P_{creatinine} = C_{creatinine},$$

where GFR = glomerular filtration rate in mL/min, $U_{creatinine}$ = urine concentration of creatinine in mg/mL, V = urine flow rate in mL/min, $P_{creatinine}$ = plasma concentration of creatinine in mg/mL, and $C_{creatinine}$ = clearance of creatinine in mL/min.

The filtration fraction (FF) is the fraction of RPF that is filtered across the glomerular capillaries and is normally about 0.20. Therefore, 20% of the RPF is filtered, leaving 80% of the RPF to leave the glomerulus via the efferent arterioles, making up the peritubular capillary circulation.

[6]

$$FF = GFR/RPF,$$

where FF = filtration fraction, GFR = glomerular filtration rate, and RPF = renal plasma flow.

Blood flow to the glomerulus is regulated by the afferent and efferent arteriolar vascular tone, which adjusts glomerular filtration pressure. Afferent arteriolar dilation or efferent arteriolar constriction increases the FF and GFR. This autoregulatory mechanism is capable of maintaining GFR across a wide range of blood pressures and is achieved, in part, by the juxtaglomerular apparatus (see later discussion).

If blood pressure falls, there is a concomitant reduction in afferent arteriolar pressure with a fall in RBF and in filtered solute. This triggers release of renin in the juxtaglomerular apparatus. Renin, a selective protease, cleaves angiotensinogen to angiotensin I, which is subsequently cleaved to angiotensin II by angiotensin-converting enzyme (ACE) in the lungs. Angiotensin II causes thirst (and water intake), vasoconstriction, and Na^+ and water retention (via aldosterone), all of which increase blood volume and pressure, renal perfusion pressure, and thus RBF. Additionally, the kidney responds to low levels of catecholamines circulating when blood pressure drops by preferential efferent arteriolar vasoconstriction, which acts to maintain GFR.[2]

Age-Related Renal Changes

RBF decreases by 10% per decade of life after age 50 years; parallel changes occur in the kidney's ability to handle acid and Na^+. Creatinine becomes increasingly unreliable as a marker of GFR in older adults owing to loss of muscle and malnutrition. The National Kidney Foundation recommends using the Cockcroft-Gault formula for calculation of GFR.[3]

[7]

$$GFR_{men} = 140 - \text{age (years)} \times \text{weight (kg)} / \text{serum creatinine (mg/dL)} \times 72$$

[8]

$$GFR_{women} = 140 - \text{age (years)} \times \text{weight (kg)} \times 0.85 / \text{serum creatinine (mg/dL)} \times 72$$

TABLE 40.1 Normal Values of Serum Potassium

Age	Serum Potassium Range (mEq/L)
0–1 mo	4.0–6.0
1 mo–2 y	4.0–5.5
2–17 y	3.8–5.0
>18 y	3.2–4.8

In neonates, when adjusted for body surface area (BSA), RBF doubles during the first 2 weeks of postnatal life and continues to increase until it reaches adult values at about 2 years of age. This change is thought to be secondary to increasing cardiac output and decreasing systemic vascular resistance. GFR parallels this rise in RBF. GFR can be estimated in children based on serum creatinine level and height, as follows:

[9]

$$\text{GFR} = \text{height (cm)} \times k / \text{serum creatinine (mg/dL)}$$

where k = 0.45 for infants, k = 0.55 for children, and k = 0.70 for adolescents. Neonates are unable to excrete K^+ efficiently; therefore, the normal range of serum potassium tends to be higher than in older children and adults. The normal serum potassium by age is summarized in Table 40.1.

The Nephron

Each kidney contains 1.0 to 1.3 million nephrons, the functional unit of the kidney.[4] The glomerulus is made up of a tuft-like network of branching capillaries covered with epithelial cells that arc into the Bowman capsule, providing a large surface area for blood filtration (Fig. 40.2).[5] Blood enters the glomerulus by an afferent arteriole and exits by an efferent arteriole. The basement membrane of the glomerulus acts as a filter. This membrane allows water, amino acids, free ions, and other solutes to pass through into the Bowman capsule; large proteins, and cellular elements, including blood cells, cannot pass.

Fluid from the Bowman capsule flows into the proximal tubule. The main function of the proximal tubule is to resorb Na^+ and water, but bicarbonate, Cl^-, glucose, amino acids, phosphate, and lactate are also transported. The loop of Henle leads from the proximal convoluted tubule to the distal convoluted tubule. Its main function is to create and maintain an increasing osmolality gradient within the renal medullary interstitium, thereby providing the downstream collecting ducts with the ability to concentrate urine by osmotic forces. The loop of Henle is also responsible for Ca^{2+} and Mg^{2+} resorption. The distal convoluted tubule carries hypotonic fluid from the loop of Henle to the collecting ducts and is responsible for final changes in Na^+, K^+, Ca^{2+}, phosphate, and acid–base homeostasis. The collecting ducts run down the steep osmotic gradient created by the loop of Henle and allow significant water resorption and thereby creation of concentrated, hypertonic urine.

The juxtaglomerular apparatus is a small structure made up of the macula densa (a portion of modified ascending limb of the loop of Henle), mesangial cells, and juxtaglomerular cells (Fig. 40.3). The juxtaglomerular cells release renin in response to β-adrenergic stimulation, a decrease in afferent arteriolar perfusion pressure (sensed by a baroreceptor mechanism), and changes in Cl^- flow within the loop of Henle (sensed by chemoreceptors).[6] The role of each segment of the nephron is summarized in Table 40.2.

TABLE 40.2 Functional Divisions of the Nephron

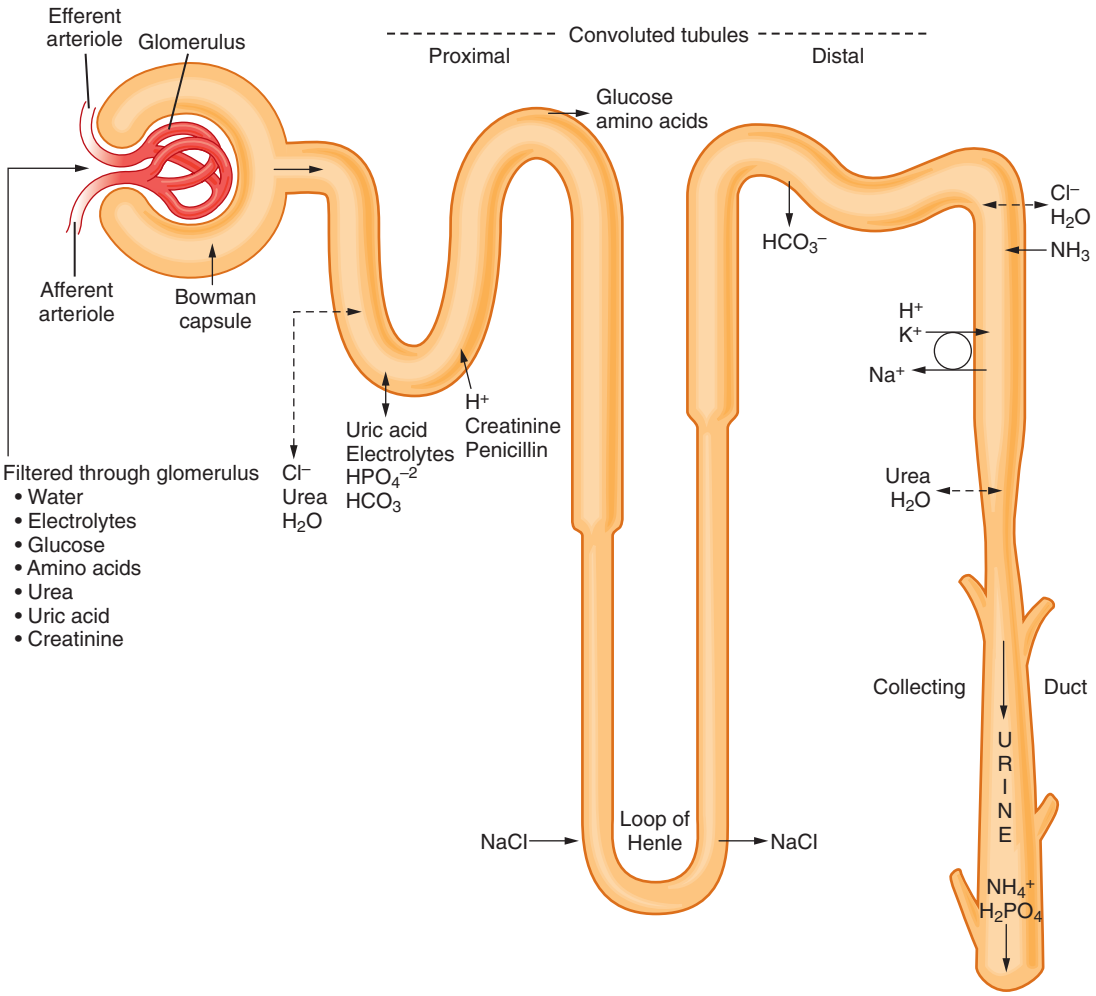
Segment	Function
Proximal tubule	Reabsorption: Na^+, Cl^-, water, bicarbonate, glucose, protein, amino acids, K^+, Mg^{2+}, Ca^{2+}, phosphate, uric acid, urea Secretion: Organic anions and cations Ammonia production
Loop of Henle	Reabsorption: Na^+, Cl^-, water, K^+, Ca^{2+}, Mg^{2+} Establishes concentration gradient within medulla
Distal tubule	Reabsorption: Na^+, Cl^-, water, K^+, Ca^{2+}, bicarbonate Secretion: H^+, K^+, Ca^{2+}
Collecting duct	Reabsorption: Na^+, Cl^-, water, K^+, bicarbonate Secretion: H^+, K^+ Ammonia production
Juxtaglomerular apparatus	Secretion of renin

Water and the Kidney

Regulation of plasma osmolarity is accomplished by varying the amount of water excreted by the kidney. Concentrated hyperosmotic urine is produced when circulating levels of antidiuretic hormone (ADH) are high. ADH, also known as *vasopressin* (see Chapter 35). ADH is released from the posterior pituitary (neurohypophysis) in response to increased osmolality (sensed by magnocellular neurons in the hypothalamus), decreased circulating plasma volume and/or angiotensin II. ADH increases the number of aquaporin channels in the collecting ducts of the nephron, facilitating water reabsorption by osmosis. ADH secretion occurs in times of water deprivation or hemorrhage, or with syndrome of inappropriate ADH (SIADH). Without ADH, dilute urine is excreted owing to reduced permeability of the distal tubules and collecting ducts to water, leading to little water reabsorption and the potential for hypernatremia (see Chapter 42).

Salt and the Kidney

Sodium is resorbed all along the nephron, but the majority is resorbed isosmotically in the proximal convoluted tubule. Sodium regulation is controlled by two main mechanisms: (1) renin-angiotensin-aldosterone (Fig. 40.4) and (2) atrial natriuretic peptide (ANP). Angiotensin II is the most powerful Na^+-retaining hormone. Its plasma levels increase with low blood pressure, hypovolemia, or salt and water loss. Angiotensin II stimulates aldosterone secretion, which increases Na^+ absorption. Additionally, angiotensin II constricts efferent arterioles, thereby raising the filtration fraction,

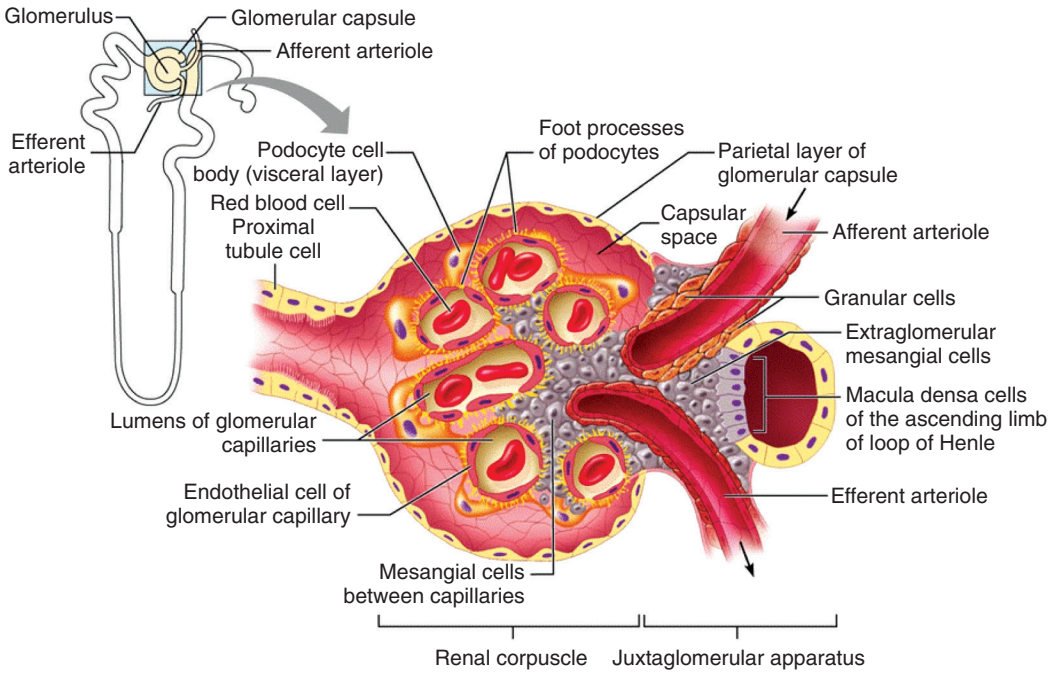


• **Fig. 40.2** The structure of the nephron. The structure of the nephron, and its specialized tubular segments in particular, is uniquely suited to sodium, water, electrolyte, and H^+ ion handling. The afferent arteriole brings blood into the glomerulus while the efferent arteriole carries blood away from the glomerulus. The Bowman capsule (or glomerular capsule) is a cup-like sac that cradles the tuft-like glomerular capillaries at the beginning of the tubular component of the nephron that performs the first step in the filtration of blood to form urine. This leads to the proximal convoluted tubule, the most proximal segment of the renal tubule. It is responsible for the reabsorption of glucose, amino acids, and the majority of ions and water that is reabsorbed. The loop of Henle separates the proximal and distal convoluted tubules. Its main function is to create an osmotic gradient in the renal medulla. By means of a countercurrent multiplier, the loop of Henle creates an area of high urine concentration deep in the medulla in the zone of the collecting duct, establishing a concentration gradient. Water present in the filtrate in the collecting duct flows down this concentration gradient (via aquaporin channels) out of the collecting duct. This process reabsorbs water and creates concentrated urine for excretion. The distal convoluted tubule follows the loop of Henle and is involved in the secretion of ammonia and urea as well as the regulation of potassium, sodium, calcium, and pH. From the distal convoluted tubule, filtrate drains into collecting ducts. Each duct receives filtrate from the distal convoluted tubules of many nephrons. Inside these collecting ducts, water can be absorbed to regulate the final concentration of urine produced by the kidneys. On leaving the collecting ducts, urine enters the renal pelvis and flows into the ureters.

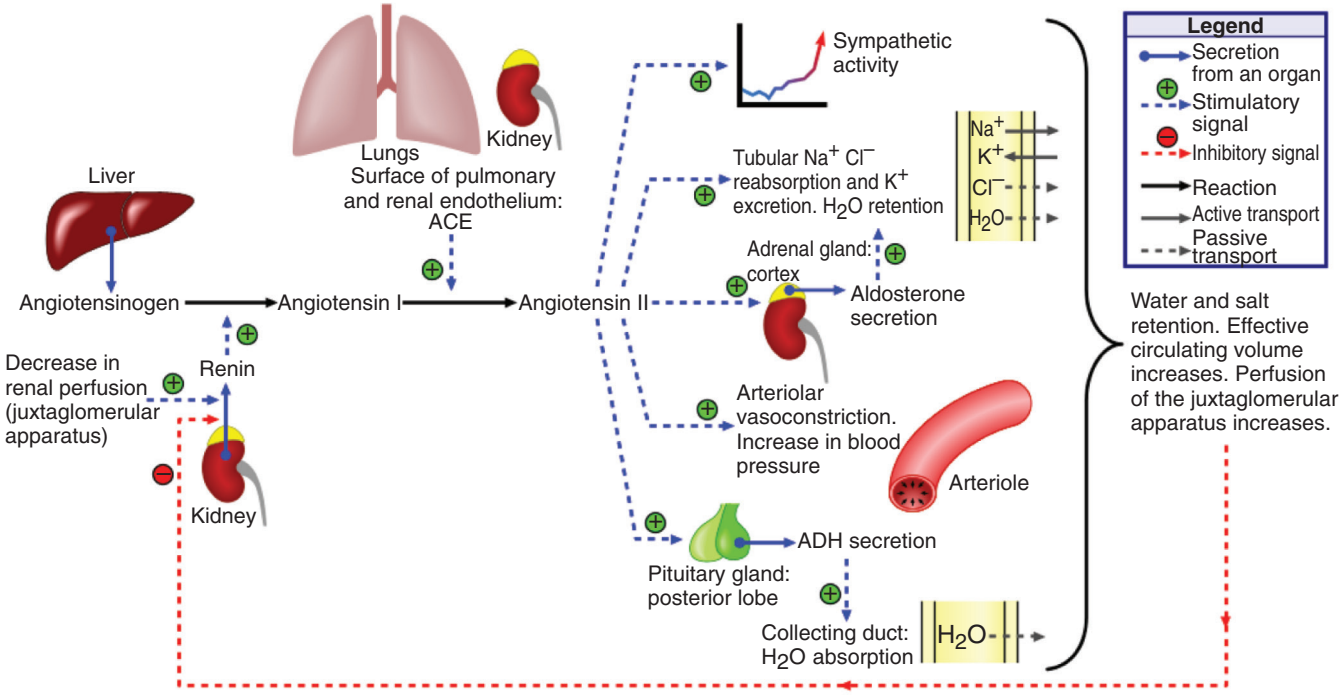
and directly stimulates Na^+ resorption in the proximal tubule. In times of salt and water overload and plasma volume expansion, the cardiac atria become distended and secrete ANP. ANP dilates the afferent arterioles in the glomerulus and constricts efferent arterioles, thus increasing GFR and increasing salt and water excretion. ANP also inhibits renin secretion, resulting in reduced angiotensin I, angiotensin II, and aldosterone production.[6]

Potassium and the Kidney

Potassium is filtered, resorbed, and secreted by the nephron. Potassium excretion can vary widely, from 1% to 110% of the filtered load depending on dietary K^+ intake, aldosterone levels, tubular flow rate, and acid–base balance. The proximal tubule reabsorbs 67% of filtered K^+ along with Na^+ and water. The loop



• **Fig. 40.3** The structure of the glomerulus and macula densa (see text for a detailed explanation). The upper left shows the position of the glomerulus and juxtaglomerular apparatus relative to the entire nephron.



• **Fig. 40.4** Renin-angiotensin-aldosterone system. The renin-angiotensin-aldosterone system regulates blood pressure and fluid balance. When blood volume is low, juxtaglomerular cells secrete renin into the circulation. Plasma renin then converts angiotensinogen released by the liver to angiotensin I. Angiotensin I is subsequently converted to angiotensin II by angiotensin-converting enzyme (ACE) found in the lungs. Angiotensin II is a potent vasoactive peptide that causes blood vessels to constrict, resulting in increased blood pressure. Angiotensin II promotes antidiuretic hormone secretion by the posterior pituitary, increasing water reabsorption by the kidneys, resulting in decreased urinary output. Angiotensin II also stimulates the secretion of the hormone aldosterone from the adrenal cortex. Aldosterone causes the tubules of the kidneys to increase reabsorption of sodium and water into the blood. This increases the volume of fluid in the body, which also increases blood pressure, closing the feedback loop.

TABLE 40.3 Causes of Hyperkalemia

Transcellular Shifts	Decreased Excretion	Increased Uptake
Acidosis	Renal failure	K^+ supplements
β-Blockers	K^+-sparing diuretics	Blood transfusions
Insulin deficiency	Cyclosporin	K^+-containing medications
Burns	NSAIDs	
Tumor lysis syndrome	ACE inhibitors	
Rhabdomyolysis	Mineralocorticoid deficiency/resistance	

ACE, Angiotensin-converting enzyme; *NSAIDs*, nonsteroidal antiinflammatory drugs.

TABLE 40.4 Causes of Hypokalemia

Transcellular Shifts	Increased Excretion	Decreased Uptake
Insulin	Vomiting	Malnutrition
β-Agonists	Diarrhea	
	Nasogastric suction	
	Laxatives	
	Diuretics	
	Cisplatin	
	Amphotericin B	
	Renal tubular acidosis	
	Corticosteroids	

of Henle resorbs an additional 20% of filtered K^+. The distal convoluted tubule and collecting duct reabsorb and secrete K^+ and are responsible for regulation of K^+ balance. Aldosterone stimulates K^+ secretion by increasing Na^+ entry into principal cells in the distal tubules.

Acidosis decreases K^+ excretion and alkalosis increases K^+ secretion. The primary mechanism by which increased hydrogen ion concentration inhibits K^+ secretion is via the Na^+, K^+ ATPase (Na^+ pump).[7] Sodium ions and K^+ effectively exchange for each other across the cell membrane via this pump. Urine flow rates also affect K^+ secretion, and drugs that increase urine flow, such as loop and thiazide diuretics, cause dilution of luminal K^+ concentration and increase the driving force for K^+ secretion (see Chapter 42). The common causes of hyperkalemia and hypokalemia are summarized in Tables 40.3 and 40.4, respectively.

Toxin and Metabolite Excretion

The kidney plays a major role in the excretion of drugs, hormones, and toxins. Uremic toxins and metabolites are cleared from the blood by filtration and secretion. The kidney freely filters water-soluble toxins, such as creatinine and urea, which are excreted in the urine. Other toxins are removed from the blood and actively secreted. Multiple pathways are used to metabolize drugs to more water-soluble metabolites, including oxidation, dealkylation, reduction, hydrolysis, glucuronidation, sulfation, methylation, acetylation, and conjugation (see Chapter 4).[8]

Acid–Base Balance

The lungs and kidneys are the main organs involved in acid–base balance. The lungs excrete a volatile acid, carbon dioxide; the kidneys are responsible for handling nonvolatile acids. The kidneys help regulate acid–base balance by excreting either acidic or basic urine. This is achieved by precise handling of the large amount of bicarbonate and acidic ions filtered continuously into the renal tubules. Volume depletion is associated with Na^+ retention, which enhances bicarbonate reabsorption. Hypokalemia enhances bicarbonate reabsorption, leading to alkalemia (contraction alkalosis).[9] There is ongoing controversy as to whether the kidney maintains acid–base homeostasis via ammonium (acid) excretion or chloride excretion.[10]

Renal Hormone Production

The kidney secretes 2 hormones, erythropoietin (EPO) and calcitriol (1,25 $[OH]_2$ vitamin D_3), as well as the enzyme renin. EPO is a glycoprotein that acts on the bone marrow to increase red blood cell production in response to any condition that reduces the quantity of oxygen to the tissues. Most often, EPO production is increased owing to anemia, low blood volumes, or hypoxemia such as that experienced by people living at high altitudes, or with prolonged cardiac or pulmonary failure.

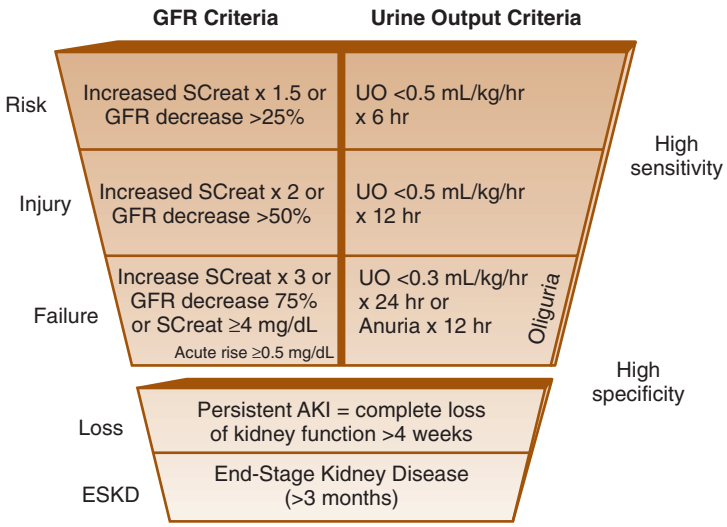
Calcitriol is the activated form of vitamin D that acts to increase the absorption of Ca^{2+} from the intestine, to mobilize stored Ca^{2+} from bone, and to reabsorb phosphate in the kidney. It is the downstream product of calciferol, which is synthesized from ingested vitamin D in skin exposed to ultraviolet light. Calciferol is subsequently converted by the liver to 25-[OH]-vitamin D_3 and transported to the kidney. There, it is converted to calcitriol in response to parathyroid hormone.

The release and function of the renal hormone renin has been described earlier.

Defining Renal Failure

Acute kidney injury (AKI; formerly known as acute renal failure) is associated with increased perioperative morbidity, mortality, increased length of hospital stay, and increased cost.[11,12] Arriving at a standardized definition of renal failure has been surprisingly difficult. Renal failure is usually classified as either AKI or chronic kidney disease (CKD; previously termed *chronic renal insufficiency* or *chronic renal failure*).[13] More than 35 definitions exist for renal failure.[14] The absence of a consensus definition has had a negative impact on basic science as well as clinical research in the field of AKI.

There is no consensus on the most effective way to assess renal function, either by defining the best markers to gauge renal function or the level of any biomarker that differentiates normal from abnormal renal function. Only recently has a unified standard for classifying and diagnosing AKI been accepted. The diagnosis of AKI requires both clinical history and relevant laboratory data. The Acute Kidney Injury Network (AKIN) introduced specific criteria for diagnosis of AKI, including a rapid time course (< 48 hours) and decrement of kidney function.[15] Reduction of kidney function was defined as either an absolute increase in serum creatinine of greater than 0.3 mg/dL, percentage increase in serum creatinine of greater than 50%, or reduction in urine output to less than 0.5 mL/kg/hr for more than 6 hours. In addition to the AKIN, the Acute Dialysis Quality Initiative (ADQI) has attempted to uniformly define and stage AKI with the RIFLE criteria (Risk, Injury, Failure, Loss, End-stage kidney disease).[16] These five categories represent three grades of increasing severity of AKI (risk, injury, and failure) and two outcome classes (loss and end-stage kidney



• **Fig. 40.5** RIFLE criteria (Risk, Injury, Failure, Loss, End-stage kidney disease). *SCreat,* Serum creatinine; *GFR,* glomerular filtration rate; *UO,* urine output; *AKI,* acute kidney injury.

disease). Absolute increase of serum creatinine, percentage increase in creatinine, percentage reduction in GFR, and decrement in urine output over time define the categories (Fig. 40.5). Rather than equating renal function and serum creatinine, the RIFLE criteria attempt to standardize the definition and severity of renal injury in order to facilitate evaluation, treatment, and communication among health care providers. A recent study demonstrated the utility of the RIFLE criteria as a predictor of mortality in patients admitted to the intensive care unit (ICU).[17]

Risk of Perioperative Acute Kidney Injury

Predicting patients at risk for perioperative AKI would allow anesthesiologists to outline properly the perioperative risk to their patients as well as tailor management toward the prevention of AKI. Risks for perioperative AKI include advanced age, revised cardiac risk index score greater than 2, American Society of Anesthesiologists Physical Status of 4 or 5, male sex, active congestive heart failure, hypertension, emergency surgery, high-risk surgery (intraperitoneal, intrathoracic, vascular), elevated preoperative creatinine, and diabetes mellitus.[18,19] Blood product transfusion, sepsis, hypovolemia, and hypotension also probably place patients at risk for AKI.[20] There is a 25% reduction in renal cortical mass by 80 years of age, which reduces metabolism and elimination of medications, resulting in longer half-lives of drugs that depend on renal elimination.[65]

Certain surgical procedures carry a higher risk for AKI than others: in particular, cardiac surgery, aortic surgery, and liver transplantation. Aortic clamping, employed in cardiac and aortic surgery, can significantly reduce renal perfusion and predispose the kidney to atheromatous emboli, possibly leading to AKI. Regardless of the position of the aortic cross-clamp in aortic surgery, RBF is reduced by about 50% during surgical preparation of the aorta.[2] Methods for renal protection during open thoracoabdominal aneurysm repair include maintaining distal aortic perfusion during aortic cross-clamping, infusing cold perfusate into the renal arteries during periods of ischemia, and use of left heart bypass to maintain perfusion pressure during aortic cross-clamping.[21] The anatomic location and extent of the aortic aneurysm have profound implications on the ability to maintain kidney perfusion during surgery.

Patients undergoing liver transplantation are at significant risk for development of AKI. These patients can have preexisting renal dysfunction and they can have intraoperative interruption of the inferior vena cava. There is significant risk of hemodynamic instability, bleeding, transfusion, and medication-induced nephrotoxicity.[22]

Cardiac surgery patients are also at high risk for AKI; half of these patients experience a significant reduction in renal function (25% increase in serum creatinine), and up to 5% will require renal replacement therapy.[61,62] Cardiopulmonary bypass (CPB) induces hypotension, reduces aortic blood flow and RBF, and induces hemolysis and inflammation. CPB not only induces an inflammatory cascade but also requires anticoagulation, both of which can lead to bleeding and worsening renal injury. Preoperative risk factors for development of AKI following cardiac surgery include advanced age, female sex, hypertension, hyperlipidemia, CKD, liver disease, peripheral vascular disease, previous stroke, smoking history, diabetes mellitus, and anemia.[63] Intraoperative risk factors for development of AKI following cardiac surgery include complex surgery, CPB duration, return to CPB, low hematocrit during CPB, aortic cross-clamp time, hypoperfusion, hypovolemia, venous congestion, emboli (cholesterol and other), and inotrope exposure (low cardiac output state).[63] Postoperative risk factors for development of AKI following cardiac surgery include vasopressor, inotrope and diuretic exposure, blood transfusion, hypovolemia, venous congestion, and cardiogenic shock.[63]

Perioperative AKI, whether it requires renal replacement therapy or not, increases ICU and hospital length of stay as well as perioperative mortality.

Acute Kidney Injury in Surgical Patients

Acutely, renal function can deteriorate over a period of hours to days and is most often the result of multiple insults. AKI is a rapid loss of kidney function, which has multiple causes that are traditionally categorized as *prerenal*, *intrinsic-renal*, or *post-renal kidney injury.* Because reversible prerenal azotemia and intrinsic-renal acute tubular necrosis from medullary ischemia are two ends of a continuum, the division is artificial, but can be useful in guiding treatment options. The most common cause of perioperative renal injury is ischemia-reperfusion injury.[23] The traditional prerenal causes of kidney injury include any mechanism that decreases effective blood flow to the kidney. Common causes of prerenal kidney injury include dehydration, hypovolemia, hemorrhage, hypotension, and heart failure. Prerenal injury is often rapidly reversible when the underlying mechanism is corrected, thus glomerular or tubular injury can be avoided.

Intrinsic causes of kidney injury can be the product of direct injury to the glomeruli, tubules, or interstitium. Common causes of intrinsic kidney injury include glomerulonephritis, acute interstitial nephritis, and acute tubular necrosis (ATN).[12] Infection and sepsis are common causes of AKI. Chronically ill patients are at risk of toxin-mediated ATN from aminoglycoside antibiotics, intravenous contrast agents, or nonsteroidal antiinflammatory medications. *Postrenal* kidney injury involves obstruction at any point along the urinary outflow tract by malignancies, renal calculi, retroperitoneal fibrosis, a hypertrophied prostate, or an obstructed bladder catheter. Iatrogenic injury to the ureter can occur in lower abdominal surgery. Treatment of any type of kidney injury is centered on treating the underlying cause while providing supportive care and avoiding nephrotoxic substances and further renal insult.

Assessment and Management of Acute Kidney Injury

Preoperative Approach

Managing AKI depends on both the cause and the severity of injury. The most common and practical way to assess renal function is by factors included in the RIFLE criteria: serum creatinine, GFR, and urine output. Although commonly used and widely accepted, serum creatinine is unfortunately insensitive and not linearly related to GFR.[22] GFR, the gold standard of renal function, is impractical to measure. In patients of advanced age, serum creatinine is often an unreliable indicator of renal function owing to decreased creatinine production secondary to reduced muscle mass. Therefore, a normal or low serum creatinine is likely to overestimate GFR. Additionally, urine output may not be a reliable marker of renal function or injury for a number of reasons, including diuretic therapy.

Patients presenting for surgery can have kidney injuries from a wide array of causes and severity. There is no proven preventive measure or treatment for AKI.[22] Therefore management of AKI centers on identifying and treating the underlying cause, supporting renal function by maintaining RBF and oxygen delivery, and avoiding nephrotoxic agents. Common prerenal causes of AKI include hypovolemia secondary to bleeding, fluid loss, reduced oral intake, or diuretic administration. Bleeding, including gastrointestinal or posttraumatic, can lead to significant hypovolemia. Excessive fluid loss from the gastrointestinal tract (due to diarrhea or preoperative bowel preparation) or from the kidneys (excessive diuresis) can also cause prerenal injury. Treatment of prerenal injury can be simple but requires quick recognition of the cause and appropriate treatment to avoid more permanent renal injury. Discontinuation of diuretics and optimization of fluid status and RBF by administration of isotonic crystalloid or colloid solutions can prevent progression of the injury. There is little convincing evidence favoring colloids over crystalloids (see Chapter 41). In acute situations, such as severe gastrointestinal bleeding, rapid administration of plasma expanders and/or blood products might be needed to restore RBF.

Sepsis should always be considered as a cause of renal injury in patients with signs of infection. Early and aggressive treatment should be initiated if sepsis is suspected including source control, appropriate antibiotics, early goal-directed therapy, lung protective ventilation in the setting of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), avoidance of severe hyperglycemia, early enteral nutrition, and possible steroid therapy for adrenal insufficiency or refractory vasoplegia.[24-27] All bacterial infections should be treated quickly and appropriately with initial empirical therapy, often dictated by local and hospital antibiograms.[28,66]

"Renal-dose" dopamine therapy remains in use probably because it is an effective diuretic and often increases urine output. It is often effective in improving renal perfusion in patients with low cardiac output and/or bradycardia. Unfortunately, several studies showed no role for dopamine in the prophylaxis or treatment of AKI (see Chapter 25).[29-31]

Loop diuretics can be used in the setting of AKI but it is essential that euvolemia be restored before administration to avoid further renal hypoperfusion and exacerbation of AKI. Loop diuretics have multiple effects on the injured kidney. Loop diuretics can relieve obstructed tubules by mechanically clearing necrotic cells with increased urine flow. They increase prostaglandin synthesis with two main downstream effects: (1) increased RBF, thereby augmenting oxygen delivery, and (2) decreased active tubular Na^+ reabsorption, decreasing metabolic demand.[22] Even so, most large studies have shown no direct positive effect of loop diuretics on prevention or treatment of AKI.[32]

Intraoperative Management of Renal Function

There are no data supporting one particular anesthetic technique over another in regard to renal function. Supporting normal blood pressure, and therefore renal perfusion, maintaining euvolemia to ensure adequate perfusion and oxygen delivery to all tissues, and avoiding nephrotoxins are reasonable.

Volatile anesthetics, used for maintenance of general anesthesia, can decrease GFR primarily as a result of decreased systemic vascular resistance and blood pressure.[22] This is worsened by hypovolemia and ADH secretion, commonly seen in the surgical stress response.[33] Sevoflurane can theoretically cause fluoride-induced renal injury via generation of the haloalkene compound A (see Chapter 4), a breakdown product produced when certain carbon dioxide absorbants are used. Compound A is nephrotoxic in laboratory animals but no studies have linked it to AKI in humans despite low-flow anesthesia for many hours. Thus, most consider this volatile agent safe for patients with renal dysfunction.[34]

After induction of general anesthesia, patients are placed on positive pressure ventilation with positive end-expiratory pressure (PEEP), which can reduce cardiac output, RBF, GFR, Na^+ excretion, and urine flow rate.[35] The extent of this effect depends on mean airway pressure, the degree of reduction in cardiac output, and activation of the renin-angiotensin-aldosterone pathway.

Sodium bicarbonate can be administered to correct severe metabolic acidosis. Because of potential side effects—such as hypercarbia, hypernatremia, rebound alkalosis, and worsening intracellular acidosis—its administration has questionable efficacy in this setting.[36] Tris-hydroxymethylaminomethane (THAM) is a buffer that appears to control acidosis during surgery safely and should be considered as an alternative to sodium bicarbonate. However, THAM accumulates in patients with renal dysfunction; thus, its universal use is not recommended.

There is emerging evidence that both anemia and blood transfusion are associated with development of AKI. However, significant bleeding during surgery often requires transfusion of blood products. Transfusion can lead to hyperkalemia, which is

most often treated with loop diuretics. Preexisting kidney dysfunction or AKI can make the loop of Henle resistant or unresponsive to these diuretics.

Pressors are often required during surgery to reverse multifactorial hypotension and vasodilation. Norepinephrine and arginine vasopressin are two commonly used agents. Norepinephrine profoundly constricts the glomerular afferent arteriole, dropping filtration pressure; thus, it can contribute to and prolong the course of AKI. In contrast, arginine vasopressin constricts the glomerular efferent arteriole; therefore, it can increase filtration pressure and, consequently, GFR.

To guide hemodynamic management during AKI, invasive monitors should be considered, including arterial, central venous, and pulmonary arterial catheters, noninvasive cardiac output monitor, and/or transesophageal echocardiography. In patients who are anesthetized and paralyzed, pulse pressure variation and stroke volume variation can help guide hemodynamic management (see Chapter 24).[37,38] It appears that surgical patients receiving perioperative hemodynamic optimization with goal-directed management are at decreased risk for renal impairment.[39] Obviously, urine output must be closely monitored with a urinary catheter. Frequent point-of-care assessment of acid–base status and electrolyte balance aid in determining whether renal replacement therapy is needed.

Anesthetic Drugs and Impaired Renal Function

Anesthetists must be aware of medications that might accumulate or have adverse effects in patients with renal dysfunction. Barbiturates can be used safely in patients with renal dysfunction, although these patients appear to have increased sensitivity, possibly secondary to acidosis, favoring more rapid entry into the brain. Most benzodiazepines undergo hepatic metabolism and conjugation before elimination in the urine; therefore, caution should be used when administering diazepam or midazolam to patients with renal impairment owing to the presence of active metabolites. Lorazepam might be the benzodiazepine of choice owing to the lack of active metabolites. Succinylcholine can be used safely in renal failure if the preadministration serum K^+ concentration is at a safe level. If serum K^+ concentration is unknown or significantly elevated, a nondepolarizing neuromuscular blocker should be used. Some consider cisatracurium as the neuromuscular blocking agent of choice, in that it is broken down by Hoffman elimination, thereby having consistent duration of action in the face of AKI or renal failure. While the elimination of vecuronium is primarily hepatic, 15% to 25% is eliminated by the kidney. Similarly, rocuronium is primarily excreted by hepatic biotransformation and hepatobiliary excretion, but the duration of action seems to have greater variability in patients with renal failure and end-stage renal disease. This might be due to decreased clearance, increased potency, or changes in protein binding.[40] Sugammadex can be used in patients with renal dysfunction who have received rocuronium. Morphine should be used with caution owing to accumulation of the active metabolite morphine-6-glucuronide. Similarly, meperidine should be avoided owing to accumulation of the toxic metabolite normeperidine, which has been associated with seizures. Fentanyl, remifentanil, sufentanil, alfentanil, and hydromorphone are the opioids of choice for patients with, or at risk for, renal impairment because these drugs do not depend on renal clearance mechanisms.

Common Perioperative Medications That Impair Renal Function

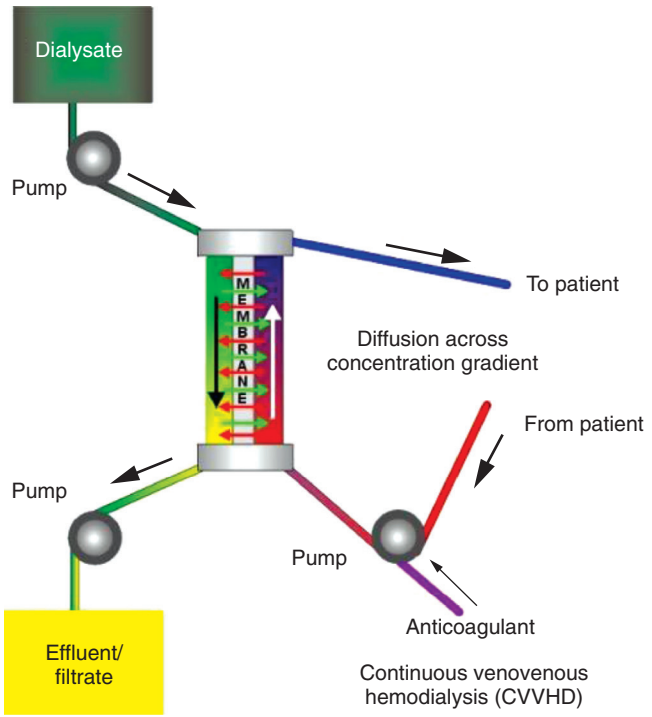
Multiple medications used in the perioperative period can have adverse effects on renal function. Calcineurin inhibitors, such as tacrolimus and cyclosporine, are immunosuppressive drugs used to prevent rejection of transplanted organs, such as the lung, heart, kidney, and liver. Calcineurin inhibitors cause profound afferent arteriolar vasoconstriction and reduce GFR.[41] Antimicrobial drugs are often administered to patients undergoing surgery and can cause ATN (aminoglycosides) or tubulo-interstitial nephritis (penicillins, cephalosporins, or fluoroquinolones). Nonsteroidal antiinflammatory drugs, including cyclooxygenase-2 inhibitors, inhibit prostaglandin synthesis and therefore prevent renal arteriolar vasodilation, potentially impairing renal autoregulation. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blocking drugs also inhibit autoregulation, but by a different mechanism (blockade of efferent arteriolar vasoconstriction).[42] Anticoagulants play a key role in various cardiac and vascular surgeries, as well as percutaneous catheter-based interventions, and direct-thrombin inhibitors and other novel anticoagulants are increasingly used owing to heparin-induced thrombocytopenia. Care must be taken with lepirudin, desirudin and, bivalrudin in the face of renal dysfunction owing to their renal clearance and/or renal metabolism rates.[64] Radiographic contrast media can cause renal injury by two mechanisms: (1) they can induce medullary vasoconstriction and reduce blood flow, resulting in ischemic injury; and (2) they can have a direct cytotoxic effect in the vulnerable kidney.[43]

While most pharmacologic strategies to prevent AKI have proven unsuccessful, the prevention of contrast-induced nephropathy (CIN) appears possible in many cases. Risk reduction involves judicious use of very low volumes of nonionic isosmolar contrast along with careful isotonic intravenous hydration with 0.9% normal saline or sodium bicarbonate to ensure adequate hydration prior to administration.[44] Use of oral or intravenous N-acetylcysteine (NAC) is controversial. It was previously advocated to reduce the incidence of CIN; however, there is increasing evidence suggesting a lack of efficacy.[45]

Perioperative Renal Replacement Therapy

Although there are several renal replacement modalities, three major types exist: (1) intermittent hemodialysis (iHD), (2) peritoneal dialysis (PD), and (3) continuous renal replacement therapies (CRRT). Intermittent hemodialysis, the standard treatment for severe renal failure, is most often used in patients without acute hemodynamic instability. Peritoneal dialysis is often used in patients with CKD, but is contraindicated in patients with ascites. There are few data validating one method over another and there is debate over the timing and dosage of RRT in the perioperative period.[12] CRRT, particularly continuous venovenous hemodialysis (CVVHD), is the most widely used and safest modality for patients with tenuous hemodynamic status. Regardless of the method of RRT, complications such as bleeding, infection, and hypotension can occur.

RRT, either iHD or CRRT, might be required in the perioperative period. Sustained low-efficiency dialysis is a hybrid form of RRT that is essentially a slower version of iHD using the same machinery with lower blood flows, longer dialysis sessions (8–10 hours vs. 3–4 hours), and possibly a lower incidence of



• **Fig. 40.6** Continuous venovenous hemodialysis (CVVHD) circuit. CVVHD is similar to standard dialysis except that it is performed continuously over a longer period of time. Red tubing is the access line; it takes blood from the patient to the hemofilter. Blue tubing is the return line; it takes blood from the hemofilter back to the patient. Green tubing is the dialysate line; it takes dialysate from the source into the hemofilter. Yellow tubing is the effluent line; it takes effluent from the dialyzer into a waste or effluent bag.

hypotension.[46] There are several forms of CRRT, including, but not limited to, slow continuous ultrafiltration, continuous venovenous hemofiltration, CVVHD, and continuous venovenous hemodiafiltration. These forms of RRT use ultrafiltration, hemofiltration, and/or hemodialysis for solute and fluid removal. Despite development of these renal replacement therapies that can rapidly correct the metabolic and biochemical derangements of AKI, improvements in mortality have not materialized. The typical CVVHD circuit is represented in Fig. 40.6. Studies of differing dialysis dose, changing frequency, or alternate modalities (CRRT, iHD) have not shown consistent benefit of one technique over another.

Hepatorenal Syndrome

Patients with liver cirrhosis are at risk for all three types of AKI, but they can also develop a unique entity known as hepatorenal syndrome (HRS).[47] HRS is a form of prerenal AKI thought to be the result of circulatory dysfunction secondary to an imbalance of circulating vasodilatory and vasoconstrictive factors. This dysfunction is likely the result of a decrease in systemic vascular resistance arising from splanchnic vasodilatation due to nitric oxide, prostaglandins, and other vasoactive substances released in patients with portal hypertension and advanced cirrhosis.[48] The vasodilatation triggers activation of the renin-angiotensin system and, along with sympathetic stimulation, results in intense renal vasoconstriction. In compensated cirrhosis, cardiac output and plasma volume both increase to restore effective arterial volume; thereby, renal perfusion and function are preserved. However, in decompensated cirrhosis, cardiac output and heart rate are already maximal and cannot increase further to augment blood pressure, resulting in a further increase in circulating vasoconstrictors and renal vasoconstriction, Na^+ and water retention, and ascites formation.[49] This results in decreased renal perfusion pressure and reduced GFR.

Two types of HRS exist: type 1 HRS is characterized by a rapid decline in renal function, while type 2 HRS entails a more chronic deterioration in renal function that is associated with ascites formation. Differentiating HRS from ATN can be difficult because diagnosing the former involves excluding other causes of AKI and there is no single test that confirms HRS.[50] Although mortality is very high among patients with cirrhosis and renal failure, patients with type 1 HRS seem to have the worst prognosis—50% survival at 1 month and 20% survival at 6 months.[51]

Therapeutic options are limited for patients with HRS. Vasopressors are effective in AKI, primarily in the setting of type 1 HRS.[50,52] The mechanism seems to be reversal of splanchnic vasodilatation and restoration of central blood volume and renal perfusion. Several vasoconstrictors have been studied, including terlipressin (a vasopressin analog), octreotide, norepinephrine, and midodrine. The strongest evidence, including recent randomized controlled trials, favors vasopressin analogs, with possible added benefit with coadministration of intravenous albumin.[52] Although they should be considered first-line therapy, vasopressin analogs can be associated with cardiovascular and ischemic complications—over 10% in some studies. Overall, vasopressin analogs can be effective in 40% to 50% of patients with HRS, but 3- and 6-month mortality benefits in these studies are lacking.[50,52]

Despite maximum pharmacologic therapy, AKI and/or HRS can cause renal function to decline to the point of metabolic disarray, acidosis, severe electrolyte abnormalities, and/or volume overload. Once renal function has reached this level of severity, the patient should be treated with renal replacement therapy. While albumin combined with vasopressin (or its analogs) is of some benefit, optimal medical management should include evaluation for liver transplantation. Diagnostic criteria for HRS are summarized in Table 40.5.

TABLE 40.5 Major Diagnostic Criteria of Hepatorenal Syndrome

Hepatic failure and ascites
Creatinine > 1.5 mg/dL
No shock, ongoing bacterial infection, nephrotoxic agents, or fluid losses
No improvement after diuretic withdrawal and fluid resuscitation
Proteinuria < 500 mg/day, normal renal sonography

Adapted from Meltzer J, Brentjens TE. Renal failure in patients with cirrhosis: hepatorenal syndrome and renal support strategies. *Curr Opin Anaesthesiol.* 2010;23:139–144.

Emerging Developments

Prevention and Biomarkers for Acute Kidney Injury

Renal function and dysfunction is an important determinant and indicator of perioperative outcome. Anesthetists often give fluid in an attempt to increase renal perfusion and reduce perioperative AKI. There is very little evidence to suggest that a particular fluid

should be used for resuscitation of patients with or at risk of AKI; however, there is some evidence that 6% hydroxyethyl starch should be avoided in the setting of AKI. This is because of an emerging body of experiments and clinical studies that show that hydroxyethyl starch can induce and/or exacerbate renal injury.[53,54,54a]

Detection and understanding of AKI is improving with time. There has been a promising search for biomarkers of renal function and injury. Serum cystatin C, a protein produced by all nucleated cells, is independent of age, sex, race, and muscle mass and is a better marker of GFR than creatinine[55]; further studies are needed for validation. Neutrophil gelatinase-associated lipocalin (NGAL) is a protein produced by renal tubular cells in the setting of renal injury.[56] It can be detected easily in the urine within minutes of induced injury and is highly sensitive and specific to AKI—levels are much less increased in CKD. Although NGAL has been used in a variety of clinical scenarios, further research is necessary before it becomes widely accepted and used in clinical practice.

Many vasoactive drugs have been studied in hopes of finding a pharmacologic approach to prevention or treatment of renal injury. Renal vasoactive medications, such as dopamine and prostaglandin infusions, have not been effective. However, fenoldopam mesylate, a dopamine-1 receptor agonist originally approved for hypertensive emergencies, has shown some potential benefit (see Chapter 26). In a variety of surgical and ICU populations, fenoldopam has been shown to reduce the risk of AKI but only in small randomized trials or meta-analyses of these trials.[58–60] Current efforts focus on the development of novel renal protection approaches, including possible protective effects of volatile anesthetics.[60a,60b]

Key Points

- The main functions of the kidney are (1) regulation of salt and water balance, (2) toxin and metabolite elimination, (3) electrolyte homeostasis, (4) acid–base balance, and (5) hormone production.
- Renal blood flow is directly proportional to the transrenal gradient, the pressure difference between the renal artery and the renal vein. Autoregulation mechanisms maintain constant renal blood flow over a range of blood pressures.
- Normal glomerular filtration rate is around 120 mL/min in men and 100 mL/min in women.
- Renal blood flow decreases by about 10% per decade of life after age 50 years; parallel changes occur in the kidney's ability to handle acid and Na^+.
- Regulation of plasma osmolarity is accomplished by varying the amount of water excreted by the kidney. Concentrated, hyperosmotic urine is produced when circulating levels of antidiuretic hormone are high.
- Na^+ regulation is controlled by 2 main mechanisms: (1) renin-angiotensin-aldosterone and (2) atrial natriuretic peptide.
- Potassium (K^+) excretion can vary widely, from 1% to 110% of the filtered load depending on dietary K^+ intake, aldosterone levels, tubular flow rate, and acid–base balance.
- Risk factors for AKI include advanced age, revised cardiac risk index score greater than 2, American Society of Anesthesiologists Physical Status 4 or 5, male sex, active congestive heart failure, hypertension, emergency surgery, high-risk surgery, elevated preoperative creatinine, and diabetes mellitus.
- Procedures associated with the highest risk of AKI are cardiac surgery, aortic surgery, and liver transplantation.
- There is no evidence-based support for one anesthetic technique over another in regard to optimal renal function. Important goals include support of normal blood pressure and, therefore, renal perfusion; maintenance of euvolemia to ensure adequate perfusion and oxygen delivery to all tissues; and avoidance of nephrotoxins.
- Norepinephrine profoundly constricts the glomerular afferent arteriole, dropping filtration pressure, and can contribute to and prolong the course of AKI.
- Arginine vasopressin constricts the glomerular efferent arteriole; therefore, it can increase filtration pressure and GFR.

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41

Intravascular Volume Replacement Therapy

CHRISTER SVENSEN AND PETER RODHE

CHAPTER OUTLINE

Historical Perspective

Conventional Concepts
- Body Water
  - *Measurement of Body Fluid Spaces*
  - *Maintenance Requirements for Water, Sodium, and Potassium*
- Interstitium
  - *Third Space*
- Fluid Shifts and Losses During Surgery, and Their Replacement
- Conventional Indices of Resuscitation
- Response to Fluid Challenge
- Static Measurements of Intravascular Volume
  - *Pulmonary Artery Occlusion Pressure*
  - *Transesophageal Echocardiography*
- Intrathoracic Blood Volume Index and Global End-Diastolic Volume Index
  - *Stroke Volume Variation and Pulse Pressure Variation*
  - *Esophageal Doppler Catheter*
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  - *Oxygen Delivery and the Microcirculation*

Body Fluid Dynamics (Modeling Fluid Therapy)
- Plasma Volume Expansion
- Volume Kinetics for Infusion Fluids
- Estimation of Volume Kinetic Parameters
- Population Kinetics for Infusion Fluids
- Pharmacodynamics of Infusion Fluids

Guiding Principles and Clinical Implications
- Crystalloids
- Colloids
  - *Sepsis and Critical Illness*
- Clinical Fluid Therapy Guidelines
  - *Basal Requirements and Rehydration*
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  - *Surgery Performed With Spinal or Epidural Block*
  - *Gastrointestinal Surgery*

Emerging Developments

Historical Perspective

Plasma volume replacement is important in the perioperative period. The body and cardiovascular system are exposed to many challenges, such as neurohumoral adaptations, evaporation, fluid redistribution, and blood loss, that necessitate interventions. To achieve this, fluids are administered intravenously following protocols based on tradition, expert recommendations, and often limited evidence. There is an ongoing debate concerning the ideal composition and amount of intravenous fluids necessary for perioperative management.[1–6] In the past century, recommendations varied from fluid restriction to giving liberal amounts for resuscitation.[7–12] Surprisingly, intravenous (IV) fluids have been regarded as rather harmless, resulting in nothing worse than volume overload, which is often viewed as a minor problem.[13] However, IV fluids can be deleterious in large amounts if not timed according to patient needs.[3–5,14,15] In the late 1970s and early 1980s, acute lung injury caused by increased filtration rate across pulmonary capillaries and subsequent pulmonary inflammation was suggested as a plausible consequence.[16] It has never been proven that large amounts of crystalloids cause acute respiratory distress syndrome; however, the link to abdominal compartment syndrome, which can be the result of large-volume crystalloid resuscitation, is compelling.[14] Traditionally, the rationale supporting liberal perioperative fluid administration included assumptions that preoperative fasting resulted in hypovolemia, that insensible losses increased considerably during surgery, and that some fluid was distributed to a "third space."[11,17] Any resulting fluid overload was considered harmless because the kidneys had the capacity to eliminate the excess.[18]

The primary problem the clinician faces is that individual hydration and volume states are unknown before surgery. There are a few simple tests or physical maneuvers that can assess reliably either the level of hydration or the intravascular volume status. The clinician usually must rely on indirect nonspecific clinical signs to estimate the volume status of the cardiovascular system. Because the vascular system is highly reactive to neurohumoral changes and positioning, predicting the disposition of IV fluids is difficult.

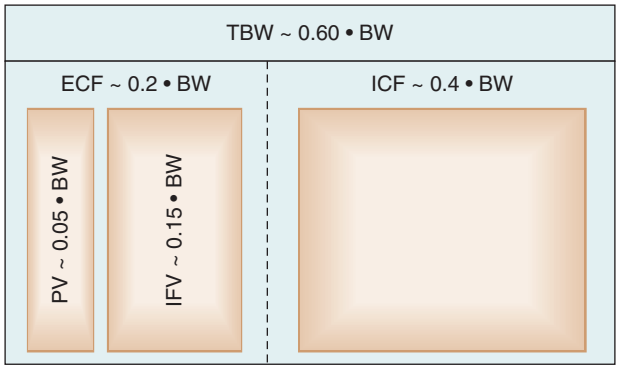
Very few healthy stable surgical patients admitted for elective minor operations require significant amounts of fluid, and thus the perioperative fluid management of these patients is straightforward.[4,15,19] In contrast, fluid management of critically ill patients can be extremely demanding, and timing is very important.[20] These patients sometimes require volume support, usually with extensive

Abstract

This chapter describes conventional concepts about body fluid spaces. It carefully describes physiological principles about fluid shifting in the body and responses to fluid challenges. It further describes different monitoring principles on how to estimate fluid volumes. Furthermore it gives a body fluid dynaimic theory in a mathematical way. Finally, it gives recommendations on how to handle fluid requirements in daily practice

Key words

body water
fluid spaces
fluid challenge
monitoring of fluid status
body fluid dynamics and volume kinetics
guiding principles for fluid



• **Fig. 41.1** A static schematic of the distribution of body water. Water constitutes about 60% of body weight and is unequally distributed between extracellular and intracellular spaces. *BW,* Body weight in kilograms; *ECF,* extracellular fluid; *ICF,* intracellular fluid; *IFV,* interstitial fluid volume; *PV,* plasma volume; *TBW,* total body water.

monitoring to guide fluid resuscitation. However, evidence suggests that several currently used monitors have limitations in measuring the adequacy of intravascular volume.[21,22]

Conventional Concepts

Body Water

With respect to traditional fluid therapy, the body is conceptualized as an interconnected group of anatomic spaces among which fluids distribute. However, this static concept hardly reflects the complexity of how fluids dynamically distribute over time. Total body water (TBW) is the amount of sodium-free water in the whole body, commonly divided into the extracellular fluid (ECF) space and the intracellular fluid (ICF) space. Under normal conditions, ECF constitutes 20% of total body weight and ICF 40% of TBW for an adult.

The ECF consists of the plasma volume and interstitial fluid volume (Fig. 41.1). The plasma volume (PV) is relatively small, which is important to understand when boluses of fluids are given. The interstitial fluid volume contains water but is mainly bound by a gel-like composition of proteoglycan filaments and collagen fibers. Infused sodium ion (Na^+) distributes mainly within ECF, which contains equal Na^+ concentrations in PV and interstitial fluid volume (approximately 140 mM). The predominant intracellular cation K^+ (potassium ion) has an intracellular concentration of approximately 150 mM.

Measurement of Body Fluid Spaces

There are several methods to measure the various fluid spaces. TBW can be estimated by anthropometric formulae, commonly validated from tracer dilution methods. Anthropometric predictions of various physiologic properties depend on height, weight, age, gender, and race; these population models naturally result in various degrees of inaccuracy when applied to individuals. For example, TBW in liters can be estimated by the formulas[23]:

$$\text{Male TBW} = 2.447 - (0.09156 \times \text{age}) + (0.1074 \times \text{height}) + (0.3362 \times \text{weight})$$

$$\text{Female TBW} = -2.097 + (0.1069 \times \text{height}) + (0.2466 \times \text{weight})$$

Inaccuracy when applied to the individual can be substantial. This equation does not take into account that TBW decreases with age.[24] The amount of body fat also influences TBW; fat varies inversely with water.[25] TBW can be measured by isotope dilution techniques, preferably with nonradioactive isotopes such as the stable water isotopes ^2H_2O and $H_2{}^{18}O$, and the precision can be as high as 1%.[26] However, these methods are not clinically feasible owing to the complex experimental setup and mixing time required for the tracer.[27] Another technique of estimating TBW is by bioelectrical impedance analysis. Although simple, quick, and cheap, there are many potential sources of error.[28]

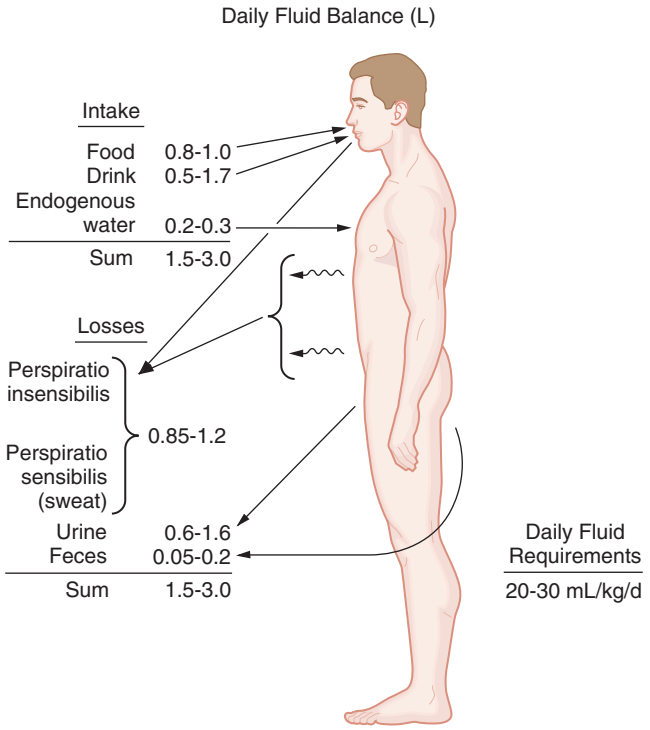
ECF can also be estimated by tracer techniques. The most commonly used tracer is the bromide anion (Br^-). Two drawbacks of using bromide as a dilution tracer are that it requires a long mixing time and does not distribute equally through the ECF.[29] The blood volume is commonly predicted by anthropometric formulae but individual variation can be considerable.[30] Because the blood volume includes erythrocytes (in ICF) and the PV, the two components can be estimated individually. The volume of erythrocytes can be determined by isotope labeling with chromium 51 (^{51}Cr) and technetium 99 (^{99}Tc), for example, but there are other nonradioactive methods such as labeling erythrocytes with fluorescein.[29] Another methods uses a semiautomated blood volume analyzer that can provide rapid and fairly accurate information when assessing blood volume in blood loss situations and making critical transfusion decisions. It uses albumin–iodine 131 (^{131}I) and results are available in 20 minutes.[31]

Maintenance Requirements for Water, Sodium, and Potassium

TBW content is regulated by the intake and output of water. Water intake includes ingested liquids plus an average of 750 mL ingested in solid food and 350 mL generated metabolically. Perspiration losses are approximately 1000 mL/day and gastrointestinal losses are about 200 mL/day (Fig. 41.2).

Thirst is the primary mechanism of controlling water intake and is triggered by an increase in plasma tonicity or by a decrease in ECV (see Chapter 42). Reabsorption of filtered water and Na^+ is enhanced by changes mediated by the hormonal factors antidiuretic hormone (ADH), atrial natriuretic peptide (ANP), and aldosterone (see Chapters 40 and 42). Renal water handling has three important components: (1) delivery of tubular fluid to the diluting segments of the nephron, (2) separation of solute and water in the diluting segment, and (3) variable reabsorption of water in the collecting ducts.[32] In the descending loop of Henley, water is reabsorbed while solute is retained to achieve a final osmolality of tubular fluid of ~1200 mOsm/kg. This concentrated fluid is then diluted by active reabsorption of electrolytes in the ascending limb of the loop of Henle and distal tubule, both of which are relatively impermeable to water. As fluid exits the distal tubule and enters the collecting duct, osmolality is ~50 mOsm/kg. Within the collecting duct water reabsorption is modulated by ADH (also called vasopressin). Vasopressin binds to V2 receptors along the basolateral membrane of the collecting duct cells and stimulates synthesis and insertion of aquaporin-2 water channels into the luminal membrane of collecting duct cells to facilitate water permeability.

Plasma hypotonicity suppresses ADH release, resulting in excretion of dilute urine. Hypertonicity stimulates ADH secretion, which increases the permeability of the collecting duct to water and enhances water reabsorption. In response to changing plasma Na^+, differences in the secretion of ADH can change urinary osmolality from 50 to 1200 mOsm/kg and urinary volume from 0.4 to 20 L/day. Other factors that stimulate ADH secretion, though



• **Fig. 41.2** Schematic of daily fluids turnover. Arrow direction indicates intake or output. Water intake is required to offset gastrointestinal, urinary and insensible losses.

none as powerfully as plasma tonicity, include hypotension, hypovolemia, and nonosmotic stimuli such as nausea, pain, and medications, including opioids.

Two powerful hormonal systems regulate total body Na^+. The natriuretic peptides, ANP, brain natriuretic peptide, and C-type natriuretic peptide, defend against Na^+ overload and the renin-angiotensin-aldosterone axis defends against Na^+ depletion and hypovolemia.[33] ANP, released from the cardiac atria in response to increased atrial stretch, produces vasodilation and increases the renal excretion of Na^+ and water. ANP secretion is decreased during hypovolemia. Even in patients with chronic (nonoliguric) renal insufficiency, infusion of ANP in low doses (i.e., that do not produce hypotension) increases Na^+ excretion and augments urinary losses of retained solutes.[34] Aldosterone is the final common pathway in a complex response to decreased effective blood volume, whether decreased effective volume is true or relative (e.g., edematous states or hypoalbuminemia). In this pathway, decreased stretch in the baroreceptors of the aortic arch and carotid body and stretch receptors in the great veins, pulmonary vasculature, and atria result in increased sympathetic tone. Increased sympathetic tone, in combination with decreased renal perfusion, leads to renin release and formation of angiotensin I from angiotensinogen. Angiotensin-converting enzyme converts angiotensin I to angiotensin II, which stimulates the adrenal cortex to synthesize and release aldosterone.[35] Acting primarily in the distal tubules, high concentrations of aldosterone cause Na^+ reabsorption and can reduce urinary excretion of Na^+ nearly to zero. Intrarenal physical factors are also important in regulating Na^+ balance. Sodium loading decreases colloid osmotic pressure, thereby increasing the glomerular filtration rate (GFR), decreasing net Na^+ reabsorption, and increasing distal Na^+ delivery, which in turn suppresses renin secretion.

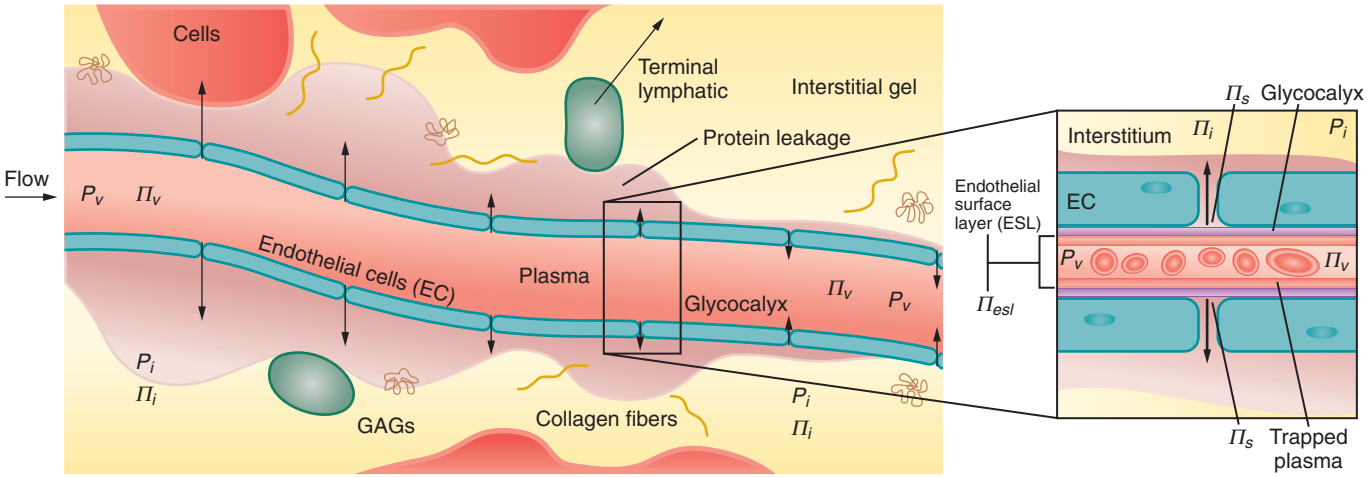
In healthy adults, sufficient water is required to offset gastrointestinal losses of 50 to 200 mL/day, insensible losses of 850 to 1200 mL/day (half of which is respiratory and half cutaneous), and urinary losses of about 1000 mL/day (see Fig. 41.2). Urinary losses exceeding 1000 mL/day can represent an appropriate physiologic response to ECV expansion or an inability to conserve salt or water.

Daily requirements for Na^+ and K^+ are approximately 75 mEq/day and 40 mEq/day, respectively, although wider ranges of Na^+ intake than K^+ intake are physiologically tolerated because conservation and excretion of Na^+ are more efficient than of K^+. Therefore healthy 70-kg adults require 2500 mL/day of water containing a Na^+ of 30 mM and a K^+ of 15 to 20 mM. Intraoperatively, fluids containing Na^+-free water (i.e., Na^+ <130 mM) are rarely used in adults because of the necessity for replacing isotonic losses and the risk of postoperative hyponatremia, particularly in children.[36]

Interstitium

During surgery and trauma, fluid extravasation is enhanced: capillary permeability increases and permits more fluid to escape to the interstitium. The ECV consists of the plasma (approximately 3.5 L in a 70-kg man), the interstitial space (approximately 10.5 L), and small amounts of transcellular fluids, such as gastrointestinal fluids, cerebrospinal fluid, and ocular fluid.[32] The interstitium is a mixture of fluid and fibrillar structures. The main nonfluid components are fibrils and the interstitial ground substance that can be subdivided into a colloid-rich and a water-rich phase. Fibrils are mainly collagenous, reticular, and elastic. The amorphous ground substance or gel-like matrix is produced by the same cell types as the fibrillar components. It contains several different glycosaminoglycans (mucopolysaccharides). Plasma proteins passing the capillary wall are mainly restricted to a random network of interstitial channels corresponding to colloid-poor, water-rich areas. Edema causes and increases hydration and depolymerization of the ground substance (Fig. 41.3).[37]

Fluid distribution within the human body is related to the distribution of osmotically active substances. The physiologic distribution is maintained by biologic barriers and adenosine triphosphate–requiring pumps. The vascular wall is impermeable to larger molecules or proteins, with normal fluid distribution subject to an intact inner lining of the endothelial wall (glycocalyx).[38–40] When outward and inward pressures are accounted for, there is a small net filtration of fluid. However, deterioration of the glycocalyx, as seen in systemic inflammatory conditions, is of greater importance than interstitial protein concentration for fluid escape through the endothelial barrier.[41] The endothelial glycocalyx consists of a variety of transmembrane and membrane-bound molecules. These are mainly syndecans and membrane-bound glypicans that contain heparan sulfate and chondroitin sulfate chains. The thickness of the glycocalyx is about 1 μm. Together with some plasma proteins that are membrane bound, hyaluronan, and dissolved glycosaminoglycans, the inner endothelial surface layer is tens of nanometers thick.[40] Degradation of the glycocalyx leads inevitably to increased capillary leakage and interstitial edema, which is strongly correlated with a decrease in tissue oxygenation.[41] Reduction of the endothelial glycocalyx, such as in sepsis, major vascular surgery with global or regional ischemia, or diabetes mellitus, can lead to changes such as increased permeability and release of proteases, tumor necrosis factor α, oxidized low-density lipoprotein, and atrial natriuretic peptide.[41,42] Even the shear force



• **Fig. 41.3** A capillary vessel with surrounding tissue. Endothelial cells permit leakage of water, small solutes, and proteins. Conditions can differ owing to pathology. Abbreviations refer to the Starling formula, which is modified by the existence of the glycocalyx. The inner lining of the glycocalyx and trapped plasma together form the endothelial surface layer *(ESL)*. A revised Starling formula would be as follows: $J_v = K_f (P_v - P_i - \sigma\Pi_{esl} - \Pi_s)$. Within the ESL there is practically no circulation. GAGs, J_v, Net filtration; K_f, filtration coefficient; P_i, interstitial hydrostatic pressure; P_v, capillary hydrostatic pressure; Π_i, interstitial oncotic pressure; Π_{esl}, oncotic pressure within the endothelial surface layer; Π_s, oncotic pressure beneath the endothelial surface layer; Π_v, venous vascular oncotic pressure; σ, reflection coefficient; (Modified from Chappell D, Jacob M, Hofmann-Kiefer K, et al. A rational approach to perioperative fluid management. *Anesthesiology.* 2008;109:723–740.)

of IV solutions infused too rapidly have been suggested to cause deterioration of the glycocalyx.[15]

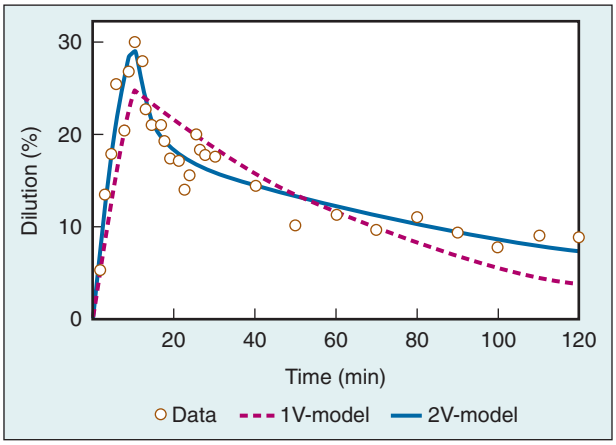
Smaller molecules such as crystalloids are probably not much affected because they can escape through the barrier anyway.[44,45] Filtration normally leads to only a moderate shift and accumulation of fluid because both increased lymph flow and interstitial hydrostatic pressure, in combination with dilution of interstitial protein, limit excess accumulation of interstitial fluid. There is also normal transcapillary escape of albumin of about 5% of the intravascular albumin per hour, which is increased in a variety of diseases.[46] Transfer of albumin back to the intravascular space occurs via the lymph, but can be impeded by surgery and inflammation.[41]

Third Space

Clinicians used to replace losses to the third space during surgical procedures. The concept of the third space has been a topic of debate and controversy for decades.[29] Loss to the interstitial space is an inevitable phenomenon that consists mainly of small molecules leaving through an intact vascular barrier. When this loss caused by trauma and surgery becomes pathologic, it can be considered an accumulation within the interstitial space or the "functional" ECV.[15] The accumulated fluid is normally removed by the lymphatic system as described earlier. However, when there is an overload, either by excessive fluid load or cessation of urinary production, the result is an even more pronounced accumulation of interstitial fluid. Fluid within the hypothetical third space is thought to be a "nonfunctional" body fluid separated from the interstitial space. Examples of third space would be fluid in the peritoneal cavity, bowel, and traumatized tissues, with the key point being that losses to these spaces are no longer in rapid equilibrium with the ECF and thus are nonfunctional.[47]

A major problem is that the third space cannot be measured, and there is considerable controversy regarding its existence.[29] It is common belief that fluid spaces can be identified by applying a tracer intravenously. The tracer is assumed to equilibrate within the desired space, and the dye or isotope enables identification of the distribution volume.[8] Unfortunately, interpretation of tracer kinetic trials is not simple. The volume measured is the volume of distribution of a tracer and might not represent a volume of any clinical relevance. Furthermore, tracers are subject to differences in perfusion and equilibration time. For example, Na^+ is rapidly transported to the intracellular compartment, bromide enters red blood cells and is excreted in bile, and the sulphate tracer $^{35}SO_4$ is bound to plasma components and can accumulate in the liver and kidneys (and during shock in muscular tissue as well).[8,48] If the time for equilibration is too short, the concentration of any tracer in blood can be incorrectly high and the calculated volume of distribution will appear contracted.[48] To overcome this, tracer spaces should be calculated from multiple blood samples with continued sampling until equilibrium is demonstrated.

The theory behind the third space concept is mainly based on studies by Shires and coworkers in the early 1960s performed on both animals and humans using $^{35}SO_4^-$ to identify the functional ECV.[17,18] This tracer has a short equilibration time and the extracellular space can thus be calculated from a single or just a few blood samples. Using this sulphate tracer it was possible to identify an apparently contracted ECF space, which led these investigators to believe this space needed replacement by crystalloids. The Shires group had considerable impact on researchers and clinicians in the 1960s, but few other researchers have managed to replicate their findings. In a study of 50 young male war casualties, ECV was estimated by measuring the $^{35}SO_4^-$ concentration in multiple blood samples.[49] Comparison of one group with minor injuries with a control group of base camp subjects revealed a general state of dehydration of the soldiers in the field. In another study, when corrected for the capillary refill phenomenon, comparison of the three shock groups with the control group of combat subjects showed that the ECV changed in accordance with calculated fluid



• **Fig. 41.4** Dilution profiles for a crystalloid load. Fluid was given over 10 minutes, reflecting the time course of preload augmentation. Hemoglobin is used as an endogenous tracer to calculate plasma dilution and the data fitted to nonlinear equations.[53] The broken *red curve* is the kinetic profile of a one-compartment (one volume [*1V*] space) model, and the continuous *blue curve* shows the dilution profile of a two-compartment model (two volume [*2V*] spaces). The dilution is maximal when the infusion is turned off. The effect is transitory and the fluid is almost eliminated from the central space within 3 hours.

balance. Other investigators studied 10 healthy young male volunteers who lost 11% to 14% of their blood volume with or without subsequent replacement with lactated Ringer (LR) solution.[50] None of the subjects developed shock, and the ECV changed in accordance with the fluid balance.

Only trials using the sulphate tracer and short equilibration times have reported a "third space contraction." Several researchers who were using tracers such as Na^+ or bromide all reported ECV expansion during surgical conditions. Trials calculating the ECV from multiple blood samples have found the ECV either unchanged or expanded after surgery.

The concept of a loss to third space needing replacement was introduced simultaneously with the conflict in Vietnam.[51] Liberal fluid administration together with improved evacuation and field surgical care (and improvement in other treatment modalities) might have saved many lives. Renal failure, which had been a major problem in World War II and the Korean conflict, was almost unheard of. On the other hand, "the wet lung syndrome" (later diagnosed as acute respiratory distress syndrome) was reported in otherwise healthy soldiers resuscitated with large amounts of fluids after traumatic injury. However, the evidence for respiratory distress caused by fluid overload is not compelling.[16]

Abdominal compartment syndrome is, however, linked to overzealous crystalloid administration. In a prospective randomized trial of patients undergoing colorectal surgery, a restricted IV fluid regimen omitting replacement of the "third space losses" significantly reduced postoperative complications compared with a standard regimen following traditional guidelines.[3] These results have been confirmed by other prospective randomized trials from more diversified elective intraabdominal procedures.[5] Fluid kinetics studies indicate that the peripheral expandable fluid space during anesthesia and surgery is similar to that in awake volunteers.[52] The peripheral expandable space is in equilibrium with infused fluid, further contradicting the argument of an ECF contraction needing replacement during surgery.[53] Nevertheless, situations with low perfusion might occur in which cell membranes are altered and fluid does indeed shift to the intracellular space. These compartmental shifts might need replacement, but the use of aggressive fluid management in elective surgical procedures is not justified by evidence.

Numerous studies have argued that it should be beneficial to vary the choice of IV fluids in certain situations. Fundamentally, crystalloids (ionic solutions with molecules of <30 kDa) should be better suited for replacing losses from the ECF, whereas colloids with larger molecules should be the ideal replacement for intravascular losses (apart from blood and plasma). Although these fluids show different properties, it has not been possible to show any differences in mortality in large randomized studies.[54–56] The crystalloid-colloid debate has in recent years focused more on safety aspects such as renal damage in critically ill patients.[57]

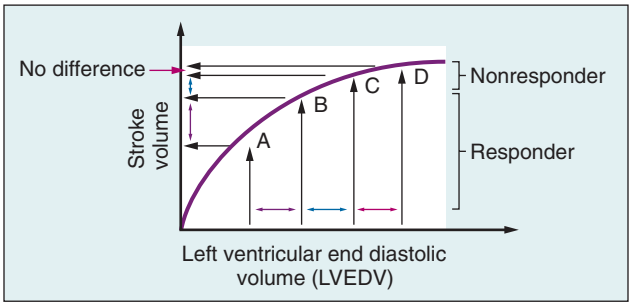
Fluid Shifts and Losses During Surgery, and Their Replacement

Because of the porous nature of the endothelium, fluid shifts of protein-poor fluid from the intravascular space to the interstitium are inevitable. Surgical manipulation per se can increase interstitial water volume, and crystalloid infusion can influence its extent.[58] Losses that consistently occur during surgical procedures include urinary output and insensible losses.[58] During trauma surgery and certain other major operations, blood loss constitutes a significant fluid loss. Urinary output and evaporation should affect the extracellular space (vascular system and interstitium) and should cause no net change in colloid osmotic pressure in the vascular system. On the contrary, intravascular loss (bleeding) contains blood components and thereby causes a change in colloid osmotic pressure with crystalloid replacement.

To replace these losses, it is logical to replace extracellular losses with crystalloid. The conventional perception of the distribution of crystalloids is that up to 80% are distributed to the interstitial space.[59] However, fluids are context-sensitive. Advanced kinetic analysis (see later "Body Fluid Dynamics" section) demonstrates a central accumulation of fluid that eventually distributes to the periphery or is eliminated as urine.[53] In simple terms, this means that a crystalloid load initially exerts a substantial volume expansion effect (Fig. 41.4), which is more pronounced during low pressure or bleeding compared with normal states, but the effect is transitory. This, however, has been challenged by those who advocate direct assessment of plasma and blood volume.[60] Colloids, on the other hand, have a more prolonged effect on intravascular volume. To replace blood loss, it is plausible to replace intravascular loss either by giving blood or a colloid. Whole blood would be preferable but this is not usually possible owing to logistical reasons and infectious and incompatibility risks.[61]

Conventional Indices of Resuscitation

Resuscitation of critically ill patients requires accurate assessment of intravascular volume status and the ability to predict the hemodynamic response to a fluid challenge. Indices of hemodynamic response, such as blood pressure, cardiac output, heart rate, and oxygen delivery, do not fully reflect the adequacy of tissue perfusion. Less than 50% of critical care patients given fluid boluses are volume responsive.[62] A reduction in renal perfusion normally results in dilatation of the afferent glomerular arteriole and constriction of the efferent arteriole so that the GFR is kept constant. However, if mean arterial pressure falls below 70 mm Hg (the kidney autoregulatory threshold), renal perfusion pressure and GFR fall, leading to oliguria. However, the kidney is affected by many factors,



• **Fig. 41.5** Relationship between preload and stroke volume. An incremental increase (A-B) in volume on the *x*-axis (left ventricular end-diastolic volume, *LVEDV*) increases stroke volume/cardiac output on the *y*-axis (*Responder*). Eventually a deflection point is reached (between C and D), after which the heart will no longer perform increased work with increasing preload (*Nonresponder*).

including cardiac function, osmotic load, intrathoracic pressure, intraabdominal pressure, and chronic renal insufficiency, which make urine output an unreliable predictor of volume status.[32] Other signs of inadequate intravascular volume are peripheral cyanosis, skin mottling, tachycardia, hypotension, and cold extremities. All these signs are nonspecific and unreliable indicators of adequate resuscitation.

Response to Fluid Challenge

An important concept for guiding rational fluid administration is the use of the Frank-Starling curve for cardiac performance (Fig. 41.5). In most clinical circumstances, a basic assumption is that the patient is on the ascending part of the Starling curve and has a submaximal cardiac output. When the subject reaches the flat part of the curve, more fluid administration has little effect on cardiac output/stroke volume and will only increase tissue edema. Although this concept applies to healthy volume-depleted patients, less than half of critically ill patients might respond to a fluid challenge.[63]

Static Measurements of Intravascular Volume

Central venous pressure (CVP) is still used as a common parameter to guide fluid therapy[64]; however, the idea that CVP reflects intravascular volume is a common misconception.[65] CVP was earlier measured in centimeters of water, but now millimeters of mercury is used (1 cm H_2O = 0.735 mm Hg or 10.2 kPa). CVP is influenced by many factors unrelated to actual fluid balance, such as venous tone, intrathoracic pressure, and left and right ventricular compliance. Consequently, there is poor correlation between CVP and the right ventricular end-diastolic volume, which it is intended to measure. Meta-analyses assessing the ability of CVP to predict fluid responsiveness show low or insignificant predictability in that there is poor association between CVP and circulating blood volume.[66] Chest radiographs and ultrasonography, including vena cava collapsibility index, have limited value in guiding fluid management.[67,68]

Pulmonary Artery Occlusion Pressure

The pulmonary artery catheter (PAC) is used to measure pulmonary artery occlusion pressure or pulmonary capillary wedge pressure, which is intended to reflect left ventricular preload.[69] However, pulmonary artery occlusion pressure is not a good indicator of preload.[70,71] The catheter measures pressure and not volume, the relationship is not direct but curvilinear, and clinical benefit is highly doubtful.[72,73] Left ventricular compliance is dependent on filling of the right ventricle, which means that the PAC has the same limitations as the central venous catheter.

Transesophageal Echocardiography

Widely used in cardiothoracic surgery, transesophageal echocardiography has not proved a reliable predictor of fluid responsiveness in critically ill patients. There are conflicting results for use of the left ventricular end-diastolic area as a good predictor because it is a static measurement.[74,75] Continuous measurements, such as positive-pressure ventilation, induced changes in vena cava diameter, and aortic flow velocity/stroke volume assessed by echocardiography, all have limitations.

Intrathoracic Blood Volume Index and Global End-Diastolic Volume Index

Transpulmonary thermodilution is a method that uses a cold bolus as a single indicator for determination of the assessment of the largest volume of blood contained in the four heart chambers, called the global end-diastolic volume. It requires the use of a specific thermodilution arterial catheter (pulse contour cardiac output monitoring) that measures temperature changes after the injection of the bolus through a central vein catheter (normally the central vein catheter is placed in the neck, the arterial line in the femoral artery). It does not appear to be a good predictor of fluid responsiveness according to available studies.[22,76,77]

Stroke Volume Variation and Pulse Pressure Variation

Intermittent positive-pressure ventilation induces cyclic changes in cardiac loading conditions. Insufflation decreases preload and increases afterload of the right ventricle (RV). The increase in RV afterload is related to inspiratory increases in transpulmonary pressure. The RV preload reduction is due to the decrease in the venous return pressure gradient, which in turn is dependent on the inspiratory increase in pleural pressure. These simultaneous changes in RV preload and afterload lead to a decrease in RV stroke volume, which is at its minimum at the end of inspiration. The inspiratory reduction in RV stroke volume corresponds to a reduction of left ventricle (LV) filling delayed two or three heartbeats because of the filling of the lungs. Thus the LV preload reduction is at its minimum during inspiration. Changes in RV and LV stroke volume are greater when the ventricles work on the steep part of the Starling curve (see Fig. 41.5). Thus change in LV stroke volume is an indicator of biventricular preload dependence.[78] According to a large systematic review, pulse pressure variation (PPV) and stroke volume variation (SVV) predict with a high degree of accuracy (receiver operating curve 0.94 and 0.84, respectively) patients who are likely to respond to a fluid challenge.[66] This suggests that currently PPV and SVV are the most accurate, dynamic tools for guidance of fluid management, but they are limited by arrhythmias and the requirement for mechanical ventilation. They are less reliable in critically ill patients receiving ventilatory support. Furthermore, PPV is a direct measurement, whereas SVV is an indirect calculation from pulse contour analysis. PPV can be affected by the tidal volume, with the recommendation that tidal volume should be at least 8 mL/kg.[21,22] the plethysmographic variability index is a measure of respiratory-induced variations in the plethysmographic waveform amplitude that, like

other dynamic indices, has been shown to predict fluid responsiveness.[79] This is a rather new method provided by noninvasive hemoglobin measurement devices.[79]

Esophageal Doppler Catheter

This technique measures blood flow velocity in the descending aorta by means of a Doppler ultrasound device placed at the tip of a flexible probe. Patients need to be anesthetized or at least sedated to tolerate the probe; once in the esophagus, the catheter is rotated so that the transducer faces the aorta.[80] Because the width of the aorta is either measured or known, the cardiac output can be calculated when the heart rate is known. The flow time corrected for heartbeats is considered an indicator for volume and afterload status. It appears to be a reliable predictor of fluid responsiveness, and has benefits for specific patient groups in reducing morbidity and hospital stay.[81–85] Performance depends on catheter positioning, but the required training for insertion is short.

Passive Leg Raising Test

Passive leg raising (PLR) represents an endogenous volume challenge that can be used to predict fluid responsiveness. This procedure rapidly returns 150 to 200 mL of blood from peripheral veins in the lower extremities to the central circulation. When ventricular preload is increased, cardiac output is augmented according to the degree of preload reserve.[86]

A PLR test can be used in patients with spontaneous or assisted breathing and irregular cardiac rhythm; therefore it can be a more useful test of fluid responsiveness in critically ill patients.[87] PLR is a simple test in which the legs are elevated by 45 degrees above the bed, but to be reliable it must be accompanied by cardiac output monitoring. Because of the ease of use, simplicity, and high diagnostic accuracy, PLR is the preferred method to assess fluid responsiveness.[88]

Oxygen Delivery and the Microcirculation

The microcirculation consists of myriads of vessels connecting the arteriolar and venous vasculature. It is here that oxygen is delivered and consumed and that metabolism generates waste products.[89] It is important to distinguish between convective oxygen transport, which depends on the availability of red cell oxygen-transporting capacity, and diffusion oxygen transport, which is related to the pressure gradient and inversely related to the distance between the capillary and the cell (specifically mitochondria). Mixed venous oxygenation (SvO_2) is a global assessment but requires a PAC. Its surrogate, central venous oxygenation ($ScvO_2$), also requires a central venous line and is a regional index (head and upper body). Although $ScvO_2$ is slightly higher than SvO_2 in critically ill patients, they usually trend together.

Several options are available to monitor the microcirculation. Brain tissue oxygenation has been measured extensively in experimental animal cardiopulmonary resuscitation models but has limited clinical applicability owing to invasiveness. Among *direct* methods, in vivo microscopy of the microcirculation is available through small cameras mainly restricted to the sublingual area. Earlier devices such as orthogonal polarized spectral and sidestream dark field imaging video microscopes were hampered by technological limitations, but recent-generation handheld microscopes perform better.[90–93] These devices make it possible to assess the two determinants of oxygen delivery. Microvascular flow index is a marker for convective oxygen transport and the diffusion distance is reflected by capillary density.

Among *indirect* methods, tonometry and capnography are based on local accumulation of carbon dioxide as a result of inadequate elimination of cellular waste, and could possibly be a useful method for guiding fluid therapy. However, there is a confounding situation when distributive failure occurs (shunting, such as in sepsis). Another method is the use of near-infrared spectroscopy, a noninvasive optical measurement in which differential absorption of infrared light at two specific wavelengths (680 and 800 nm) by deoxyhemoglobin is used to define hemoglobin saturation level in vessels located under the probe.[94]

Body Fluid Dynamics (Modeling Fluid Therapy)

How do we analyze and quantify the volume and equilibrating process induced by infusing fluid intravascularly? Is it possible to compare effects of different fluid therapies given in various clinical situations? A key problem in studying these phenomena is that infused fluid is added to a highly regulated system that attempts to maintain intravascular, interstitial, and intracellular volume through homeostatic adaptation. We can use dynamic models to predict more accurately the time course of these volume changes.[80,95] These analyses should permit estimation of peak volume expansion and rates of clearance of infused fluid and covariate analysis of other effects, such as changes in cardiac output or cardiac filling pressures.

The traditional clinical assumption of the distribution of infused crystalloids, one-third intravascular and two-thirds peripheral, is not always accurate owing to large variations between individuals (Fig. 41.6). The response to hypovolemia or hypervolemia depends highly on the starting hydration level, underlying pathology, and general ability to eliminate and distribute fluid via homeostatic mechanisms.[96]

Hemoglobin can be used as an endogenous marker to compute intravascular expansion. If the intravascular volume V_b (in milliliters) is defined as the distribution volume of hemoglobin (Hb), it is natural to use Hb as an endogenous tracer when analyzing volume expansion; assuming no loss of red cells, as plasma volume expands, Hb concentration decreases. Consider the relationship between the amount of Hb (X_{Hb}) and its concentration C_{Hb} (in millimoles per milliliter):

(1)

$$C_{Hb} = \frac{X_{Hb}}{V_b}$$

If V_b is assumed to be a completely closed but expandable space (Fig. 41.7), and fluid is infused by a constant rate R_i (in milliliters per minute), the concentration at any time t can be computed as

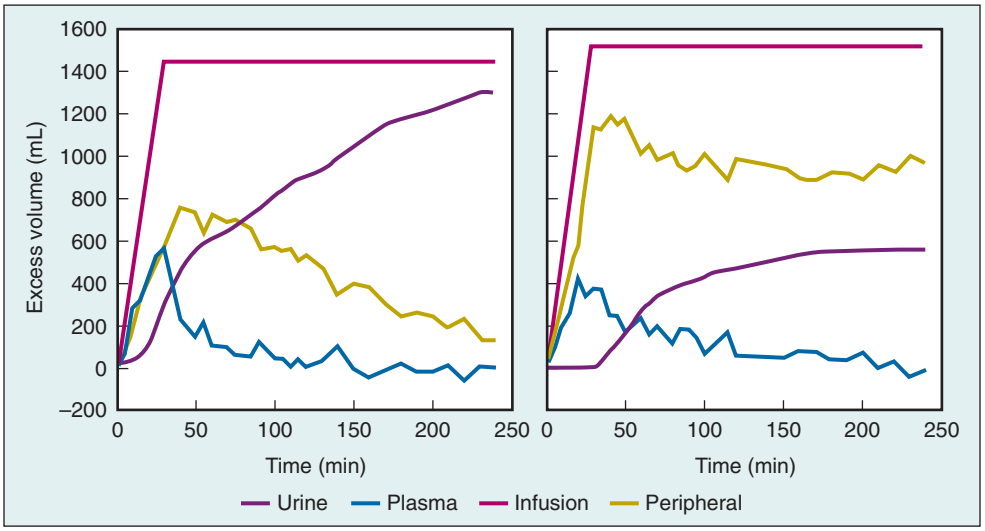
(2)

$$C_{Hb}(t) = \frac{X_{Hb}}{V_b + R_i \cdot t}$$

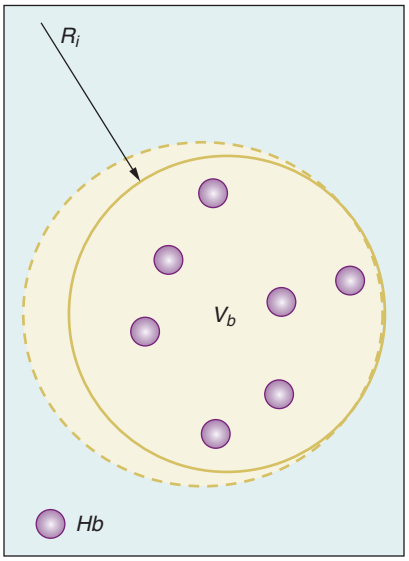
Because X_{Hb} is considered to be constant during infusion, Eqs. (1) and (2) can be combined:

(3)

$$V_b \cdot \left(\frac{C_{Hb}(0)}{C_{Hb}(t)} - 1 \right) = R_i \cdot t,$$



• **Fig. 41.6** Mass balance computations for fluid infused over 30 minutes.[99] The figures illustrate the distribution of infused Ringer solution in milliliters *(dark pink)* between plasma *(blue line)*, accumulated urine *(purple line)*, and the peripheral fluid space *(yellow line)* for two subjects over time in minutes. The subject in the left panel responds quickly to the hypervolemia and has eliminated almost all the infused fluid during the observation time. The subject in the right panel has a less pronounced and slower elimination. (Reprinted with permission from Rodhe P, Drobin D, Hahn RG, et al. Modelling of peripheral fluid accumulation after a crystalloid bolus in female volunteers—a mathematical study. *Computat Math Method Med*. 2010;11:341–351.)



• **Fig. 41.7** Closed volume approach. Fluid is infused at a rate of R_i, which causes an expansion of the intravascular volume V_b. This in turn lowers the concentration of the endogenous marker hemoglobin *(Hb)*.

rewriting Eq. (3) as

(4)

$$\frac{1}{R_i}\cdot\left(\frac{C_{Hb}(0)}{C_{Hb}(t)}-1\right)=Y=\frac{1}{V_b}\cdot t\cong\theta\cdot t+\varepsilon$$

Eq. (4) allows us to compute Y and ε (the residual error) by regression, and to obtain an estimate of theta ($1/V_b$). The method is straightforward and only needs Hb data as an input. Fig. 41.8 shows an example of experimental data obtained using the closed volume approach. In the right panel, the Hb infusion estimation overestimates V_b by nearly 1 L. Although the predictions, based on gender, height, and weight, can differ considerably between individuals, the estimates based on the closed volume approach should be adjusted by an empirical correction term. This overestimation phenomenon might arise from (1) underestimating the rate of infusion or, more likely, (2) fluid disappearing from the intravascular fluid space during infusion. Therefore the complexity of the fluid distribution model must be increased to understand intravascular volume changes.

Plasma Volume Expansion

The plasma volume, at any time t, can be computed from the hematocrit (HCT) as

(5)

$$v_p(t)=v_b(t)\cdot(1-HCT(t))$$

If the volume of erythrocytes is considered constant during the observation time T (which is not true if bleeding is present), then the relation

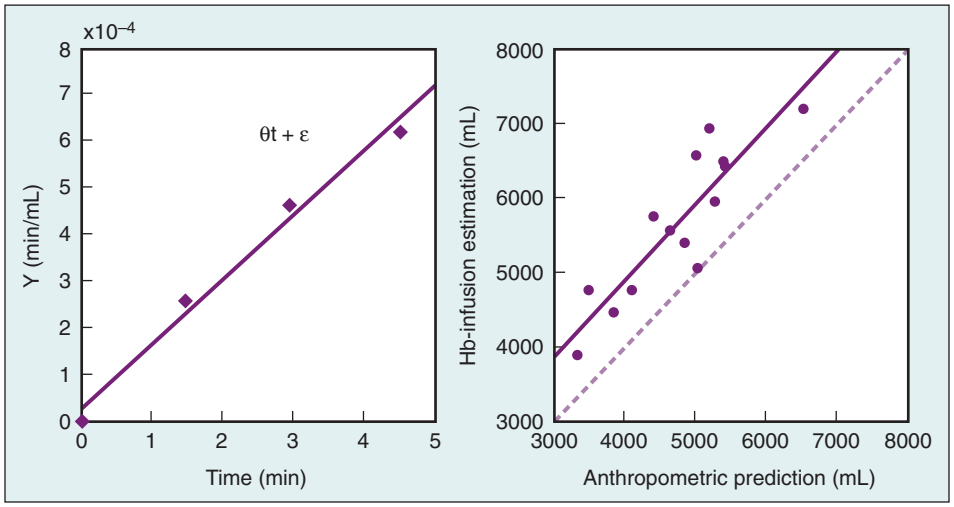
(6)

$$HCT(t)=\frac{HCT(0)\cdot V_b}{v_b(t)}$$

holds for $0\le t\le T$ where $V_b = v_b(0)$. Furthermore, the amount of Hb is constant and the relation

(7)

$$v_b(t)=\frac{C_{Hb}(0)\cdot V_b}{C_{Hb}(t)}=\frac{C_{Hb}(0)\cdot V_p}{C_{Hb}(t)\cdot(1-HCT(0))}$$



• **Fig. 41.8** An example of data analyzed using the closed volume approach. The analysis is based on data from Fig. 41.7. *Left, Y* is estimated by linear regression *(solid line)* from three consecutive time points (t = 1.5, 3, 4.5 min; *diamonds*) corresponding to three hemoglobin (*Hb*) values for one subject. Distribution volume (V_b) is then estimated by 1/*y*. *Right,* The distribution volume V_b was computed from 14 subjects *(circles)* receiving 1.5 mL/kg per minute of lactated Ringer solution.[100] Hb values were taken from arterial blood samples. Although there was a 1:1 relation between the anthropometric prediction and the Hb infusion estimation, a bias of 770 mL was present.[30] The *dotted line* represents the line of identity, whereas the *solid line* represents the linear regression.

also holds, $V_p = v_p(0)$. The *amount* of fluid a_p is now defined as $a_p(t) = v_p(t) - V_p$ and the relative change of plasma volume is defined as

(8)

$$D_p(t) = \frac{a_p(t)}{V_p}$$

where D_p is dimensionless, referred to as the *dilution*. Using Eqs. (1) and (5) through (8), a more compact formula can be derived:

(9)

$$D_p(t) = \frac{\frac{C_{Hb}(0)}{C_{Hb}(t)} - 1}{(1 - HCT(0))}$$

Repeated measurements of Hb concentration can then be transformed into the dilution-time domain to describe plasma volume expansion (Fig. 41.9). This constitutes a model for intravascular fluid therapy that enables simulations to predict the effects of various fluids and dosing regimens.

The transformation of Hb concentration into dilution enables analysis of fluid infusion using pharmacokinetic models. This field is commonly referred as *volume kinetics for infusion fluids* or *fluid kinetics*. One conceptual problem with this approach is that we infuse fluid into fluid, where both fluids consist mainly of water. The term *concentration* becomes somewhat ambiguous from a unit perspective (Table 41.1).

Volume Kinetics for Infusion Fluids

Adaptation of pharmacokinetic/pharmacodynamic (PK/PD) nomenclature for infusion fluids has many advantages, not the least of which is treating infusion fluids as drugs, introducing concepts such as absorption, distribution, metabolism, and elimination. The process of *pharmacokinetic* modeling involves breaking down drug movement within the body into a finite number of compartments. Once the drug has reached its target area, the effect site, the field of *pharmacodynamics* characterizes in quantitative terms the effects of the drug.[97] PK/PD modeling usually starts with some physiologic assumptions about the underlying process. From the closed volume approach, the following relation is derived:

TABLE 41.1 Basic Differences Between Traditional Pharmacokinetic Expressions and Their Similarities in Volume Kinetics

	Pharmacokinetics	Volume Kinetics
Observed agent	*X* (mg)	*a* (mL)
Concentration	*C* (mg/mL)	*D* (no unit)
Distribution volume	*V* (mL)	*V* (mL)
Mass at time *t*	*C(t)* • *V* (mg)	*D(t)* • *V* (mL)

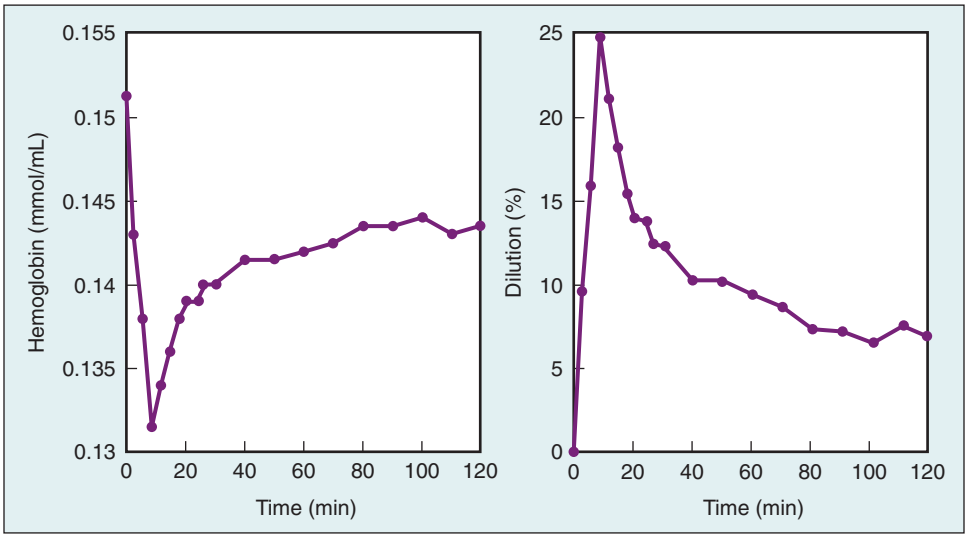
(10)

$$v_b(t) = v_p(t) + VOE = a_p(t) - V_p + VOE = V_b + R_i(t) - U(t)$$

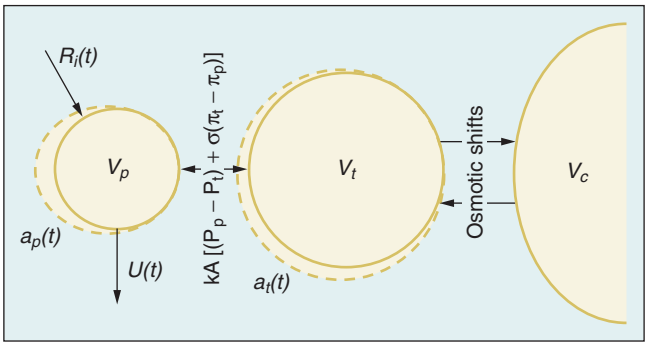
where $U(t)$ is a time-dependent loss of fluid caused by the perturbation introduced by the infusion $R_i(t)$. Differentiating Eq. (10) and considering *VOE* constant, the following relation is derived:

(11)

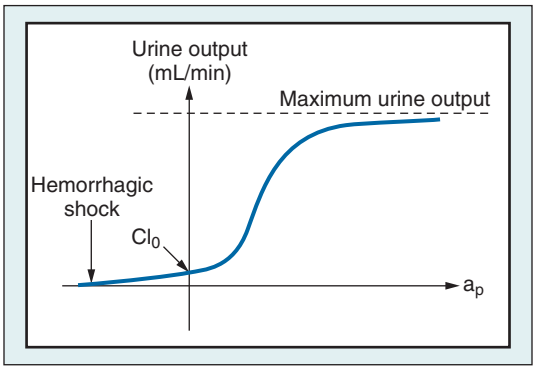
$$\frac{da_p}{dt} = \frac{dR_i}{dt} - \frac{dU}{dt}$$



• **Fig. 41.9** Example of hemoglobin concentration decrease *(left)* and corresponding dilution *(right)* following a crystalloid infusion over 10 minutes. (Reprinted with permission from Svensen C, Olsson J, Rodhe P, et al. Arteriovenous differences in plasma dilution and the kinetics of lactated Ringer's solution. *Anesth Analg*. 2009;108:128–133.)



• **Fig. 41.10** Basic volume kinetic model used to characterize the movement of fluid in the body. An infusion $R_i(t)$ of fluid causes an expansion by $a_p(t)$ in the central compartment V_p. This fluid is eliminated as $U(t)$ mL. There is also exchange of fluid with a peripheral compartment, here denoted by V_t (*t* for tissue). This exchange can be thought of as a whole body generalized effect of filtration mechanisms based on the Starling equation. If the administered fluid, given orally or intravenously, introduces osmotic imbalances, a third compartment representing the cellular fluid volume, V_c, is required. *kA,* Filtration coefficient.



• **Fig. 41.11** Relationship between intravascular volume expansion and urine output. The *x*-axis (a_p), denotes the plasma volume expansion. If a_p is zero, the plasma volume is considered to be at its optimal volume, or its baseline, with a basal elimination of Cl_0. a_p, Plasma volume expansion [mL]; Cl_0, basal elimination [mL/min].

Eq. (11) forms the basis for volume kinetic modeling. Fig. 41.10 shows the general pathways of fluid. Fluid is largely eliminated by renal clearance. This clearance (Cl) is mainly proportional to the volume expansion and therefore in its simplest form, renal clearance can be modeled by a first-order approximation:

(12)

$$\frac{dU(t)}{dt} = Cl_1 \cdot D + Cl_0$$

Cl_0 (in milliliters per minute) is often referred to as *basal elimination* and reflects ongoing losses of water as the result of respiration, sweating, and basal renal filtration. For an adult, Cl_0 is about 0.5 to 1.5 mL/min, which is consistent with findings from volume kinetics computations.[98] If the total urine (U_{tot}) is known during observation time *T,* then either Cl_1 or Cl_0 can be computed from

(13)

$$\int_0^T \frac{dU(t)}{dt}\,dt = U_{tot} = Cl_1 \cdot \int_0^T D \cdot dt + Cl_0 \cdot T \approx Cl_1 \cdot AUC(D) + Cl_0 \cdot T$$

The mechanisms of renal clearance are far more complex, governed by a feedback system that involves hormones, including antidiuretic hormone, renin-angiotensin, atriopeptin, aldosterone, and angiotensin II. Specialized receptors are also involved, including baroreceptors and osmoreceptors that regulate salt and water homeostasis. It is, however, possible to generalize fluid clearance from an intravascular expansion viewpoint, disregarding the turnover of Na^+ and other ions, within certain limits. The physiologic homeostatic mechanisms to maintain blood volume seem to be among the most highly developed.

Fig. 41.11 displays a theoretical representation of intravascular volume expansion versus urine output. Normally, this oscillates

around $a_p = 0$ depending on fluid intake and fluid and salt homeostasis. In a clinical setting, or for pathologic reasons, this relationship might be challenged. In this case, the linear relationship in Eq. (12) will not hold, and a nonlinear model must be used, reflecting the shape of the relationship shown in Fig. 41.11 for renal elimination.[99]

The exchange of fluid with the peripheral fluid space V_t can also be approximated in a linear relationship as

(14)

$$\frac{dQ(t)}{dt} = Cl_d \cdot \left(\frac{a_p}{V_p} - \frac{a_t}{V_t} \right),$$

where Cl_d (in milliliters per minute) is the distribution clearance, reflecting a generalized impact of perfusion and permeability properties in various tissues.[100] During infusion, the initial intravascular volume expansion causes a flow into V_t when $Q > 0$. If $Q < 0$, the peripheral fluid space is thought to be saturated in relation to V_p, which results in a flow back to the intravascular space.[101]

In summary, the linear volume kinetic equations of an isoosmotic IV fluid, with no bleeding, can be represented by

(15)

$$\frac{da_p}{dt} = \frac{dR_i(t)}{dt} - Cl_1 \cdot D_p - Cl_0 - Cl_t \cdot (D_p - D_t)$$
$$\frac{da_t}{dt} = Cl_t \cdot (D_p - D_t)$$

This model for infusion of fluid can be rewritten and extended in many ways, depending on the type of fluid and the clinical scenario in which the fluid is given.[99–105] If given orally, one needs to model the pathway before entering the central fluid space. If it contains glucose, effects of glucose uptake and the associated osmolar shifts should be added.[104]

The main point of these models is to provide a platform to compare the effects of various fluids and dosing regimens on volume expansion, and the distribution and elimination of fluids. Although clinicians are sometimes intimidated by the mathematics, it is only necessary to understand the models in conceptual terms. The central fluid space, V_p, includes tissues that quickly equilibrate with the intravascular volume, which is why V_p sometimes is referred as a functional distribution volume rather than the plasma volume.[99,100] If the infused fluid is eliminated rapidly, there might be no exchange of fluid with the peripheral fluid space and no expansion in V_t. In this case, Cl_t will not be an identifiable parameter and Eq. (15) will collapse into

(16)

$$\frac{da_p}{dt} = \frac{dR_i(t)}{dt} - Cl_1 \cdot D_p - Cl_0$$

Estimation of Volume Kinetic Parameters

Currently, there is no standardization for volume kinetic experiments regarding the ideal length of an infusion or optimal rate. To evaluate the linear volume kinetic properties of a fluid, a brisk infusion for 10 to 30 minutes is recommended.[95] Empirical Hb values are then transformed into the dilution-time plane with Eq. (9). The volume kinetic model governed by the parameters Cl_0, Cl_1, Cl_d, V_p, and V_t (Eq. (15)) is then fitted by nonlinear regression to the empirical values of Hb obtained. In this model, Cl_1 can be regarded as the *elimination efficacy*—that is, the ability to eliminate excess fluid. Cl_1 is typically reduced by hypovolemia, general and spinal anesthesia, and pregnancy (although it is increased during preeclampsia).[106–108] Cl_1 is also variably reduced by surgery.[109,110] In the linear form, Cl_1 can vary between individuals depending on hydration status (see Fig. 41.11).[102]

V_p is often close to the expected plasma volume for crystalloid solutions but is reduced significantly for "volume-potent" solutions such as 7.5% saline solution or dextran 70 owing to the simultaneous osmotic shifts into the vascular space.[53] V_t is assumed to reflect the volume of interstitial fluid space, but volume kinetics findings indicate a smaller volume than expected.[107] The reason for this is that some parts of the interstitial space are not reachable during the time frame of volume kinetic evaluations and/or some parts are not expandable.[95] The parameter Cl_d reflects the rate and proportion that the peripheral fluid space accumulates fluid owing to expansion of the intravascular volume. A high Cl_d indicates that fluid is transported readily into the peripheral fluid space, thus potentially forming edema if not given carefully.

Population Kinetics for Infusion Fluids

Volume kinetics for infusion fluids offers a tool for describing the dynamics of intravascular volume expansion with a set of a few parameters. However, these methods only provide an understanding of the *intrasubject* processes during fluid infusion. To develop dosing guidelines for different clinical situations and IV fluids, one needs to analyze how the effect of fluid administration varies across subjects and the volume effects of gender, age, weight, or type of anesthesia.

Population kinetic methodology is based on the statistical assumption of the presence of *mixed effects* to the basic model that arise from random effects and fixed effects. The fixed effects can be coupled to individual characteristics. V_p seems to have a strong correlation to predicted blood volume, which is in turn dependent on height and weight. Therefore it is reasonable to assume that weight might have a fixed effect on V_p.

The *random effect* is commonly modeled from two sources of variability: interindividual, which is the random variability between individuals, and the residual error, which can be caused by noise in data. These effects, either random or fixed, are estimated along with the structural parameters to quantify variabilities. Population kinetic modeling of infusion fluids is a nascent area of study even though some analyses exist.[80,111,112]

Pharmacodynamics of Infusion Fluids

Application of pharmacodynamics to infusion fluids can be confusing when one of the active compounds is water. Where and what is the effect compartment in volume kinetics? In volume kinetics, the focus is mainly on the intravascular expansion effect of infused fluids. From this one can create nomograms for different types of fluids to produce a certain level of dilution and therefore a targeted level of volume expansion.[113]

One of the most important end points of fluid therapy is adequate perfusion of critical organs. This effect, or capillary filtration, depends on hydrostatic pressure, the status of the endothelial glycocalyx, osmolar and oncotic content, and cardiac output. To fully evaluate the dynamics of infused fluid with respect to the filtration effect, capillary pressure, serum osmolarity, and albumin concentration, among others, should be measured. Therapeutic interventions to repair the glycocalyx is an area needing further research.[39]

As the fluid dynamic model grows in complexity, it is necessary to increase the resolution of the pharmacokinetic model to adequately describe arteriovenous differences owing to net filtration effects, perfusion and flow through specific organs (especially the kidney), variability of vessel compliance, turnover of proteins, and adequacy of the lymphatic pump. This is beyond traditional PK/PD modeling and enters the physiologic domain, sometimes referred to as *physiologic-based pharmacokinetics*. Fluid dynamics is commonly modeled by the "lumped element method," which simplifies hydrodynamics into a compartmental model with expandable volumes. Flows, fluidity, and resistance govern the flows between compartments.[114,115] They can also be referred to as their *electrical analogs*, in that they can be modeled by electrical circuits.[116] They can be further extended to include the dynamics of osmolar and oncotic content.[117] From these methodologies, full-body simulators have been developed, which in a more comprehensive way, quantify intravascular fluid expansion and fluid distribution owing to infusion fluids.[117–119]

Guiding Principles and Clinical Implications

Fluid distribution is guided by both *osmolality* and *tonicity*. Osmolality is the number of particles dissolved in water solution, which is normally 295 mOsm in blood and extravascular fluids. However, tonicity also determines the distribution of fluids. Tonicity is the degree to which the solution moves fluid in or out of the ICF. Sodium chloride 0.9%, for instance, does not move fluid from the ICF and is thereby both iso-osmotic and isotonic. In comparison, ethanol raises the osmolality but does not redistribute water. Osmolality and tonicity are thus not equivalent.[98] Hypotonic solutions are solutions with an osmolality lower than what is found in plasma. They are poor expanders and should be regarded as "water," which distributes to all compartments of the body.[98] Isotonic solutions are solutions with an osmolality close to the extracellular osmolality of the body. This includes solutions that contain Na^+ such as sodium chloride 0.9%, and acetated or LR solution. Both acetate and lactate are metabolized to bicarbonate that acts as a buffer. Isotonic solutions expand the whole of extracellular volume (ECV).[98] Hypertonic solutions have an osmolality higher than ECF. These include solutions such as hypertonic saline solution and mannitol, which rapidly expand ECV by mobilizing water from the intracellular volume. If hypertonic solutions do not contain colloids, the volume effect is transitory such that after 1 to 2 hours most of the plasma volume expansion is gone.

Crystalloids

Crystalloids are solutions that contain solutes with molecular weights less than 30 kDa, usually either salt or glucose; they can crystallize, hence the name. Crystalloids can be hypotonic, isotonic, or hypertonic (Table 41.2).

Normal saline solution—sodium chloride 9 mg/mL (0.9%) in water—is a widely used crystalloid. It is used for expansion of the extracellular space and mixing carrier for IV drug infusions. It is the most used crystalloid in the world. It is, however, not an ideal crystalloid and certainly not "normal." Its chloride content far exceeds the level of plasma and in addition lacks a buffer. Normal saline solution causes a metabolic acidosis and the level of bicarbonate is remarkably lowered after its infusion.[1] The explanation for this is a dilution of the bicarbonate buffer in the ECF. An alternative explanation would be that pH is guided by the balance between positive and negative ion dissociation (strong ion difference [SID], the net sum of sodium, potassium, and magnesium minus the sum of chloride and lactate). The sum of SID should be +40 but

TABLE 41.2 Properties and Components of Selected Crystalloid Solutions Compared With Plasma

Solution	Osmolality (mOsm)	pH	Na^+ (mM)	K^+ (mM)	HCO_3^- (mM Equivalent)	Cl^- (mM)	Glucose % (mM)
Plasma	295	7.4	140	3.6–5.1	30	100	5
0.9% saline (normal saline; 9 mg/mL)	308	5.0	154	0	0	154	0
3% saline (30 mg/mL)	1026		513	0	0	513	0
7.5% saline (75 mg/mL)	2400	3.5–7	1250	0	0	1250	0
Ringer lactate	273	6.5	130	4	28	109	0
Ringer acetate	270	6	130	4	30	110	0
Ringerfundin[a]	309	5.1–5.9	140	4	24	127	5
Plasmalyte A[a]	294	7.4	140	5	50	98	0
Hartmann[b]	280	6.5	131	5	29	111	0
Buffered glucose (2.5%[c] and 5%)	270 (2.5%)–440 (5%)	6–7	70	0	25	45	2.5–5
5% glucose in 0.9% saline (D5NS)	560	4	154	0	0	154	(278)
5% glucose in water (D5W)	253	4	0	0	0	0	(278)
5% glucose in 0.45% saline	505	4	77	0	0	77	(278)

[a]Balanced—electrolyte content similar to plasma.
[b]Very similar to lactated Ringer solution.
[c]Sometimes called Rehydrex.

in sodium chloride it is 0. A lowering of SID creates acidosis. The consequences of acidosis are (1) deteriorated kidney function with a reduced GFR,[121] (2) large amounts of sodium chloride that can create abdominal pain, (3) reduced perfusion of gut mucosa, and (4) increased incidence of postoperative nausea and vomiting.

Hypertonic saline solution is used to move fluid from ICF to ECF. The solutions were originally developed for prehospital use (7.5 %) because quick restoration of blood volume was desirable (the small size of bags was attractive). However, large randomized trials have shown no clinical benefits.[122,123] A concentration of 3% NaCl is mostly used to raise the sodium level during hyponatremia and in the acute treatment of cerebral edema.

Ringer solutions are named for a British physiologist, and *Hartmann solution* is named for a U.S. pediatrician who in 1930 added lactate as a buffer to prevent acidosis in septic children.[122,124] Ringer solutions are either *lactated* or *acetated,* with lactated Ringer being the most used (see Table 41.2) as the initial crystalloid for resuscitation and perioperative maintenance. Acetated Ringer solution is mostly used in Scandinavia. Although both ions are metabolized to bicarbonate, acetate is more quickly metabolized.[125] Lactate is metabolized in the liver and kidneys, whereas acetate is metabolized in most tissues but primarily in the liver. Furthermore, lactate requires more oxygen for metabolism and causes a slight increase in plasma glucose, providing a theoretical advantage for acetated Ringer solution.[126]

Ringer solutions are the balanced fluids of choice for almost every situation. Although they are slightly hypotonic and low caloric, few side effects are observed. All Ringer solutions are slightly vasodilatory and inflammatory. They distribute from the plasma to the interstitium in 25 to 30 minutes with a distribution half-time of 8 minutes.[103] However, this is a static concept of distribution. The fluid load is either readily eliminated or distributed to the interstitium. The volume effect of a crystalloid such as LR could be substantial depending on the effects of anesthesia, surgery, trauma, and hemorrhage.[80] If LR is used to compensate for blood loss, conventional practice was to give three times the lost volume as replacement following the static distribution profile mentioned earlier based on studies in controlled hemorrhage models.[51] However, these studies have limitations and do not fully emulate the clinical environment. Ringer solutions should be used as initial fluids in major hemorrhage according to Advanced Trauma Life Support protocols but with caution.[127] If there is ongoing bleeding, surgical hemostasis is necessary. For perioperative fluid management, Ringer solutions are ideal for maintenance.

PlasmaLyte is a development of LR that has been introduced in the United States. The osmolality och level of chloride are more in agreement with plasma. The buffer capacity is slightly higher than for Ringer because PlasmaLyte also contains gluconate, a weak, slow-acting buffer.

The following are important guiding principles governing the use of maintenance fluids:

- The extracellular deficit after fasting is low.[128]
- Basal fluid loss via insensible mechanisms is also low and approximately 0.5 mL/kg per hour, up to 1 mL/kg per hour with more extensive surgery.[58]
- Evidence for a fluid-consuming third space is not compelling.[29]
- Fluids are context-sensitive, meaning that they should be infused according to needs and not too rapidly.[95,129]

Crystalloids in general accumulate peripherally during surgery because of neurohumoral protective mechanisms, such as increased release of antidiuretic hormone, renin, and aldosterone. Caution must be used when crystalloids are infused for purposes other than replacement of extracellular losses because edema can result.

Glucose solutions are distributed to all body fluid compartments because glucose is eventually metabolized to carbon dioxide and water.[98] Elimination of glucose occurs by insulin-dependent transporter–mediated uptake and cell metabolism. In healthy volunteers, the half-time is 15 minutes but it is considerably longer during surgery.[104,130] Although glucose solutions initially have volume-expanding efficacy similar to or even better than Ringer solutions, they are seldom used for that purpose.[104] Solutions that contain 2.5% (hypotonic) or 5% glucose (isotonic) are readily distributed to the ICF because of the osmotic strength of glucose.

Glucose-containing solutions are not commonly administered in the perioperative setting, in part because of the potential adverse effects of hyperglycemia. When they are administered perioperatively, they are never given plain but are usually part of a buffered mixture such as buffered glucose 2.5% (see Table 41.2). Establishing and maintaining a stable plasma glucose level in critically ill patients is an issue of great recent interest.[131,132] Glucose solutions with ongoing insulin therapy perioperatively might be necessary in some patients, but they require frequent serum glucose checks and careful standardization of care.

Colloids

Colloids solutions contain high-molecular-weight compounds that cross endothelial cells with difficulty (Table 41.3). Plasma losses from the circulation should ideally be replaced by iso-oncotic colloids, presuming the vascular barrier is intact and recognizing that colloidal volume effects are context-sensitive.[15] Colloids are mainly advocated because of superior volume efficacy and attractive rheologic and antiinflammatory properties. However, in large randomized studies, colloids have no superiority over crystalloids in terms of major outcome measures such as mortality.[55,56] They are more expensive than crystalloids and can have unfavorable side effects.

Albumin is a natural colloid abundant in plasma (molecule weight 69 kDa) commercially available at 3.5% to 5% strengths. Hyperoncotic albumin, 20% to 25%, is also available in some regions. There is normal translocation of albumin across the endothelium to the interstitium, and 60% of albumin is located extravascularly. Albumin is transported back to the circulation system via the lymphatic system. Albumin 5% expands plasma volume by 80% of the infused volume; infusion of 10 mL/kg albumin 5% increases serum albumin by 10% for 6 to 8 hours. In critically ill patients, there is increased leakage of albumin and supplementation of more albumin only contributes to peripheral edema (i.e., "albumin trapping"). Despite excellent volume-expanding efficacy of albumin, randomized clinical trials have found no superiority over crystalloids.[54,133]

Dextran is a complex branched glucan (polysaccharide) synthetized from sucrose by certain lactic-acid bacteria. When used as a component of colloid solutions, dextrans are mixed in normal saline solution as isotonic solutions. A hypertonic mixture is limited to prehospital use for treatment of hypotension during bleeding, but the benefit is doubtful.[122,123]

The isotonic versions of dextran solutions are either 6% or 10%. The molecular sizes of dextran molecules are 40, 60, or 70 kDa. The most widely used plasma expander, 6% dextran 70 (Macrodex) expands plasma with the same volume as the infused amount, and the solution resides in the plasma for about 3 to 4 hours.[53] Dextrans have excellent rheologic properties, and 10%

TABLE 41.3 Properties and Components of Selected Intravenous Colloid Solutions

Solution	Osmolality (mOsm)	Na^+ (mM)	Molecular Weight (kDa)—Mean Values/ Degree of Substitution (DS)—C_2/C_6 Ratio	Initial Volume Expansion (%)	Plasma Half-Life (hr)/Dosage Limit	Possible Side Effects
Plasma	295	140	Varying	Low		TRALI
Albumin 4%, 5%	300	130–160	69	70–100	16–24; No limit	Anaphylaxis (rare), fever, rash
Albumin 20%, 25%	1500	125	69	200–300	16–24; No limit	Anaphylaxis (rare), fever, rash, fluid overload
Hespan (hexastarch) 6% in 0.9% sodium chloride	309	154	600/0.75	100–160	20 mL/kg per day	Alteration of coagulation Pruritus Renal dysfunction
Hextend (hexastarch with added calcium) 6% in lactated electrolyte solution	307	143	670/0.75	100–160	1.4 hr/20 mL/kg per day	Alteration of coagulation Pruritus Renal dysfunction
Voluven (tetrastarch) 6% in 0.9% sodium chloride	296	140	130/0.40/9:1	1:1	50 mL/kg per day	Alteration of coagulation Pruritus Renal dysfunction
Venofundin	309	154	130/0.42/6:1	1:1	50 mL/kg per day	Alteration of coagulation Pruritus Renal dysfunction
Volulyte 6% in balanced salt solution	296	140	130/0.4/691	1:1	50 mL/kg per day	Alteration of coagulation Pruritus Renal dysfunction
Gelofusine 4% solution in 0.9% saline	274	154	30	1:1 initially but effect transient	No upper limit Hypervolemia is a concern	Anaphylaxis
10% dextran 40 (Rheomacrodex)[a] in 0.9% saline	350	154	40	175	1.5 g/kg per day	Anaphylaxis Alteration of coagulation Renal dysfunction
3% dextran 60 (Plasmodex)[a] in 0.9% saline	270	130	60	50	1.5 g/kg per day	Anaphylaxis Alteration of coagulation Renal dysfunction
6% dextran 70 (Macrodex)[a] in 0.9% saline	300	154	70	100	1.5 g/kg per day	Anaphylaxis Alteration of coagulation Renal dysfunction
HyperHES 7.2% NaCl with 6% starch	2464	1232	200	7–8 times NS	4 mL/kg BW 2–5 minutes Titrate to response	Anaphylaxis (rare) Hypernatremia (transient)
Hypertonic saline-dextran (HSD), 7.5% NaCl with dextran 70, RescueFlow	2567	1283	70	7–8 times NS	4 mL/kg BW 2–5 minutes Titrate to response	Anaphylaxis (rare) Hypernatremia (transient)

BW, Body weight; *Na^+,* sodium ion; *NaCl,* sodium chloride; *NS,* normal saline solution; *TRALI,* transfusion-related acute lung injury.
[a]Preinduce with Hapten (dextran 1) 20 mL 2 minutes before infusion.

dextran 40 (Rheomacrodex) is used for this purpose in vascular surgeries. It has larger plasma volume-expanding efficacy but shorter half-life than 6% dextran 70. Dextran molecules are excreted by the kidneys or metabolized by endogenous hydrolase (dextranase) to carbon dioxide and water. Dextrans have been associated with anaphylactic reactions. These are rare and can be reduced by infusing a low-molecular-weight dextran (dextran 1, hapten) a few minutes before the infusion of the main solution.

Hetastarches are synthetic colloids consisting of polysaccharides prepared from either grain or corn. Artificial starch–containing solutions for plasma volume expansion are characterized by their molar substitution and molecular weight. The molar substitution is an expression for how many hydroxyethyl groups there are per 100 glucose units. This prevents the molecule from degradation by amylase. The average molecular weights range from 70 to 670 kDa depending on the type of solution. Hydroxyethyl groups

are attached by ether linkage primarily at C2 of the glucose unit and to a lesser extent at C3 and C6. The polymer resembles glycogen, and polymerized D-glucose units are joined primarily by α-1,4 linkages with occasional α-1,6 branching linkages.

There has been a trend to focus on development of starch solutions with a molecular weight of around 130 kDa (tetrastarch). The older hetastarch solutions and pentastarches have been associated with considerable side effects such as renal and coagulation problems.[57,134] The degree of substitution seems to be optimal, around 0.45 to 0.60 and a C2/C6 ratio less than 8 seems advantageous (see Table 41.3). Starches are mixed in normal saline solution (Hespan, Voluven) or balanced salt solution (Hextend, Volulyte). During normal conditions, they all expand plasma volume by 1:1. This does not seem to be the case during critical illness when the volume effect of colloids is much less. Elimination of starch occurs mostly by renal elimination; larger molecules are cleaved by endogenous α-amylase in the plasma into smaller fragments and excreted or subjected to phagocytosis by the reticuloendothelial system. The expected plasma half time is 3 to 4 hours for low-molecular-weight starch (130 kDa) in a patient with intact endothelium.

Starches are used for plasma volume expansion with a substantial effect. They have been used during perioperative goal-directed therapy wherein cardiac output or SVV measurement shows real-time effects of the therapy, although there is currently no clinical outcome difference between colloids and crystalloids in the perioperative setting.[56,81,82,135] There has been a long-standing issue with renal compromise with high-molecular starch (200/0.5) for critically ill patients.[57,136] A randomized clinical trial showed that for low-molecular starch (130/0.42) there was increased mortality and need for renal replacement therapy for patients with severe sepsis and septic shock.[137] However, a randomized study of patients in an intensive care unit given either HES 130/0.4 or saline solution showed no increased mortality within 90 days, but there was an issue with increased need for renal replacement therapy.[138]

The *gelatin* Gelofusine is a 4% solution of succinylated gelatin mixed in normal saline solution. When the molecule is succinylated, it becomes negatively charged and its volume expands. These solutions consist of proteins derived from bovine sources that have a transient volume effect lasting for 2 to 3 hours.

Sepsis and Critical Illness

Although most protocols for trauma and sustained surgery have focused on replacement of actual losses, patients with sepsis or septic shock are not associated with volume depletion. Sepsis is characterized by cardiac depression, vasodilation, and microcirculatory dysfunction, and patients with sepsis are poor fluid responders. In the Rivers study from 2001 the concept of early goal-directed therapy was introduced which significantly reduced mortality.[150] This groundbreaking single-center study in the early 2000s has been difficult to replicate and the concept of early goal-directed therapy for this category of patients has been questioned.[139,140] Treating sepsis is based more on understanding that venous return has been compromised by increased CVP owing to fluid loading compared with the existent mean circulatory filling pressure . The vascular system in sepsis is impaired by vasoplegia, reduced left ventricular function, reduced diastolic compliance, and increased leakage from capillaries. The widely accepted rationale in fluid resuscitation in sepsis is to improve cardiac output and organ perfusion. The logic thereby requires stroke volume to be increased when giving a fluid bolus. If stroke volume does not increase there is no benefit of a fluid bolus, but there is evidence for early treatment by norepinephrine.

Clinical Fluid Therapy Guidelines

Basal Requirements and Rehydration

Daily fluid requirements are 20 to 25 mL/kg in older adults and 25 to 30 mL/kg in middle-aged adults. This basal fluid requirement compensates for perspiration and urinary and fecal losses.

Elective surgical patients should be normovolemic when they arrive; considering modern preoperative fasting rules, most patients present in a slightly dehydrated state that would, even for a minor surgery, benefit from a small amount of crystalloid solution (1–1.5 L) before and during surgery.[19] Larger deficits, such as during intestinal obstruction, should be carefully scrutinized and more than 50% of the deficit needs to be replaced before surgery starts.

Day Surgery Cases: Minor Surgery

For most brief outpatient surgery cases, 1 to 1.5 L of a crystalloid should be adequate to address the preoperative fluid deficit and ongoing maintenance needs. Treating mild hypotension with large volumes of resuscitation fluid is typically unnecessary.

Surgery Performed With Spinal or Epidural Block

Recent evidence shows that preloading before spinal and epidural blocks has little impact on hemodynamic stability after the block.[141] Crystalloids are minimally effective and then only when given as a rapid load immediately after induction of the block (coload). Most experts agree that treating hypotension with a vasopressor in this setting is preferred.

Gastrointestinal Surgery

Most recent fluid therapy outcome studies are focused on gastrointestinal surgery. Optimal fluid therapy for open abdominal surgery has been a matter of controversy for decades. The study by Brandstrup and colleagues sparked the debate regarding liberal versus restrictive fluid therapy that continues today.[3] Restrictive fluid therapy aimed for a net balance in water intake and output as measured by body weight before and after surgery, Numerous studies have shown a lower rate of perioperative complications when more restrictive fluid therapy regimens are used.[5] The more liberal fluid therapies might be associated with more complications in part because evaporative fluid loss is often grossly overestimated (and replaced) as are losses to the presumed third space that might not exist.[29,142] The following guidelines are gaining acceptance:

- The current practice in many parts of Europe is to apply an enhanced recover after surgery (ERAS) concept to perioperative fluid management of patients undergoing gastrointestinal surgery.[143]
- Perioperative fluid management in this setting is guided by using semi-invasive devices such as the esophageal Doppler where small incremental boluses (150–200 mL) of colloids are given in addition to a low maintenance rate of crystalloids (2–3 mL/kg per hour). The concept is to incrementally give fluids to a deflection point on the Frank-Starling curve.

Emerging Developments

Historically, providers gave large amounts of fluids because fluids were regarded as rather harmless. In the past 20 years or so, there has been increasing concern that IV fluid therapy needs to be

more individualized. The long-lasting debate on the choice of fluids—crystalloids or colloids—has been replaced by a more fruitful one on the amount, rate, and timing for giving IV fluids. Colloids have been targeted as deleterious to the kidneys during serious conditions such as sepsis. Discussions are focused on the benefits of zero fluid balance and individualized protocols during goal-directed guidance. Noninvasive monitoring devices seem promising to guide fluid therapy in the future.

One area that will attract much interest in the coming years is the treatment of sepsis. The understanding of sepsis has improved and has been recognized as a state where cellular and microcirculatory alterations cause an acute circulatory failure. The patient is certainly not hypovolemic but is affected by vasodilation and myocardial depression. Still, the current Surviving Sepsis Campaign guidelines recommend a rapid IV infusion of 30 mL/kg of an isotonic crystalloid.[144] In the syndrome of sepsis it has lately been understood that cardiac output may be preserved, increased, or depressed in sepsis. Furthermore, IV fluid loading has little, if any, effect on cardiac output in critical illness and an increase in blood pressure will not be sustained.[145,146] Cellular hypoxia is not observed in either experimental models or in clinical trials, and lactate is produced aerobically, most likely as a response to adrenergic stimulation. Because there now is evidence that (1) the injudicious of IV fluids in sepsis will affect outcome[147,148] and (2) the only randomized clinical study addressing this topic (FEAST [Fluid Expansion as Supportive Therapy] trial) showed an increased mortality in those patients who received large amounts of fluid,[149] a restricted approach in combination with a vasopressor is most likely beneficial. Because the FEAST trial was performed in sub-Saharan Africa where access to intensive care was limited, the need for performing a large randomized clinical trial in Western countries is needed.

Key Points

- The body consists to a large part of water. Intake of approximately 2 L daily is crucial to maintain homeostasis in adults.
- Fluid therapy has conventionally been recognized as harmless, but should be regarded as an individual therapy with considerable side effects.
- The relevance of the so-called third space is controversial and should not be overzealously treated with crystalloid solutions.
- It is difficult to continuously measure the physiologic effects of fluid therapy. Static measurements such as CVP or systemic arterial blood pressure do not adequately show the efficacy of administered fluids. Instead, pulse pressure or SVV measured invasively or noninvasively better reflect the results of administered fluids.
- Fluid kinetics, which has similarities to pharmacokinetics, is a tool to better understand the dynamics of fluid distribution.
- Fluid effects are context-sensitive. They distribute intravascularly if there is space for them (bleeding), otherwise they are eliminated, either renally or more likely interstitially during anesthesia and surgery.
- Crystalloids and colloids have different physiologic properties. However, in large randomized clinical studies there is no significant difference in outcomes.
- Restrictive fluid therapy is supported by evidence for specific procedures such as gastrointestinal surgeries.
- The guidelines for fluid treatment in sepsis have changed to less aggressive fluid treatment in combination with early infusion of norepinephrine.

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42

Electrolytes and Diuretics

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CHAPTER OUTLINE

Electrolytes

- **Sodium**
  - Physiologic Role
  - Hyponatremia
  - Hypernatremia
- **Potassium**
  - Physiologic Role
  - Hypokalemia
  - Hyperkalemia
- **Calcium**
  - Physiologic Role
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  - Physiologic Role
  - Hypophosphatemia
  - Hyperphosphatemia
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  - Physiologic Role
  - Hypomagnesemia
  - Hypermagnesemia
- **Diuretics**
  - Proximal Convoluted Tubule–Carbonic Anhydrase Inhibitors
  - Ascending Loop of Henle: Loop Diuretics
  - Thiazides
  - Potassium-Sparing Diuretics
  - Osmotic Diuretics
  - Diuretics in Heart Failure
  - Adverse Effects of Diuretics
    - *Volume Depletion*
    - *Azotemia*
    - *Hypokalemia*
    - *Hyponatremia*
- **Emerging Developments**

Electrolyte concentrations are tightly controlled within physiologic ranges, which are essential for human health. The major electrolytes, sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), phosphate (PO_4^{3-}), and magnesium (Mg^{2+}), are critical to basic physiologic functions, including action potential generation, cardiac rhythm control, muscle contraction, and energy storage, among many others. Electrolytes, most notably Mg^{2+}, are also important cofactors for the proper function of many crucial enzymes involved in DNA and protein synthesis and energy metabolism. Because appropriate electrolyte concentrations are so critical in human physiology, sophisticated homeostatic mechanisms maintain their concentrations within a narrow range.

When pathologic states alter electrolyte concentrations, severe physiologic aberrations can result. Therapies to increase or decrease electrolyte concentrations are thus important, especially in critical care. Sometimes electrolyte supplementation is necessary; in this context intravenous (IV) and oral preparations are viewed as drugs.

For each major electrolyte, we discuss physiologic roles, common pathologic alterations, and appropriate therapies, including the use of electrolytes as drugs. We also discuss the physiology and therapeutic considerations related to diuretics, a group of drugs that play an important role in perioperative medicine and have a pronounced influence on electrolyte homeostasis.

ELECTROLYTES

Sodium

Physiologic Role

Sodium ion (Na^+) is the principal extracellular cation and solute and is essential for generation of action potentials in nervous and cardiac tissue. Pathologic increases or decreases in *total body* Na^+ are associated with corresponding increases or decreases in extracellular volume (ECV) and plasma volume (PV). Disorders of Na^+ *concentration* (i.e., hyponatremia and hypernatremia) usually result from relative excesses or deficits, respectively, of water. Regulation of total body Na^+ and plasma Na^+ concentration (Na^+) is accomplished primarily by the endocrine and renal systems (Table 42.1). Secretion of aldosterone and antinatriuretic peptide control *total body* Na^+. Antidiuretic hormone (ADH) is secreted in response to increased osmolality or decreased blood pressure, and primarily regulates Na^+.

Hyponatremia

Hyponatremia, defined as Na^+ less than135 mEq/L or mM, is the most common electrolyte disturbance in hospitalized patients with a prevalence reaching 30%.[1,2] It is associated with a high mortality.[3–5] In most cases of hyponatremic hospitalized patients, total body Na^+ is either normal or increased. The most common clinical associations with hyponatremia include the postoperative state,

Abstract

This chapter deals with electrolytes and diuretics. It thoroughly goes through pertinent facts about electrolytes such as sodium, potassium, calcium, phosphate, and magnesium. Particular attention is paid to hypo- and hypernatremia. Furthermore, diuretics is discussed.

Keywords

electrolytes
sodium
potassium
calcium
phosphate
magnesium
diuretics

acute intracranial disease, malignant disease, medications, and acute pulmonary disease.

The signs and symptoms of hyponatremia depend on both the rate and severity of the decrease in plasma Na^+. Symptoms that can accompany severe hyponatremia ($Na^+ < 120$ mM) include anorexia, nausea, vomiting, cramps, weakness, altered level of consciousness, coma, and seizures. Acute central nervous system (CNS) manifestations relate to brain swelling. Because the blood-brain barrier is poorly permeable to Na^+ but freely permeable to water, a rapid decrease in plasma Na^+ promptly increases both extracellular and intracellular brain water. Because the brain rapidly compensates for changes in osmolality, acute hyponatremia produces more severe symptoms than chronic hyponatremia. The symptoms of chronic hyponatremia probably relate to depletion of brain electrolytes. Once brain volume has compensated for hyponatremia, rapid increases in Na^+ can lead to abrupt brain dehydration[4] (Fig. 42.1).

TABLE 42.1 Mechanisms of Regulation of Electrolytes

Electrolyte	Regulated by
Sodium	Aldosterone Atrial natriuretic peptide Na^+ altered by antidiuretic hormone
Potassium	Aldosterone Epinephrine Insulin Intrinsic renal mechanisms
Calcium	Parathyroid hormone Vitamin D
Phosphorus	Primarily renal mechanisms Minor: parathyroid hormone
Magnesium	Primarily renal mechanisms Minor: parathyroid hormone, vitamin D

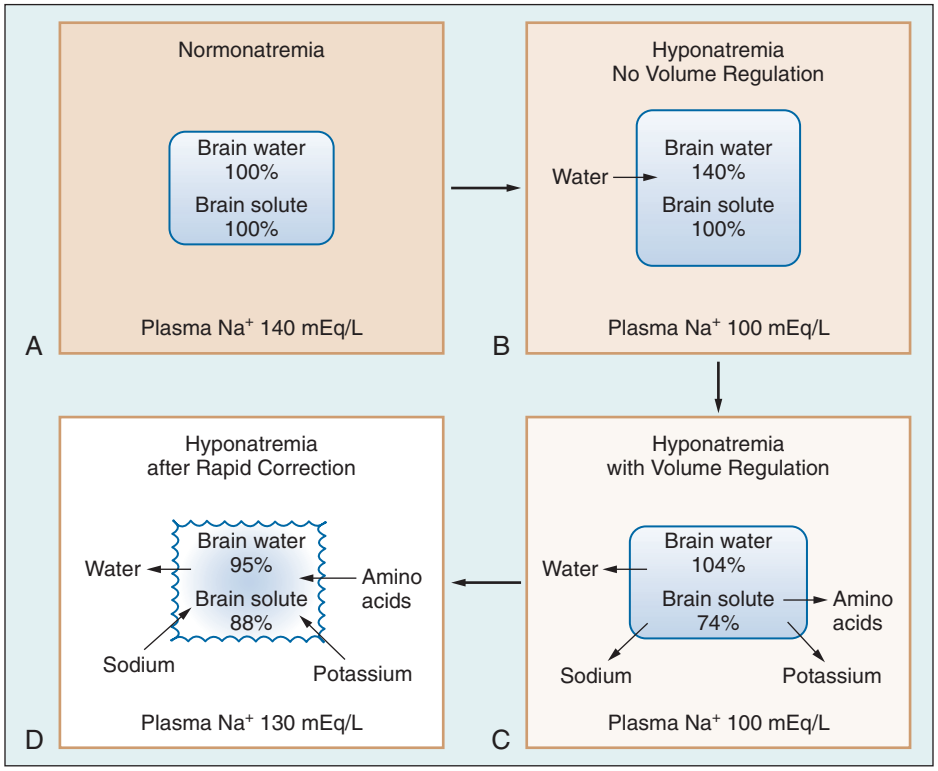
Na^+, Sodium ion.

Hyponatremia can be classified as true hypoosmotic hyponatremia, pseudohyponatremia, or syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (Tables 42.2, 42.3, and 42.4). Pseudohyponatremia is an artifact associated with the use of flame photometry, now an obsolete technique, to measure plasma Na^+ in severely hyperproteinemic or hyperlipidemic patients. The current analytic method, direct potentiometry, directly measures Na^+ and is uninfluenced by plasma components such as proteins and lipids.

Hyponatremia can be isotonic (plasma osmolality [P_{osm}] 280–295 mOsm/kg), hypotonic ($P_{osm} < 280$ mOsm/kg), or hypertonic ($P_{osm} > 295$ mOsm/kg). Calculated plasma osmolality is determined by the following formula:

$$P_{osm} = 2.0 \times [Na^+] + Glucose/18 + BUN/2.8,$$

where serum Na^+ is measured in millimoles, and blood glucose and blood urea nitrogen (BUN) are expressed as milligrams per deciliter. Other minor solutes such as Ca^{2+}, Mg^{2+}, and K^+ make a small contribution to plasma osmolality. Considering plasma is



• **Fig. 42.1** Brain water and solute concentrations in hyponatremia. If normal plasma sodium (Na^+) (A) suddenly decreases, the theoretical increase in brain water is proportional to the decrease in plasma Na^+ (B). However, because of adaptive loss of cerebral intracellular solute, cerebral edema is minimized in chronic hyponatremia (C). Once adaptation occurs, a rapid return of plasma Na^+ concentration toward normal results in brain dehydration (D).

TABLE 42.2 Causes of True Hypo-osmotic Hyponatremia

Hypovolemia

Renal losses (urinary sodium > 20 mEq/L)
- Diuretic therapy
- Mineralocorticoid deficiency
- Cerebral salt-wasting syndrome (e.g., subarachnoid hemorrhage)
- Renal disease
- Renal tubular acidosis (bicarbonaturia with renal tubular acidosis and metabolic alkalosis)
- Renal tubular defect (salt-wasting nephropathy)

External losses (urinary sodium <20 mEq/L)
- Gastrointestinal disease—vomiting, diarrhea, gastric suctioning
- Skin losses—burns, sweating, cystic fibrosis
- Pancreatitis
- Trauma

Hypervolemia

Renal causes (urinary sodium >20 mEq/L)
- Renal failure

Other causes (urinary sodium <20 mEq/L)
- Congestive heart failure
- Hepatic cirrhosis
- Nephrotic syndrome
- Pregnancy

Euvolemia (Urinary Sodium >20 mEq/L)

Glucocorticoid deficiency

Hypothyroidism

Syndrome of inappropriate antidiuretic hormone

Reset osmostat—psychosis, malnutrition

TABLE 42.3 Causes of Pseudohyponatremia

Normal Plasma Osmolality
- Hyperlipidemia
- Hyperproteinemia
- Transurethral resection of prostate, hysteroscopy

Increased Plasma Osmolality
- Hyperglycemia
- Mannitol administration

TABLE 42.4 Causes of Syndrome of Inappropriate Secretion of Antidiuretic Hormone

Malignancy
- Lung (especially small cell carcinoma)
- Central nervous system
- Pancreas

Pulmonary
- Pneumonia
- Tuberculosis
- Fungal
- Abscess

Neurologic
- Infection
- Trauma
- Cerebrovascular accident

Drugs
- Amitriptyline
- Chlorpropamide
- Cyclophosphamide
- Desmopressin
- Morphine
- Nicotine
- Nonsteroidal antiinflammatory drugs
- Oxytocin
- Selective serotonin reuptake inhibitors
- Vincristine

93% water and Na^+ is not completely dissociated into solution, these factors tend to cancel out.

Patients with disorders such as hypoproteinemia or hyperlipidemia that cause increased osmolality and pseudohyponatremia have an abnormal osmolality gap. These disorders highlight the importance of measuring plasma osmolality in hyponatremic patients. Hyponatremia with a normal or high serum osmolality results from the presence of a nonsodium solute, such as glucose or mannitol, that holds water within the extracellular space and results in dilutional hyponatremia. The presence of a nonsodium solute resulting in "factitious" hyponatremia can be inferred if measured osmolality exceeds calculated osmolality by more than 10 mOsm/kg. For example, plasma Na^+ decreases approximately 2.4 M for each 100-mg/dL rise in glucose concentration, with perhaps even greater decreases for glucose concentrations higher than 400 mg/dL.[5]

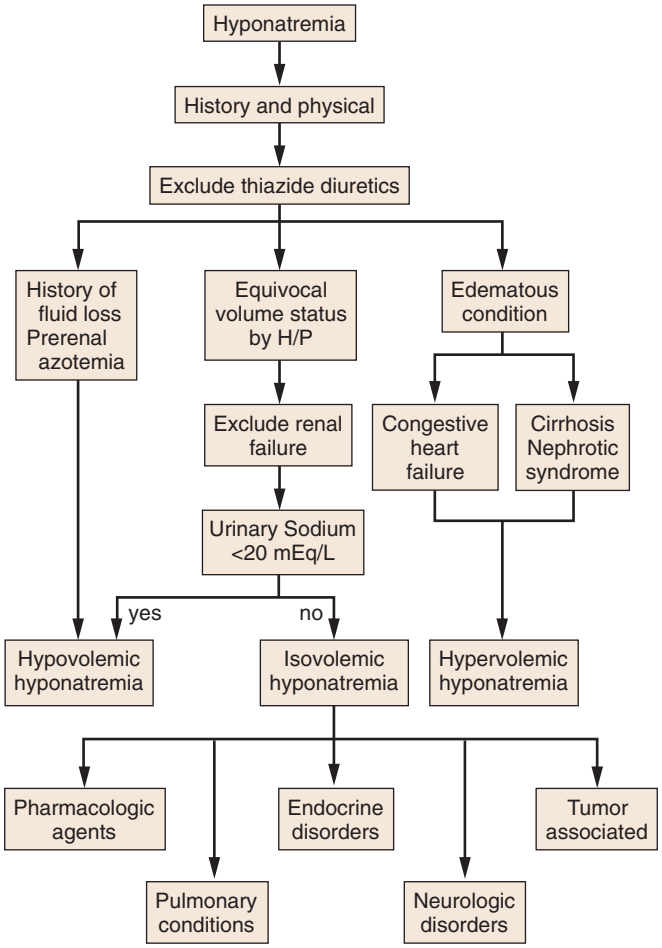
In anesthesia practice, a common cause of hyponatremia associated with a normal osmolality is the absorption of large volumes of sodium-free irrigating solutions (containing mannitol, glycine, or sorbitol) during transurethral resection of the prostate.[6] Neurologic symptoms are minimal if mannitol is used because the agent does not cross the blood-brain barrier and is excreted with water in the urine. In contrast, as glycine or sorbitol is metabolized, hypoosmolality can gradually develop and cerebral edema can appear as a late complication. Consequently, hypoosmolality is more important in generating symptoms than hyponatremia per se.[6] The problem of excessive fluid absorption during transurethral resection of the prostate can be monitored by using small amounts of alcohol in the irrigating fluid; the level of alcohol can be detected in expired air as a quantitative measure of irrigating fluid absorption.[7] True hyponatremia with a normal or elevated serum osmolality also can accompany renal insufficiency. BUN, included in the calculation of total osmolality, distributes throughout both ECV and intracellular volume (ICV). Calculation of *effective* osmolality ($2\ Na^+$ + glucose/18) excludes the contribution of urea to tonicity and demonstrates true hypotonicity.

True hyponatremia (Fig. 42.2, Table 42.5) with low serum osmolality can be associated with a high, low, or normal total body Na^+ and PV. Therefore hyponatremia with hyposmolality is evaluated by assessing total body Na^+ content, BUN, serum creatinine (SCr), urinary osmolality, and urinary Na^+. Hyponatremia with increased total body Na^+ is characteristic of edematous states—that is, congestive heart failure (CHF),[8] cirrhosis, nephrosis, and renal failure. Aquaporin 2, the vasopressin-regulated water channel, is upregulated in experimental CHF[9] and cirrhosis[10] and decreased by chronic vasopressin stimulation. In patients with renal insufficiency, reduced

TABLE 42.5 Classification of Hypotonic Hyponatremia by Volume Status

HYPOVOLEMIC		EUVOLEMIC	HYPERVOLEMIC
Extrarenal Na^+ Loss (FE_{Na} < 1%, U_{Na} < 20 mEq/L)	**Renal Na^+ Loss (FE_{Na} > 2%, U_{Na} > 20 mEq/L)**	**(FE_{Na} < 1%, U_{Na} > 20 mEq/L)**	**(U_{Na} < 20 mEq/L)**
Dehydration	Diuretics	Glucocorticoid deficiency	CHF
Diarrhea	Osmotic diuresis	SIADH	Liver disease
Vomiting	Salt-losing nephropathy	Hypothyroidism	Nephrotic syndrome
Gastrointestinal suctioning	Mineralocorticoid deficiency	Psychogenic polydipsia (>15 L/day)	Pregnancy
Skin losses		Beer potomania/malnutrition (alcoholism, anorexia)	
Trauma			
Pancreatitis			

CHF, Congestive heart failure; *FE_{Na}*, fractional excretion of sodium; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; *U_{Na}*, urine sodium.



• **Fig. 42.2** Decision tree for evaluation of hyponatremia. *H/P*, History and physical examination.

urinary diluting capacity can lead to hyponatremia if excess free water is given.

The underlying mechanism of *hypovolemic hyponatremia* is secretion of ADH in response to volume contraction with ongoing oral or IV intake of hypotonic fluid.[11] Angiotensin II also decreases renal free water clearance. Thiazide diuretics, unlike loop diuretics, promote hypovolemic hyponatremia by interfering with urinary dilution in the distal tubule of the nephron.[11] Hypovolemic hyponatremia associated with a urinary Na^+ greater than 20 mM suggests mineralocorticoid deficiency, especially if serum K^+, BUN, and SCr are increased.[11]

The cerebral salt-wasting syndrome is an often severe, symptomatic salt-losing diathesis that appears to be mediated by brain natriuretic peptide[12] and is independent of SIADH. Patients at risk include those with cerebral lesions caused by trauma, subarachnoid hemorrhage, tumors, and infection.[13]

Euvolemic hyponatremia most commonly is associated with nonosmotic vasopressin secretion—for example, glucocorticoid deficiency, hypothyroidism, thiazide-induced hyponatremia, SIADH, and the reset osmostat syndrome. Total body Na^+ and ECV are relatively normal and edema is rarely evident. SIADH can be idiopathic but also is associated with CNS or pulmonary diseases (see Table 42.4). Euvolemic hyponatremia is usually associated with exogenous ADH administration, pharmacologic potentiation of ADH action, drugs that mimic the action of ADH in the renal tubules, or excessive ectopic ADH secretion. Tissues from some small cell lung cancers, duodenal cancers, and pancreatic cancers increase ADH production in response to osmotic stimulation.[14]

At least 4.0 % of postoperative patients develop plasma Na^+ less than 130 mM. Although neurologic manifestations usually do not accompany postoperative hyponatremia, signs of hypervolemia are occasionally present.[15] Much less frequently postoperative hyponatremia is accompanied by mental status changes, seizures, and transtentorial herniation, attributable in part to IV administration of hypotonic fluids, secretion of ADH, and other factors, including drugs and altered renal function, that influence perioperative water balance.[1] Menstruating women are particularly vulnerable to brain damage secondary to postoperative hyponatremia.[16] Smaller patients change plasma Na^+ more in response to similar volumes of hypotonic fluids. Based on a report of apparent postoperative SIADH in a 30-kg, 10-year-old girl,[17] it has been suggested that children receive no sodium-free water perioperatively.[18] Postoperative hyponatremia can develop even with infusion of isotonic fluids if ADH is persistently increased. Twenty-four hours after surgery, mean plasma Na^+ in patients undergoing uncomplicated gynecologic surgery decreased from 140 to 136 mM.[19] Although the patients retained Na^+ perioperatively, they retained proportionately more water (an average of 1.1 L of electrolyte-free water). Careful postoperative attention to fluid and electrolyte balance can minimize the occurrence of symptomatic hyponatremia.

If both Na^+ and measured osmolality are below the normal range, hyponatremia is further evaluated by first assessing volume status using physical findings and laboratory data (see Fig. 42.2 and Table 42.5). In hypovolemic patients or edematous patients, the ratio of BUN to SCr should be greater than 20:1. Urinary Na^+ is generally less than 20 mM in edematous states and volume depletion, and greater than 20 mM in hyponatremia secondary to renal salt wasting or renal failure with water retention.

Criteria for the diagnosis of SIADH include hypotonic hyponatremia, urinary osmolality greater than 100 to 150 mmol/kg, absence of ECV depletion, normal thyroid and adrenal function, and normal cardiac, hepatic, and renal function. Urinary Na^+ should be greater than 20 mM unless fluids have been restricted. The diagnosis of SIADH is inaccurately applied to functionally hypovolemic postoperative patients, in whom, by definition, ADH secretion would be "appropriate."[18]

Treatment of hyponatremia associated with normal or high serum osmolality requires reduction of the elevated concentrations of the responsible solute. Uremic patients are treated by free water restriction or dialysis. Treatment of edematous (hypervolemic) patients necessitates restriction of both sodium and water. Therapy is directed toward improving cardiac output and renal perfusion and using diuretics to inhibit Na^+ reabsorption. In hypovolemic, hyponatremic patients, blood volume must be restored, usually by infusion of 0.9 % saline solution, and excessive Na^+ losses must be curtailed. Correction of hypovolemia usually results in removal of the stimulus for ADH release accompanied by a rapid water diuresis.

The cornerstone of SIADH management is free water restriction and elimination of precipitating causes. Water restriction, sufficient to decrease total body water (TBW) by 0.5 to 1.0 l/day, decreases ECV even if excessive ADH secretion continues. The resultant reduction in glomerular filtration rate (GFR) enhances proximal tubular reabsorption of salt and water, thereby decreasing free water reabsorption, and stimulates aldosterone secretion. As long as free water losses (i.e., renal, skin, gastrointestinal) exceed free water intake, serum Na^+ will increase. During treatment of hyponatremia, increases in plasma Na^+ are determined by both the composition of the infused fluid and the rate of renal free water excretion. Free water excretion can be increased by administering furosemide. However, the correction of hyponatremia continues to generate controversy.[20–22] When plasma Na^+ is less than 130 mM or hyponatremia is present together with cerebral symptoms, it is recommended to immediately administer one or more IV boluses of 2 mL/kg of 3% NaCl.[1] This should result in a prompt response and should be followed by boluses every 5 to 10 minutes as needed. Symptoms should disappear when plasma Na^+ has risen by 4 to 6 mM.

This approach differs from a previously advocated focus on a separation between acute and chronic causes for hyponatremia. Apart from the fact that this can be very difficult to distinguish based on history and physical examination, when hyponatremia is seriously symptomatic the problem must be addressed expeditiously. When cerebral function has been restored, there is an inadvertent risk of overcorrection with the risk of osmotic demyelination. There are no prospective studies of the absolute safe speed for correction of hyponatremia. Goals can be set to 8 mM in 24 hours, 14 mM in 48 hours, and 16 mM in 72 hours.[1,20] A formula for predicting changes of plasma Na^+ is shown in the following equation:

$$[Na^+]_2 = \frac{[Na^+]_1 \times TBW + \Delta(Na^+ + K^+)}{TBW + \Delta TBW},$$

where Na^+_1 is the initial plasma Na^+ and Na^+_2 is the concentration in plasma Na^+ that results from the change in the external balances of water (TBW + ΔTBW) and cations Δ Na^+ + K^+). Treatment should be interrupted or slowed when symptoms improve. Frequent determinations of Na^+ are important to prevent too rapid correction.[1] It is also important to insert a bladder catheter for close tracking production of urine, which should be analyzed to determine Na^+ and K^+.

Although delayed correction of hyponatremia can result in neurologic injury, inappropriately rapid correction can result in abrupt brain dehydration (see Fig. 42.1), permanent neurologic sequelae, cerebral hemorrhage, or CHF. The symptoms of the syndrome vary from mild (transient behavioral disturbances or seizures) to severe (including pseudobulbar palsy and quadriparesis).[23] The principal determinants of neurologic injury appear to be the magnitude and chronicity of hyponatremia and the rate of correction. The syndrome is more likely when hyponatremia has persisted longer than 48 hours. Most patients in whom the syndrome is fatal have undergone correction of plasma Na^+ of more than 20 mM/day. Even a moderate decrease in Na^+ in pigs can cause significant brain edema.[24] Other risk factors for development of the syndrome include alcoholism, poor nutritional status, liver disease, burns, and hypokalemia.

For patients who require long-term pharmacologic therapy of hyponatremia, demeclocycline is the drug of choice.[11] Although better tolerated than lithium, demeclocycline can induce nephrotoxicity, a concern in patients with hepatic dysfunction. Hemodialysis is occasionally necessary in severely hyponatremic patients whose condition cannot be adequately managed with drugs or hypertonic saline solution. Once hyponatremia has improved, careful fluid restriction is necessary to avoid recurrence.

Vasopressin receptor antagonists (arginine vasopressin [AVP] antagonists) are a class of drugs that exert their effects by inhibiting 1 of 3 subtypes of vasopressin receptors. Vasopressin receptors $V1_a$ and $V1_b$ act via the inositol trisphosphate pathway to increase cytosolic Ca^{2+} as a second messenger, whereas V2 receptors act via the adenylyl cyclase pathway to increase cyclic adenosine monophosphate (cAMP) as a second messenger. $V1_a$ activation produces vasoconstriction, platelet aggregation, inotropic stimulation, and myocardial protein synthesis. $V1_b$ activation leads to pituitary adrenocorticotrophic hormone secretion. V2 activation causes antidiuretic effects by activity on the renal collecting ducts. The ideal treatment would increase Na^+ free water clearance and increase serum Na^+. Conivaptan is a dual antagonist of $V1_a$ and V2 receptors used for euvolemic or hypervolemic hyponatremia. Tolvaptan is an orally active, nonpeptide, selective V2 receptor antagonist. It increases free water clearance, decreases urine osmolality, and increases Na^+ and can be used for hyponatremic patients with heart failure and SIADH that resists water restriction.[26,27]

Hypernatremia

Hypernatremia (Na^+ > 150 mM) indicates an absolute or relative water deficit. The condition can exist in several forms categorized in terms of the adequacy of intravascular volume.

Hypovolemic hypernatremia (water deficit > Na^+ deficit). Adipsic hypernatremia is secondary to decreased thirst. This can be behavioral or, rarely, secondary to damage to the hypothalamic thirst centers. Hypovolemia can result from extrarenal losses (e.g., diarrhea, vomiting, fistulas, and significant burns) and renal losses (e.g., osmotic diuretics, diuretics, postobstructive diuresis, and intrinsic renal disease).

Hypervolemic hypernatremia (Na^+ gain > water gain). Hypernatremia with hypervolemia is often iatrogenic (e.g., administration of excessive hypertonic saline solution or sodium bicarbonate) or accidental (e.g., ingestion of seawater or high–salt content infant formula because of an error in formula preparation). Less common pathologic causes include excess mineralocorticoid (i.e., Cushing disease or syndrome).

Euvolemic hypernatremia (Na^+ gain without volume change). Hypernatremia with normal volume status can be divided into causes stemming from extrarenal water losses and renal water losses. A common pathologic condition resulting in excessive renal losses of free water is diabetes insipidis (DI), both central and nephrogenic. Although rare, extrarenal loss of free water sufficient to produce hypernatremia can result from excessive insensible fluid loss such as with prolonged hyperventilation. Normally, even slight increases in tonicity or Na^+ stimulate thirst and ADH secretion. Therefore severe, persistent hypernatremia occurs only in patients who cannot respond to thirst by voluntary ingestion of fluid such as obtunded patients, anesthetized patients, and infants.

Hypernatremia produces neurologic symptoms (including stupor, coma, and seizures), hypovolemia, renal insufficiency (occasionally progressing to renal failure), and decreased urinary concentrating ability.[28,29] Because hypernatremia frequently results from DI or osmotically induced losses of Na^+ and water, many patients are hypovolemic or bear the stigmata of renal disease. Postoperative neurosurgical patients who have undergone pituitary surgery are at risk of developing transient or prolonged DI. Polyuria can be present for only a few days within the first week of surgery, can be permanent, or can demonstrate a triphasic sequence: early DI, return of urinary concentrating ability, then recurrent DI.

The clinical consequences of hypernatremia are most serious at the extremes of age and when hypernatremia develops abruptly. Geriatric patients are at increased risk of hypernatremia because of decreased renal concentrating ability and thirst.[30] Brain shrinkage secondary to rapidly developing hypernatremia can damage delicate cerebral vessels, leading to subdural hematoma, subcortical parenchymal hemorrhage, subarachnoid hemorrhage, and venous thrombosis. Polyuria can cause bladder distention, hydronephrosis, and permanent renal damage.[31] At the cellular level, restoration of cell volume occurs remarkably quickly after normal tonicity is restored.[32] Although the mortality of hypernatremia rate is 40% to 55%, it is unclear whether hypernatremia is the cause or a marker of severe associated disease. Surprisingly, if plasma Na^+ is initially normal, moderate acute increases in plasma Na^+ do not appear to precipitate osmotic demyelination (which is much more likely in the setting of correcting hyponatremia). However, larger accidental increases in plasma Na^+ have produced severe consequences in children. In experimental animals, acute severe hypernatremia (acute increase from 146 to 170 mM) caused neuronal damage at 24 hours, suggestive of early osmotic demyelination.[33]

Hypernatremia indicates an absolute or relative water deficit and is always associated with hypertonicity. Hypernatremia can be generated by hypotonic fluid loss, as in burns, gastrointestinal losses, diuretic therapy, osmotic diuresis, renal disease, mineralocorticoid excess or deficiency, and iatrogenic causes, or can be generated by isolated water loss, as in central or nephrogenic DI. The acquired form of nephrogenic DI is more common and usually less severe than the congenital form. As chronic renal failure advances, most patients have defective concentrating ability resulting in resistance to ADH with hypotonic urine. Because hypovolemia accompanies most pathologic water loss, signs of hypoperfusion also can be present. In many patients, preceding the development of hypernatremia, an increased volume of hypotonic urine suggests an abnormality in water balance. Although uncommon as a cause of hypernatremia, isolated Na^+ gain occasionally occurs in patients who receive large quantities of Na^+, such as treatment of metabolic acidosis with 8.4 % sodium bicarbonate, in which Na^+ is approximately 1000 mM, or perioperative or prehospital treatment with hypertonic saline solution resuscitation solutions. In large randomized trials in the prehospital area, harmful effects of transiently increased Na^+ have not been seen.[34]

Plasma Na^+ does not reflect total body Na^+, which must be estimated separately based on signs of the adequacy of ECV. For polyuric hypernatremic patients, the differential diagnostic decision is between solute diuresis and DI. Measurement of urinary Na^+ and osmolality can help differentiate the various causes. Urinary osmolality less than 150 mOsm/kg in the setting of hypertonicity and polyuria is diagnostic of DI.

Treatment of hypernatremia produced by water loss consists of repletion of water and correction of associated deficits in total body Na^+ and other electrolytes (Table 42.6). Common errors in treating hypernatremia include excessively rapid correction, failure to appreciate the magnitude of the water deficit, and failure to account for ongoing maintenance requirements and continued fluid losses. The first step in treating hypernatremia is to estimate the TBW deficit, which can be accomplished using the measured plasma Na^+ and the following equation:

$$\text{TBW deficit} = 0.6 \times \text{body weight (kg)} \times (Na^+ - 140)/140,$$

where 140 is the middle of the normal range for Na^+.

Hypernatremia must be corrected slowly because of the risk of neurologic sequelae such as seizures or cerebral oedema (see Fig. 42.1).[35] At the cellular level, restoration of cell volume occurs remarkably quickly after tonicity is altered; as a consequence, acute treatment of hypertonicity can result in overshooting the original, normal tonic cell volume.[35] The water deficit should be replaced over 24 to 48 hours, and plasma Na^+ should not be reduced by more than 1 to 2 mM/hr. Reversible underlying causes should be treated. Hypovolemia should be corrected promptly with 0.9 % saline solution. Although the Na^+ of 0.9 % saline solution is

TABLE 42.6 Acute Treatment of Hypernatremia

Sodium Depletion (Hypovolemia)
Hypovolemia correction (0.9% saline solution)
Hypernatremia correction (hypotonic fluids)
Sodium Overload (Hypervolemia)
Enhance sodium removal (loop diuretics, dialysis)
Replace water deficit (hypotonic fluids)
Normal Total Body Sodium (Euvolemia)
Replace water deficit (hypotonic fluids)
Control diabetes insipidus
Central diabetes insipidus:
DDAVP, 10-20 µg intranasally; 2-4 µg SC
Aqueous vasopressin, 5 U every 2-4 hr IM or SC
Nephrogenic diabetes insipidus:
Restrict sodium, water intake
Thiazide diuretics

DDAVP, Desmopressin; *IM,* intramuscularly; *SC,* subcutaneously.

154 mM, the solution is effective in treating volume deficits and will reduce Na^+ that exceeds 154 mM. Once hypovolemia is corrected, water can be replaced orally or with IV hypotonic fluids depending on the ability of the patient to tolerate oral hydration. In the occasional sodium-overloaded patient, Na^+ excretion can be accelerated using loop diuretics or dialysis.

The management of hypernatremia secondary to DI varies according to whether the cause is central or nephrogenic. The two most suitable agents for correcting central DI (an ADH deficiency syndrome) are desmopressin (DDAVP) and aqueous vasopressin. DDAVP, given subcutaneously in a dose of 1 to 4 μg or intranasally in a dose of 5 to 20 μg every 12 to 24 hours, is effective in many patients. It is less likely than vasopressin to produce vasoconstriction and abdominal cramping.[36] Incomplete ADH deficits (partial DI) often are effectively managed with pharmacologic agents that stimulate ADH release or enhance the renal response to ADH. Chlorpromazine, which potentates the renal effects of vasopressin, and carbamazepine, which enhances vasopressin secretion, have been used to treat partial central DI, but are associated with clinically important side effects. In nephrogenic DI, salt and water restriction or thiazide diuretics induce contraction of ECV, thereby enhancing fluid reabsorption in the proximal tubules. When less filtrate passes through the collecting ducts, less water is excreted.

TABLE 42.7 Causes of Renal Potassium Loss

Drugs	Bicarbonaturia
Diuretics	**Distal Renal Tubular Acidosis**
Thiazide diuretics	**Treatment of Proximal Renal Tubular Acidosis**
Loop diuretics	**Correction Phase of Metabolic Alkalosis**
Osmotic diuretics	**Magnesium Deficiency**
Antibiotics	**Other Less Common Causes**
Penicillin and penicillin analogs	Cisplatin
Amphotericin B	Carbonic anhydrase inhibitors
Aminoglycosides	Leukemia
Hormones	Diuretic phase of acute tubular necrosis
Aldosterone	**Intrinsic Renal Transport Defects**
Glucocorticoid-excess states	Barter syndrome
	Gitelman syndrome

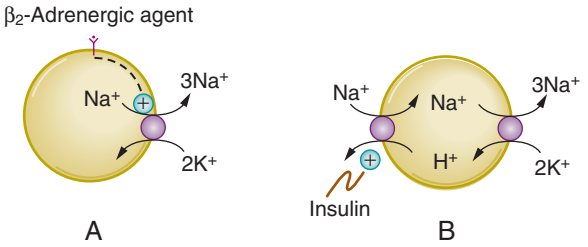
Potassium

Physiologic Role

Potassium ion (K^+) is perhaps the most frequently supplemented electrolyte.[37] Potassium plays an important role in cell membrane physiology, especially in maintaining resting membrane potential and in generating action potentials in the nervous system and heart. Potassium is actively transported into cells by sodium potassium adenosine triphosphatase (Na,K-ATPase; Na^+ pump), which maintains intracellular K^+ at least 30-fold greater than extracellular K^+. Intracellular K^+ concentration (K^+) is normally 150 mM, while the extracellular concentration is only 3.5 to 5.0 mM. Serum K^+ measures about 0.5 mM higher than plasma K^+ owing to cell lysis during clotting. Total body K^+ in a 70-kg adult is approximately 4256 mEq, of which 4200 mEq is intracellular; of the 56 mEq in the ECV, only 12 mEq is in the PV. Common causes of K^+ losses are shown in Table 42.7. The ratio of intracellular to extracellular K^+ contributes to the resting potential difference across cell membranes and therefore to the integrity of cardiac and neuromuscular transmission.

Extracellular K^+ is determined by catecholamines, the renin-angiotensin-aldosterone system, glucose, and insulin, as well as direct release from exercising or injured muscle.[37] The primary mechanism that maintains K^+ inside cells is transport of three Na^+ ions out of the cell for every two K^+ ions transported in by the Na,K-ATPase pump.[38] Both insulin and β- adrenergic agonists promote K^+ entry into cells[38] (Fig. 42.3). In contrast, α-adrenergic agonists impair cellular K^+ uptake.[39] Metabolic acidosis tends to shift K^+ out of cells, whereas metabolic alkalosis favors movement into cells.

Usual K^+ intake is 50 to 150 mEq/day. Freely filtered at the glomerulus, most K^+ excretion is urinary with some fecal elimination. Most filtered K^+ is reabsorbed; excretion is usually approximately equal to intake. As long as GFR is greater than > 8 mL/kg, dietary K^+ intake, unless greater than normal, can be excreted. Assuming plasma K^+ of 4.0 mM and normal GFR of 180 L/day, 720 mEq of K^+ is filtered daily, of which 85% to 90% is reabsorbed in the proximal convoluted tubule and loop of Henle. The remaining



• **Fig. 42.3** Extracellular signals that shift potassium into cells. (A) β_2-Adrenergic agents and insulin. (B) adrenergic agents. *H^+,* Hydrogen ion; *K^+,* potassium ion; *Na^+,* sodium ion.

10% to 15% reaches the distal convoluted tubule, which is the major site at which K^+ excretion is regulated. Excretion of K^+ ions is a function of open K^+ channels and the electrical driving force in the cortical collecting duct.[38]

The two most important regulators of K^+ excretion are plasma K^+ and aldosterone, although there is some evidence to suggest involvement of the CNS and of an enteric reflex mediated by potassium-rich meals. Potassium secretion into the distal convoluted tubules and cortical collecting ducts is increased by hyperkalemia, aldosterone, alkalemia, increased delivery of Na^+ to the distal tubule and collecting duct, high urinary flow rates, and the presence in luminal fluid of non-reabsorbable anions such as carbenicillin, phosphates, and sulfates. As Na^+ reabsorption increases, the electrical driving force opposing reabsorption of K^+ is increased. Aldosterone increases Na^+ reabsorption by inducing opening of the epithelial Na^+ channel[40]; potassium-sparing diuretics (amiloride and triamterene) and trimethroprim block the epithelial Na^+ channel, thereby increasing K^+ reabsorption. Magnesium depletion contributes to renal K^+ wasting.

Hypokalemia

Uncommon among healthy persons, hypokalemia (K^+ < 3.0 mM) is a frequent complication of treatment with diuretic drugs (see the

"Diuretics" section) and occasionally complicates other diseases and treatment regimens. Generally, a chronic decrement of 1.0 mM in plasma K^+ corresponds to a total body deficit of approximately 200 to 300 mEq. In uncomplicated hypokalemia, the K^+ deficit exceeds 300 mEq if plasma K^+ is less than 3.0 mM and 700 mEq if plasma K^+ is less than 2.0 mM. Plasma K^+ poorly reflects total body K^+; hypokalemia can occur with normal, low, or high total body K^+.

Hypokalemia causes muscle weakness and, when severe, even paralysis. With chronic K^+ loss, the ratio of intracellular to extracellular K^+ remains relatively stable; in contrast, acute redistribution of K^+ from the extracellular to the intracellular space substantially changes resting membrane potential.

Cardiac rhythm disturbances are among the most dangerous complications of hypokalemia. Acute hypokalemia causes hyperpolarization of cardiac cells that can lead to ventricular escape activity, reentrant phenomena, ectopic tachycardias, and delayed conduction. In patients taking digoxin, hypokalemia increases toxicity by increasing myocardial digoxin binding and pharmacologic effectiveness. Hypokalemia contributes to systemic hypertension, especially when combined with a high-sodium diet.[41] In diabetic patients, hypokalemia impairs insulin secretion and end-organ sensitivity to insulin. Although no clear threshold has been defined for a level of hypokalemia below which safe conduct of anesthesia is compromised, K^+ less than 3.5 mM has been associated with an increased incidence of perioperative dysrhythmias, especially atrial fibrillation/flutter, in cardiac surgical patients.[42]

Potassium depletion also induces defects in renal concentrating ability, resulting in polyuria and a reduction in GFR. Potassium replacement improves GFR, although the concentrating deficit might not improve for several months after treatment. If hypokalemia is sufficiently prolonged, chronic renal interstitial damage can occur. In experimental animals, hypokalemia is associated with intrarenal vasoconstriction and a pattern of renal injury similar to that produced by ischemia. Hypokalemia can result from chronic depletion of total body K^+ or from acute redistribution of K^+ from the ECV to the ICV. Redistribution of K^+ into cells occurs when the activity of the Na,K-ATPase pump is acutely increased by hyperkalemia or increased intracellular concentration of Na^+, as well as by insulin, carbohydrate loading (which stimulates release of endogenous insulin), β_2-adrenergic agonists, or aldosterone.[38] Both metabolic and respiratory alkalosis lead to decreases in plasma K^+.[38]

Causes of chronic hypokalemia include those associated with renal K^+ conservation (extrarenal K^+ losses; low urinary K^+) and those with renal K^+ wasting.[38] Low urinary K^+ suggests inadequate dietary intake or extrarenal depletion (in the absence of recent diuretic use). Diuretic-induced urinary K^+ losses are frequently associated with hypokalemia secondary to increased aldosterone secretion, alkalemia, and increased renal tubular flow. Aldosterone does not cause renal K^+ wasting unless Na^+ is present (i.e., aldosterone primarily controls Na^+ reabsorption, not K^+ excretion). Renal tubular damage owing to nephrotoxins such as aminoglycosides or amphotericin B can also cause renal K^+ wasting.

Initial evaluation of hypokalemia includes a medical history (diarrhea, vomiting, diuretic or laxative use), physical examination (hypertension, cushingoid features, and edema), measurement of serum electrolytes (Mg^{2+}), arterial pH assessment, and evaluation of the electrocardiogram (ECG). Many trauma patients develop hypokalemia that returns to normal within 24 hours without specific therapy. Measurement of 24-hour urinary excretion of Na^+ and K^+ can distinguish extrarenal from renal causes. Magnesium deficiency, associated with aminoglycoside and cisplatin therapy, can generate hypokalemia that is resistant to replacement therapy.

TABLE 42.8 Treatment of Hypokalemia

Correct Precipitating Factors
Increased pH
Decreased Mg^{2+}
Drugs
Mild Hypokalemia ($K^+ > 2$ mEq/L)
Intravenous KCl infusion ≤ 10 mEq/hr
Severe Hypokalemia ($K^+ \leq 2$ mEq/L, Paralysis or ECG Changes)
Intravenous KCl infusion ≤40 mEq/hr
Continuous ECG monitoring
If life-threatening, 5-6 mEq bolus

ECG, Electrocardiogram*l* K^+, potassium ion; *KCl*, potassium chloride; Mg^{2+}, magnesium cation.

Plasma renin and aldosterone levels can be helpful in the differential diagnosis. Characteristic electrocardiographic changes associated with hypokalemia include flat or inverted T waves, prominent U waves, and ST-segment depression.[43]

The treatment of hypokalemia consists of K^+ repletion, correction of alkalemia, and removal of offending drugs (Table 42.8). Hypokalemia secondary only to acute redistribution might not require treatment. There is no urgent need for K^+ replacement therapy in mild to moderate hypokalemia (3–3.5 mM) in asymptomatic patients. If total body K^+ is decreased, oral K^+ supplementation is preferable to IV replacement. Potassium is usually replaced as the chloride salt because coexisting chloride deficiency can limit ability of the kidney to conserve K^+.

Potassium repletion must be performed cautiously, usually at a rate of 10 to 20 mEq/hr or lower, because the magnitude of K^+ deficits is unpredictable. Plasma K^+ and the ECG must be monitored during rapid repletion (10–20 mEq/hr) to avoid hyperkalemic complications.[44] Particular attention should be given to patients with concurrent acidemia, type IV renal tubular acidosis, diabetes mellitus (DM), or those receiving nonsteroidal antiinflammatory agents, angiotensin-converting enzyme (ACE) inhibitors, or β blockers, all of which delay movement of extracellular K^+ into cells.

In patients with life-threatening dysrhythmias secondary to hypokalemia, serum K^+ must be rapidly increased. Assuming PV in a 70-kg adult is 3.0 L, administration of 6.0 mEq of potassium over a minute will increase serum K^+ by no more than 2.0 mM because redistribution into interstitial fluid will decrease the quantity remaining in plasma.[38]

Hypokalemia associated with hyperaldosteronemia (e.g., primary aldosteronism, Cushing syndrome) usually responds favorably to reduced Na^+ intake and increased K^+ intake. Hypomagnesemia, if present, aggravates the effects of hypokalemia, impairs K^+ conservation, and should be treated. Potassium supplements or potassium-sparing diuretics should be given cautiously to patients who have DM or renal insufficiency, which limit compensation for acute hyperkalemia. In patients who are both hypokalemic and acidemic, such as those who have diabetic ketoacidosis, K^+ administration should precede correction of acidosis to avoid a precipitous decrease in plasma K^+ as pH increases.

Hyperkalemia

The most lethal manifestations of hyperkalemia ($K^+ > 5.0$ mM) involve the cardiac conduction system: dysrhythmias, conduction

abnormalities, and cardiac arrest. A classic example of hyperkalemic cardiac toxicity is associated with the administration of succinylcholine to paraplegic, quadriplegic, or severely burned[45] patients. If plasma K^+ is less than 6.0 mM, cardiac effects are negligible. As K^+ increases further, the ECG shows tall peaked T waves, especially in the precordial leads. With further increases, the PR interval becomes prolonged, followed by a decrease in the amplitude of the P wave. Finally, the QRS complex widens into a pattern resembling a sine wave as a prelude to cardiac standstill.[45] Hyperkalemic cardiotoxicity is enhanced by hyponatremia, hypocalcemia, or acidosis. Because progression to fatal cardiotoxicity is unpredictable and often swift, the presence of hyperkalemic electrocardiographic changes mandates immediate therapy. The life-threatening cardiac effects usually require more urgent treatment than other manifestations of hyperkalemia. However, ascending muscle weakness appears when plasma K^+ approaches 7.0 mM and can progress to flaccid paralysis, inability to phonate, and respiratory arrest.

The most important diagnostic issues are history, emphasizing recent drug therapy, and assessment of renal function. If hyponatremia is also present, adrenal function should be evaluated. Although the ECG can provide the first suggestion of hyperkalemia in some patients, and despite the well-described effects of hyperkalemia on cardiac conduction and rhythm, the ECG is an insensitive and nonspecific method of detecting hyperkalemia.[46]

Hyperkalemia can occur with normal, high, or low total body K^+ stores. Deficiency of aldosterone, a major regulator of K^+ excretion, leads to hyperkalemia in adrenal insufficiency and hyporeninemic hypoaldosteronism, a state associated with DM, renal insufficiency, and advanced age. Because the kidneys excrete K^+, severe renal insufficiency commonly causes hyperkalemia. Patients with chronic renal insufficiency can maintain normal plasma K^+ despite markedly decreased GFR because urinary K^+ excretion depends on tubular secretion rather than glomerular filtration when the GFR exceeds 8 mL/min.

Drugs are now the most common cause of hyperkalemia, especially in elderly patients. Drugs that can limit K^+ excretion include nonsteroidal antiinflammatory drugs, ACE inhibitors, cyclosporin, and potassium-sparing diuretics such as triamterene. Drug-induced hyperkalemia most commonly occurs in patients with other predisposing factors, such as DM, renal insufficiency, advanced age, or hyporeninemic hypoaldosteronism. ACE inhibitors are particularly likely to produce hyperkalemia in patients who have CHF.[47]

In patients with normal total body K^+, hyperkalemia can accompany a sudden shift of K^+ from the ICV to the ECV because of acidemia, increased catabolism, or rhabdomyolysis. Metabolic acidosis and respiratory acidosis can also cause an increase in plasma K^+. However, organic acidosis (lactic acidosis, ketoacidosis) has little effect on K^+, whereas mineral acids cause significant cellular shifts. In response to increased hydrogen ion activity because of addition of acids, K^+ will increase if the anion remains in the extracellular volume.[38] Neither lactate nor ketoacids remain in the extracellular fluid (ECF). Therefore hyperkalemia in these circumstances reflects tissue injury or lack of insulin.[38] Pseudohyperkalemia, which occurs when K^+ is released from cells in blood collection tubes, can be diagnosed by comparing serum and plasma K^+ levels from the same blood sample. Hyperkalemia usually accompanies malignant hyperthermia.

The treatment of hyperkalemia is aimed at eliminating the cause, reversing membrane hyperexcitability, and removing K^+ from the body.[38] Emergent management of severe hyperkalemia is shown in Table 42.9. Hyperkalemia is best treated with insulin plus glucose, β agonists (see Fig. 42.3), and furosemide.[37]

TABLE 42.9 Treatment of Severe Hyperkalemia[a]

Reverse Membrane Effects
Calcium (10 mL of 10% calcium chloride IV over 10 min)
Transfer Extracellular K^+ Into Cells
Glucose and insulin ($D_{10}W$ + 5-10 U regular insulin per 25-50 g glucose)
Sodium bicarbonate (50-100 mEq over 5-10 min)
β_2 agonists
Remove Potassium From Body
Diuretics, proximal or loop
Potassium-exchange resins (sodium polystyrene sulfonate)
Hemodialysis
Monitor ECG and Serum K^+

ECG, Electrocardiogram; *IV*, intravenously; *K+*, potassium ion.
[a]Potassium concentration (K^+) > 7 mEq/L or electrocardiographic changes.

Mineralocorticoid deficiency can be treated with 9-αα-fludrocortisone (0.025–0.10 mg/day). Hyperkalemia secondary to digitalis intoxication can be resistant to therapy because attempts to shift K^+ from the ECV to the ICV are often ineffective. In this situation, use of digoxin-specific antibodies has been successful.

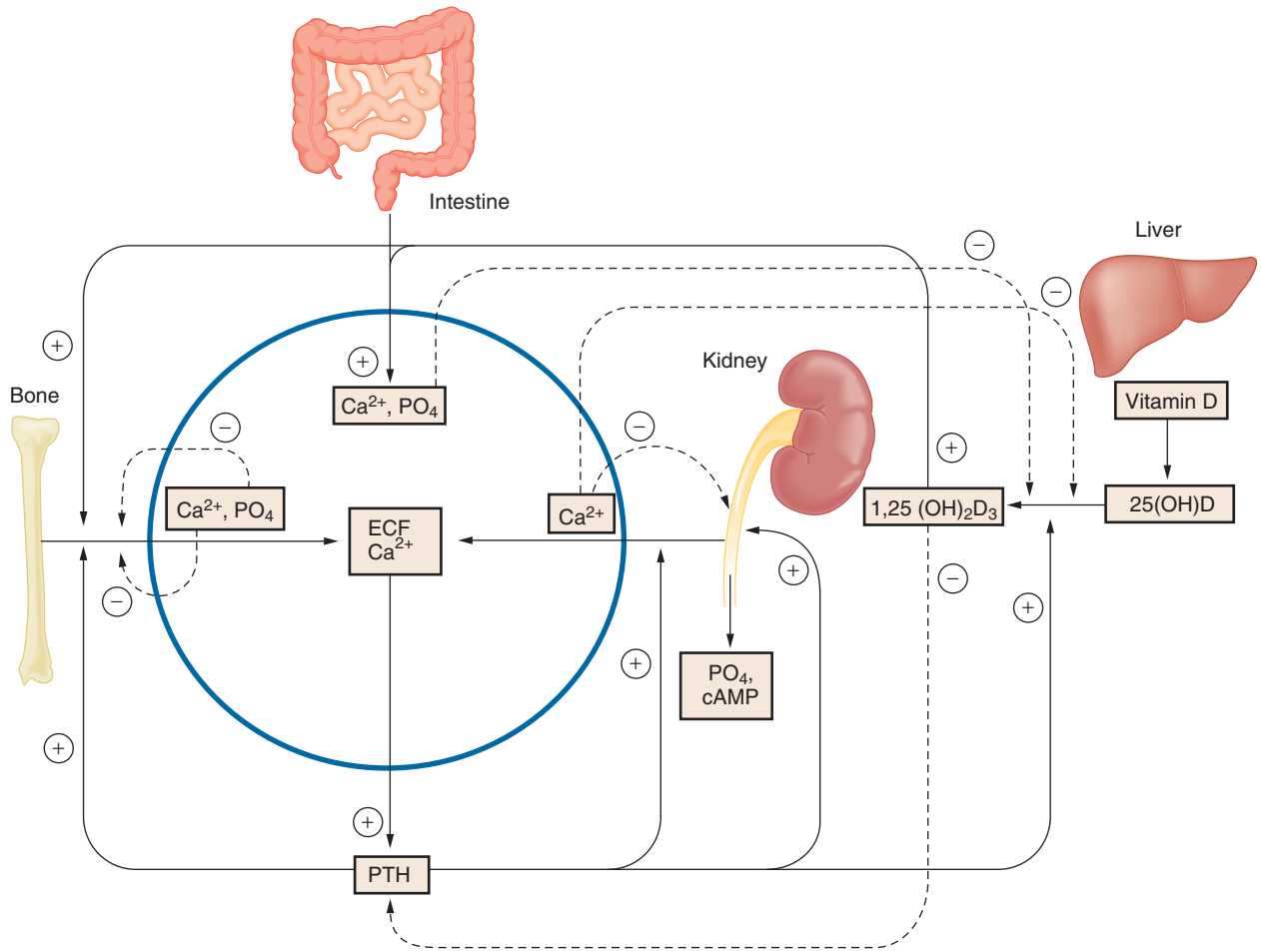
Membrane hyperexcitability can be antagonized by translocating K^+ from the ECV to the ICV, removing excess K^+, or (transiently) by infusing calcium chloride to depress the membrane threshold potential. Pending definitive treatment, rapid infusion of calcium chloride (1 g over 3 minutes, or 2–3 ampoules of 10% calcium gluconate over 5 minutes) can stabilize cardiac rhythm. Calcium should be given cautiously if digitalis intoxication is likely. Acute alkalinization using sodium bicarbonate (50–100 mEq over 5-10 minutes in a 70-kg adult) transiently promotes movement of K^+ from the ECV to the ICV. Bicarbonate can be administered even if pH exceeds 7.40; however, it should not be administered to patients with congestive cardiac failure or hypernatremia. When used alone, bicarbonate is relatively ineffective and is no longer favored. Insulin, in a dose-dependent fashion, causes cellular uptake of K^+ by increasing the activity of the Na,K-ATPase pump. Insulin increases cellular uptake of K^+ best when high insulin levels are achieved by IV injection of 5 to 10 U of regular insulin, accompanied by 50 mL of 50% glucose.[47] β_2-Adrenergic drugs such as salbutamol and albuterol also increase K^+ uptake by skeletal muscle and reduce plasma K^+, an action that can explain hypokalemia with severe acute illness.

Potassium can also be removed from the body by the renal or gastrointestinal routes. Furosemide promotes kaliuresis in a dose-dependent fashion. Sodium polystyrene sulfonate resin (Kayexalate), which exchanges Na^+ for K^+, can be given orally (30 g) or as a retention enema (50 g in 200 mL of 20% sorbitol). However, Na^+ overload and hypervolemia are potential risks. Rarely, when temporizing measures are insufficient, emergency hemodialysis can remove 25 to 50 mEq/hr. Peritoneal dialysis is less efficient.

Calcium

Physiologic Role

Calcium is a divalent cation found primarily in the ECF. The free calcium concentration Ca^{2+} in ECV is approximately 1 mM, whereas



• **Fig. 42.4** Regulatory system maintaining extracellular Ca^{2+} homeostasis. The *solid arrows* and *lines* delineate effects of parathyroid hormone and 1,25 $(OH)_2D_3$ on their target tissues; *dashed arrows* and *lines* show examples of how extracellular Ca^{2+} or phosphate ions act directly on tissues regulating mineral ion metabolism. *Ca,* Calcium; *Ca^{2+},* calcium ion; *cAMP,* cyclic adenosine monophosphate; *PO_4,* phosphate; *ECF,* extracellular fluid; *PTH,* parathyroid hormone; *1,25 $(OH)_2D_3$,* 1,25 dihydroxyvitamin D; *25(OH)D,* 25-hydroxyvitamin D; negative signs indicate inhibitory actions and plus signs indicate stimulatory effects.

the free Ca^{2+} in the ICV approximates 100 nM, a gradient of 10,000 to 1. Circulating Ca^{2+} consists of a protein-bound fraction (40%), a chelated fraction (10%), and an ionized fraction (50%), which is the physiologically active and homeostatically regulated component.[48] Acute acidemia increases and acute alkalemia decreases ionized Ca^{2+}. Because mathematical formulae that "correct" total Ca^{2+} measurements for albumin concentration are inaccurate in critically ill patients, ionized Ca^{2+} should be directly measured.

In general, Ca^{2+} is essential for all movement that occurs in mammalian systems. Essential for normal excitation-contraction coupling, Ca^{2+} is also necessary for proper function of muscle tissue, swallowing, mitosis, neurotransmitter release, enzyme secretion, and hormonal secretion. cAMP and phosphoinositides, which are major second messengers regulating cellular metabolism, function primarily through the regulation of Ca^{2+} movement. Activation of numerous intracellular enzyme systems requires Ca^{2+}. Calcium is important both for generation of cardiac pacemaker activity and for generation of the cardiac action potential for which it is the primary ion responsible for the plateau phase of the action potential. Calcium also plays vital functions in membrane and bone structure.

Serum Ca^{2+} is regulated by multiple factors (Fig. 42.4), including a Ca^{2+} receptor and several hormones. Parathyroid hormone (PTH) and calcitriol, the most important neurohumoral mediators of serum Ca^{2+},[49] mobilize Ca^{2+} from bone, increase renal tubular reabsorption of Ca^{2+}, and enhance intestinal absorption of Ca^{2+}. Vitamin D, after ingestion or cutaneous manufacture under the stimulus of ultraviolet light, is 25-hydroxylated to calcidiol in the liver and then is 1-hydroxylated to calcitriol, the active metabolite, in the kidney. Even in the absence of dietary Ca^{2+} intake, PTH and vitamin D can maintain a normal circulating Ca^{2+} by mobilizing Ca^{2+} from bone.

Hypocalcemia

Hypocalcemia occurs frequently in critical care, affecting 80% to 90% of patients, and is associated with increased mortality in this population.[37] Hypocalcemia (ionized Ca^{2+} < 4.0 mg/dL or < 1.0 mM) occurs as a result from failure of PTH or calcitriol action or because of Ca^{2+} chelation or precipitation, not because of Ca^{2+} deficiency alone. PTH deficiency can result from surgical damage or removal of the parathyroid glands or from suppression of the

parathyroid glands by severe hypomagnesemia or hypermagnesemia. Burns, sepsis, and pancreatitis can suppress parathyroid function and interfere with vitamin D action. Vitamin D deficiency can result from lack of dietary vitamin D or vitamin D malabsorption in patients with low sunlight exposure.

Hyperphosphatemia-induced hypocalcemia can occur as a consequence of overzealous phosphate therapy, from cell lysis secondary to chemotherapy, or as a result of cellular destruction from rhabdomyolysis. Precipitation of calcium hydrogen phosphate ($CaHPO_4$) complexes occurs with hyperphosphatemia. However, ionized Ca^{2+} decreases only approximately 0.019 mM for each 1.0-mM increase in phosphate concentration. In massive transfusion, citrate can produce hypocalcemia by chelating Ca^{2+}; however, decreases are usually transient and produce no cardiovascular effects. A healthy, normothermic adult who has intact hepatic and renal function can metabolize the citrate present in 20 units of blood per hour without becoming hypocalcemic. However, when citrate clearance is decreased (e.g., by hepatic or renal disease or hypothermia) and when blood transfusion rates are rapid (e.g., >2 mL/kg per minute), hypocalcemia and cardiovascular compromise can occur. Alkalemia resulting from hyperventilation or sodium bicarbonate injection can acutely decrease Ca^{2+}. Furthermore, resuscitation-induced hemodilution is an important causative factor of early hypocalcemia in trauma patients.[37] This is an iatrogenic rather than adaptive complication of treatment and can have deleterious effects on blood coagulation and cardiovascular function.

The hallmark of hypocalcemia is increased neuronal membrane irritability and tetany (Table 42.10). Early symptoms include sensations of numbness and tingling involving fingers, toes, and the circumoral region. In frank tetany, tonic contraction of respiratory muscles can lead to laryngospasm, bronchospasm, or respiratory arrest. Smooth muscle spasm can result in abdominal cramping and urinary frequency. Mental status alterations include irritability, depression, psychosis, and dementia. Hypocalcemia can impair cardiovascular function and has been associated with heart failure, hypotension, dysrhythmias, insensitivity to digitalis, and impaired β-adrenergic action.

Reduced *ionized* serum Ca^{2+} occurs in as many as 88% of critically ill patients, 66% of less severely ill patients in intensive care units (ICUs), and 26% of non-ICU hospitalized patients.[50] Patients at particular risk include patients after multiple trauma and cardiopulmonary bypass. In most patients, ionized hypocalcemia is clinically mild (Ca^{2+} 0.8– 1.0 mM).

Initial diagnostic evaluation should concentrate on history and physical examination, laboratory evaluation of renal function, and measurement of serum phosphate concentration. Latent hypocalcemia can be diagnosed by tapping on the facial nerve to elicit the Chvostek sign or by inflating a sphygmomanometer to 20 mm Hg above systolic pressure, which produces radial and ulnar nerve ischemia and causes carpal spasm known as the Trousseau sign.

The differential diagnosis of hypocalcemia can be approached by addressing four issues: age, serum phosphate concentration, general clinical status, and duration of hypocalcemia.[51] High phosphate concentrations suggest renal failure or hypoparathyroidism. In renal insufficiency, reduced phosphorus excretion results in hyperphosphatemia, which downregulates the 1α-hydroxylase responsible for renal conversion of calcidiol to calcitriol. This, combined with decreased production of calcitriol secondary to reduced renal mass, causes reduced intestinal absorption of Ca^{2+} and hypocalcemia.[49] Low or normal phosphate concentrations imply vitamin D or Mg^{2+} deficiency. An otherwise healthy patient with chronic hypocalcemia probably is hypoparathyroid. Chronically ill adults with hypocalcemia often have disorders such as malabsorption, osteomalacia, or osteoblastic metastases.

The definitive treatment of hypocalcemia necessitates identification and treatment of the underlying cause (Table 42.11). Symptomatic hypocalcemia usually occurs when serum ionized Ca^{2+} is less than 0.7 mM. The clinician should carefully consider whether mild, asymptomatic ionized hypocalcemia requires therapy, particularly in ischemic and septic states in which experimental evidence suggests that Ca^{2+} can increase cellular damage.

Unnecessary offending drugs should be discontinued. Hypocalcemia resulting from hypomagnesemia or hyperphosphatemia is treated by repletion of Mg^{2+} or removal of phosphate. Treatment of a patient with tetany and hyperphosphatemia requires coordination of therapy to avoid the consequences of metastatic soft tissue calcification.[52] Potassium and other electrolytes should be measured and abnormalities corrected. Hyperkalemia and hypomagnesemia potentiate hypocalcemia-induced cardiac and neuromuscular irritability. In contrast, hypokalemia protects against hypocalcemic tetany; therefore correction of hypokalemia without correction of hypocalcemia can provoke tetany.

Mild, ionized hypocalcemia should not be overtreated. For instance, in most patients after cardiac surgery administration of Ca^{2+} only increases blood pressure[53] and actually attenuates the β-adrenergic effects of epinephrine.[53] In normocalcemic dogs,

TABLE 42.10 Clinical Manifestations of Hypocalcemia

Cardiovascular
- Dysrhythmias
- Digitalis insensitivity
- Electrocardiographic changes
- Heart failure
- Hypotension

Neuromuscular
- Tetany
- Muscle spasm
- Papilledema
- Seizures
- Weakness
- Fatigue

Respiratory
- Apnea
- Laryngeal spasm
- Bronchospasm

Psychiatric
- Anxiety
- Dementia
- Depression
- Psychosis

TABLE 42.11 Acute Treatment Hypocalcemia

Administer Calcium
- IV: 10 mL 10% calcium gluconate[a] over 10 min, followed by elemental calcium 0.3-2 mg/kg per hour
- Oral: 50-100 mg elemental calcium every 6 hr

Administer Vitamin D
- Ergocalciferol: 1200 μg/day ($t_{1/2}$ = 30 days)
- Dihydrotachysterol: 200-400 μg/day ($t_{1/2}$ = 7 days)
- 1,25-dihydroxycholecalciferol: 0.25-1 μg/day ($t_{1/2}$ = 1 day)

Monitor Electrocardiogram

$t_{1/2}$, Half-life.
[a]Calcium gluconate contains 93 mg elemental calcium per 10-mL vial.

calcium chloride primarily acts as a peripheral vasoconstrictor, with transient reduction of myocardial contractility; in hypocalcemic dogs, Ca^{2+} infusion significantly improves contractile performance and blood pressure.[54] Therefore Ca^{2+} infusions should be of limited value in surgical patients unless there is evidence of hypocalcemia.[54] Calcium salts appear to confer no benefit to patients already receiving inotropic or vasoactive agents.

The cornerstone of therapy for confirmed, symptomatic, ionized hypocalcemia ($Ca^{2+} < 0.7$ mM) is Ca^{2+} administration. In patients who have severe hypocalcemia or hypocalcemic symptoms, Ca^{2+} should be administered intravenously. In emergency situations in an average-sized adult, the "rule of 10s" advises infusion of 10 mL of 10% calcium gluconate (93 mg elemental calcium) over 10 minutes, followed by a continuous infusion of elemental calcium of 0.3 to 2 mg/kg per hour (i.e., 3–16 mL/h of 10 % calcium gluconate for a 70-kg adult). Calcium salts should be diluted in 50 to 100 mL of dextrose 5% in water (D_5W) (to limit venous irritation and thrombosis), should not be mixed with bicarbonate (to prevent precipitation), and must be given cautiously to patients using digoxin because Ca^{2+} increases its toxicity. Continuous ECG monitoring during initial therapy will detect cardiotoxicity (e.g., heart block, ventricular fibrillation). During Ca^{2+} replacement, serum Ca^{2+}, Mg^{2+}, phosphate, K^+, and creatinine should be monitored. Once the ionized Ca^{2+} is stable in the range of 4 to 5 mg/dL (1.0–1.25 mM), oral calcium supplements can substitute for parenteral therapy. Urinary Ca^{2+} should be monitored in attempt to avoid hypercalciuria (>5 mg/kg per 24 hours) and possible urinary tract stone formation.

When supplementation fails to maintain normal serum Ca^{2+}, or if hypercalciuria develops, vitamin D can be added. Although the principal effect of vitamin D is to increase enteric Ca^{2+} absorption, osseous Ca^{2+} resorption is also enhanced. When rapid changes in dosage are anticipated or an immediate effect is required (e.g., postoperative hypoparathyroidism), shorter-acting calciferols such as dihydrotachysterol are preferable. Because the effect of vitamin D is not regulated, the dosages of Ca^{2+} and vitamin D should be adjusted to raise serum Ca^{2+} into the low normal range.

Adverse reactions to Ca^{2+} and vitamin D include hypercalcemia and hypercalciuria. If hypercalcemia develops, Ca^{2+} and vitamin D should be discontinued and appropriate therapy given. The toxic effects of vitamin D metabolites persist in proportion to their biologic half-lives (ergocalciferol, 20–60 days; dihydrotachysterol, 5–15 days; calcitriol, 2–10 days). Glucocorticoids can antagonize the toxic effects of vitamin D metabolites.

Hypercalcemia

Although ionized Ca^{2+} most accurately demonstrates hypercalcemia (ionized $Ca^{2+} > 1.5$ mM or total serum $Ca^{2+} > 10.5$ mg/dL), hypercalcemia customarily is defined in terms of total serum Ca^{2+}. In hypoalbuminemic patients, total serum Ca^{2+} can be estimated by assuming an increase of 0.8 mg/dL for every 1 g/dL of albumin concentration below 4.0 g/dL. Patients with total serum Ca^{2+} less than 11.5 mg/dL are usually asymptomatic. Patients with moderate hypercalcemia (total serum Ca^{2+} 11.5–13 mg/dL) can show symptoms of lethargy, anorexia, nausea, and polyuria. Severe hypercalcemia (total serum $Ca^{2+} > 13$ mg/dL) is associated with more severe neuromyopathic symptoms, including muscle weakness, depression, impaired memory, emotional lability, lethargy, stupor, and coma. The cardiovascular effects of hypercalcemia include hypertension, arrhythmias, heart block, cardiac arrest, and digitalis sensitivity. Skeletal disease occurs secondary to direct osteolysis or humoral bone resorption.

Hypercalcemia impairs urinary concentrating ability and renal excretory capacity for Ca^{2+} by irreversibly precipitating Ca^{2+} salts within the renal parenchyma and by reducing renal blood flow and GFR. In response to hypovolemia, renal tubular reabsorption of Na^+ enhances renal Ca^{2+} reabsorption. Effective treatment of severe hypercalcemia is necessary to prevent progressive dehydration and renal failure leading to further increases in total serum Ca^{2+}, because volume depletion exacerbates hypercalcemia.[55] Hypercalcemia occurs when Ca^{2+} enters the ECV more rapidly than the kidneys can excrete the excess. Clinically, hypercalcemia most commonly results from an excess of bone resorption over bone formation, usually secondary to malignant disease, hyperparathyroidism, hypocalciuric hypercalcemia, thyrotoxicosis, immobilization, and granulomatous diseases. Granulomatous diseases produce hypercalciuria and hypercalcemia as the result of conversion by granulomatous tissue of calcidiol to calcitriol.[56]

Malignancy can produce hypercalcemia either through bone destruction or secretion by malignant tissue of hormones that promote hypercalcemia.[57] Although weakness, weight loss, and anemia associated with primary hyperparathyroidism might suggest malignancy, these can result simply from the primary disease process. Hypercalcemia associated with granulomatous diseases (e.g., sarcoidosis) results from the production of calcitriol by granulomatous tissue. To compensate for increased gut absorption or bone resorption of Ca^{2+}, renal excretion can readily increase from 100 to more than 400 mg/day. Factors that promote hypercalcemia might be offset by coexisting disorders such as pancreatitis, sepsis, or hyperphosphatemia that cause hypocalcemia.

Although definitive treatment of hypercalcemia requires correction of underlying causes, temporizing therapy can be necessary to avoid complications and to relieve symptoms. Total serum Ca^{2+} exceeding 14 mg/dL represents a medical emergency. General supportive treatment includes hydration, correction of associated electrolyte abnormalities, removal of offending drugs, dietary Ca^{2+} restriction, and increased physical activity. Because anorexia and antagonism by Ca^{2+} of ADH action invariably lead to Na^+ and water depletion, infusion of 0.9 % saline solution will dilute serum Ca^{2+}, promote renal excretion, and can reduce total serum Ca^{2+} by 1.5 to 3 mg/dL. Urinary output should be maintained at 200 to 300 mL/hr. As GFR increases, Na^+ increases Ca^{2+} excretion by competing with Ca^{2+} for reabsorption in the proximal renal tubules and loop of Henle.

Furosemide further enhances Ca^{2+} excretion by increasing tubular Na^+. Patients who have renal impairment require higher doses of furosemide. During saline solution infusion and forced diuresis, careful monitoring of cardiopulmonary status and electrolytes, especially Mg^{2+} and K^+, is required. Intensive diuresis and saline administration can achieve net Ca^{2+} excretion of 2000 to 4000 mg/24 hr, a rate eight times greater than saline solution alone but still somewhat less than the rate of removal achieved by hemodialysis (6000 mg/8 hr). Patients treated with phosphates should be well hydrated.

Bone resorption, the primary cause of hypercalcemia, can be minimized by increasing physical activity and initiating drug therapy. Bisphosphonates, currently the first-line therapy for acute hypercalcemia, inhibit osteoclast function and viability. Bisphosphonates are the principal drugs for the management of hypercalcemia mediated by osteoclastic bone resorption.[58] Pamidronate, unlike earlier biphosphonates, does not appear to worsen renal insufficiency. More recently released biphosphonates include alendronate, risedronate, and zoledronic acid. Risedronate has been associated with fewer nonvertebral fractures than alendronate.[59] Zoledronic

acid has the most rapid onset of action among the biphosphonates and prolongs the duration before relapse of hypercalcemia; however, it has been associated with compromised renal function.[60]

Other osteoclast-inhibiting agents used to treat hypercalcemia include mithramycin and calcitonin.[61] Mithramycin, a cytotoxic agent, lowers serum Ca^{2+} primarily by inhibiting bone resorption, probably because of toxicity to osteoclasts. The hypocalcemic effect, usually seen within 12 to 24 hours after a single IV dose of 25 μg/kg, peaks at 48 to 72 hours and persists 5 to 7 days. Major toxic effects of mithramycin, more likely to occur in patients with renal insufficiency, include thrombocytopenia, nephrotoxicity, and hepatotoxicity. Calcitonin lowers serum Ca^{2+} within 24 to 48 hours and is more effective when combined with glucocorticoids.[60] Usually calcitonin reduces total serum Ca^{2+} by only 1 to 2 mg/dL. Although calcitonin is relatively nontoxic, more than 25% of patients do not respond. Thus calcitonin is unsuitable as a first-line drug during life-threatening hypercalcemia.

Hydrocortisone is effective in treating hypercalcemic patients with lymphatic malignancies, vitamin D or A intoxication, and diseases associated with production by tumor or granulomas of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) or osteoclast-activating factor. Glucocorticoids rarely improve hypercalcemia secondary to malignancy or hyperparathyroidism. In the future, Ca^{2+} receptor agonists could become treatments of choice for suppressing primary and secondary hyperparathyroidism. Currently undergoing initial clinical trials, these agents also reduce inorganic phosphate concentration and the calcium × phosphate product.[62]

Phosphates lower serum Ca^{2+} by causing deposition of Ca^{2+} in bone and soft tissue. Because the risk of extraskeletal calcification of organs such as the kidney and myocardium is less if phosphates are given orally, the IV route should be reserved for patients with life-threatening hypercalcemia or patients in whom other measures have failed.

Phosphate

Physiologic Role

Inorganic phosphate (PO_4^{3-}; P_i) is distributed in similar concentrations throughout intracellular and ECF. Of total body phosphorus, 90% is in bone, 10% is intracellular, and less than 1% is in the ECF. Phosphate circulates as the free ion (55%), complexed ion (33%), and in a protein-bound form (12%). Plasma levels vary widely; normal total P_i ranges from 2.7 to 4.5 mg/dL in adults.

Control of P_i is achieved by altered renal excretion and redistribution between body compartments. Absorption occurs in the duodenum and jejunum and is largely unregulated. Phosphate reabsorption in the kidney is primarily regulated by PTH, dietary intake, and insulin-like growth factor.[63] Phosphate is freely filtered at the glomerulus and its concentration in the glomerular ultrafiltrate is similar to plasma. Filtered phosphate is then reabsorbed in the proximal tubule, where it is passively cotransported with Na^+.[63,64] Cotransport is regulated by phosphorus intake and PTH.[65] Phosphate excretion is increased by volume expansion and decreased by respiratory alkalosis.

Phosphoryl bonds provide the primary energy bond in ATP and creatine phosphate. Therefore severe phosphate depletion can result in cellular energy depletion. Phosphate is an essential component of second-messenger systems, including cAMP and phosphoinositides, and of nucleic acids, phospholipids, and cell membranes. As part of 2,3-diphosphoglycerate, phosphate promotes release of oxygen from hemoglobin. Phosphate also functions in protein phosphorylation and acts as a urinary buffer.

Hypophosphatemia

Hypophosphatemia is characterized by low levels of phosphate-containing cellular components, including ATP, 2,3-diphosphoglycerate, and membrane phospholipids. Serious life-threatening organ dysfunction can occur when serum P_i falls below 1 mg/dL. Neurologic manifestations of hypophosphatemia include paresthesias, myopathy, encephalopathy, delirium, seizures, and coma.[66] Hematologic abnormalities include dysfunction of erythrocytes, platelets, and leukocytes. Because hypophosphatemia limits the chemotactic, phagocytic, and bactericidal activity of granulocytes, associated immune dysfunction contributes to the susceptibility of hypophosphatemic patients to sepsis. Muscle weakness and malaise are common. Respiratory muscle failure and myocardial dysfunction are potential problems of concerns in anesthesiology. Rhabdomyolysis is a complication of severe hypophosphatemia.[67]

Common in postoperative and traumatized patients, hypophosphatemia ($P_i < 2.5$ mg/dL) is caused by three primary abnormalities in P_i homeostasis: intracellular shift of P_i, increase in renal P_i loss, or reduced gastrointestinal P_i absorption. Carbohydrate-induced hypophosphatemia (refeeding syndrome),[68] mediated by insulin-induced cellular P_i uptake, is the type most commonly encountered in hospitalized patients. Hypophosphatemia also occurs as catabolic patients become anabolic, and during medical management of diabetic ketoacidosis. Acute alkalemia, which can reduce serum P_i to 1 to 2 mg/dL, increases intracellular consumption of P_i by increasing the rate of glycolysis. Hyperventilation significantly reduces P_i and, importantly, the effect is progressive after cessation of hyperventilation.[69]

Acute correction of respiratory acidemia can also result in severe hypophosphatemia. Respiratory alkalosis probably explains the hypophosphatemia associated with gram-negative bacteremia and salicylate poisoning. Excessive renal loss of P_i explains the hypophosphatemia associated with hyperparathyroidism, hypomagnesemia, hypothermia, diuretic therapy, and renal tubular defects in P_i absorption. Excess gastrointestinal loss of P_i is most commonly secondary to use of P_i-binding antacids or to malabsorption syndromes.

Measurement of urinary P_i aids in differentiation of hypophosphatemia owing to renal losses from that owing to excessive gastrointestinal losses or redistribution of P_i into cells. Extrarenal causes of hypophosphatemia cause avid renal tubular P_i reabsorption, reducing urinary excretion to less than 100 mg/day.

Patients who have severe (<1 mg/dL) or symptomatic hypophosphatemia require IV phosphate administration.[65,69] In chronically hypophosphatemic patients, 0.2 to 0.68 mmol/ kg (5–16 mg/kg elemental phosphorus) should be infused over 12 hours. For moderately hypophosphatemic adult patients with critical illnesses, use of 15 mmol boluses (465 mg) mixed with 100 mL of 0.9% sodium chloride and given over a 2-hour period safely repletes phosphate.[70] The dosage is then adjusted as indicated by serum P_i because the cumulative deficit cannot be predicted accurately. Oral therapy can be substituted for parenteral P_i once the serum P_i exceeds 2.0 mg/dL. Continued therapy with P_i supplements is required for 5 to 10 days to replenish body stores.

Phosphate should be administered cautiously to hypocalcemic patients because of the risk of precipitating more severe hypocalcemia. In hypercalcemic patients, P_i can cause soft tissue calcification. Phosphorus must be given cautiously to patients with renal insufficiency because of impaired excretory ability. During treatment, close monitoring of serum P_i, Ca^{2+}, Mg^{2+}, and K^+ is essential to avoid complications.

Hyperphosphatemia

The clinical features of hyperphosphatemia (P_i > 5.0 mg/dL) relate primarily to development of hypocalcemia and ectopic calcification. Hyperphosphatemia is caused by three basic mechanisms: inadequate renal excretion, increased movement of P_i out of cells, and increased P_i or vitamin D intake. Rapid cell lysis from chemotherapy, rhabdomyolysis, and sepsis can cause hyperphosphatemia, especially when renal function is impaired. Renal failure is the most common cause of hyperphosphatemia.[66] Renal excretion of P_i remains adequate until the GFR falls below 20 to 25 mL/min.

Measurements of BUN, creatinine, GFR, and urinary P_i are helpful in the differential diagnosis of hyperphosphatemia. Normal renal function accompanied by high P_i excretion (>1500 mg/day) indicates an oversupply of P_i. Elevated BUN, elevated creatinine, and low GFR suggest impaired renal excretion of P_i. Normal renal function and P_i excretion less than 1500 mg/day suggest increased P_i reabsorption (i.e., hypoparathyroidism).

Hyperphosphatemia is corrected by eliminating the cause of P_i elevation and correcting the associated hypocalcemia. Calcium supplementation of hypocalcemic patients should be delayed until serum phosphate has fallen below 2.0 mM (6.0 mg/dL).[56] Serum P_i is reduced by restricting intake, increasing urinary excretion with saline solution and acetazolamide (500 mg every 6 hours), and increasing gastrointestinal losses by enteric administration of aluminum hydroxide (30–45 mL every 6 hours). Aluminum hydroxide absorbs P_i secreted into the bowel lumen and increases P_i loss even if none is ingested. Hemodialysis and peritoneal dialysis are effective in removing P_i in patients with renal failure.

Magnesium

Physiologic Role

Magnesium is a physiologically important, multifunctional, divalent cation present primarily in the intracellular space (intracellular Mg^{2+} ~ 2400 mg; extracellular Mg^{2+} ~ 280 mg). About 50% of Mg^{2+} is in bone, 25% in muscle, and less than 1 % of total body Mg^{2+} circulates in plasma. Of normal circulating total Mg^{2+} (1.5-1.9 mEq/L or 0.75–0.95 mM or 1.7–2.2 mg/dL),[71] there are three components: protein-bound (30%), chelated (15%), and ionized (55%), of which only ionized Mg^{2+} is active.

Magnesium is necessary for enzymatic reactions involving DNA and protein synthesis, energy metabolism, glucose utilization, and fatty acid synthesis and breakdown.[72,73] As a primary regulator or cofactor in many enzyme systems, Mg^{2+} is important for regulation of the Na/K-ATPase, calcium adenosine triphosphatase (Ca-ATPase) enzymes, adenylyl cyclase, proton pumps, and Ca^{2+} channels. Magnesium has been called an endogenous Ca^{2+} antagonist, because modulation of Ca^{2+} channels contributes to maintenance of normal vascular tone, prevention of vasospasm, and perhaps to prevention of Ca^{2+} overload in many tissues. Because Mg^{2+} partially regulates PTH secretion and is important for maintenance of end-organ sensitivity to both PTH and vitamin D, abnormalities in ionized Mg^{2+} concentration (Mg^{2+}) can result in abnormal Ca^{2+} metabolism. Magnesium functions in K^+ metabolism primarily through regulating Na/K ATPase, which controls K^+ entry into cells, especially in K^+-depleted states, and controls reabsorption of K^+ by the renal tubules. In addition, Mg^{2+} functions as a regulator of membrane excitability and serves as a structural component in both cell membranes and the skeleton.

Because Mg^{2+} stabilizes axonal membranes, hypomagnesemia decreases the threshold of axonal stimulation and increases nerve conduction velocity. Magnesium also influences release of acetylcholine at the neuromuscular junction by competitively inhibiting Ca^{2+} entry into presynaptic nerve terminals. The concentration of Ca^{2+} required to trigger Ca^{2+}-induced Ca^{2+} release and the rate at which Ca^{2+} is released from the sarcoplasmic reticulum are inversely related to Mg^{2+} concentration. Thus the net effect of hypomagnesemia is muscle that contracts more in response to stimuli and is tetany prone.

Magnesium is widely available in foods and is absorbed through the gastrointestinal tract, although dietary consumption appears to have decreased over several decades.[73] The distal tubule is the major site of Mg^{2+} regulation. Plasma Mg^{2+} regulates Mg^{2+} reabsorption through the Ca^{2+}/Mg^{2+}–sensing receptor, located on the capillary side of cells in the thick ascending limb.[74] Although both Mg^{2+} and P_i are primarily regulated by intrinsic renal mechanisms,[72] PTH exerts a greater effect on renal loss of P_i.

Magnesium has been used to help manage an array of clinical problems in patients who are not hypomagnesemic.[75] Therapeutic hypermagnesemia is used to treat patients with premature labor, preeclampsia, and eclampsia. Because Mg^{2+} blocks release of catecholamines from adrenergic nerve terminals and the adrenal glands, it has been used to reduce the effects of catecholamine excess in patients with tetanus and pheochromocytoma. Magnesium administration can influence dysrhythmias by direct effects on myocardial membranes; by altering cellular K^+ and Na^+ concentrations; by inhibiting cellular Ca^{2+} entry; by improving myocardial oxygen supply and demand; by prolonging the effective refractory period; by depressing conduction, by antagonizing catecholamine action on the conducting system; and by preventing vasospasm. Administration of Mg^{2+} reduces the incidence of dysrhythmias after myocardial infarction and in patients with CHF.[76] In humans with ischemic myocardium, Mg^{2+} prevents ischemic increases in action potential duration and membrane repolarization. After acute myocardial infarction, IV Mg^{2+} decreased short-term mortality.[77] In addition, Mg^{2+} can be useful as treatment for torsades de pointes, even in normomagnesemic patients.[78]

Hypomagnesemia

The clinical features of hypomagnesemia (Mg^{2+} < 1.8 mg/dL), like those of hypocalcemia, are characterized by increased neuronal irritability and tetany.[79] Symptoms are rare when serum Mg^{2+} is 1.5 to 1.7 mg/dL; in most symptomatic patients serum Mg^{2+} is less than 1.2 mg/dL. Patients frequently complain of weakness, lethargy, muscle spasms, paresthesias, and depression. When severe, hypomagnesemia can induce seizures, confusion, and coma. Cardiovascular abnormalities include coronary artery spasm, cardiac failure, dysrhythmias, and hypotension. Severe hypomagnesemia can reduce the response of adenylyl cyclase to stimulation of the PTH receptor.[80] Hypomagnesemia can aggravate digoxin toxicity and CHF.

Rarely resulting from inadequate dietary intake, hypomagnesemia most commonly is caused by inadequate gastrointestinal absorption, excessive losses, or failure of renal conservation. Excessive Mg^{2+} loss is associated with prolonged nasogastric suctioning, gastrointestinal or biliary fistulas, and intestinal drains. Inability of the renal tubules to conserve Mg^{2+} complicates a variety of systemic and renal diseases, although advanced renal disease with decreased GFR can lead to Mg^{2+} retention. Polyuria, whether secondary to ECV expansion or to pharmacologic or pathologic diuresis, can

result in excessive urinary Mg^{2+} excretion. Various drugs, including aminoglycosides, *cis*-platinum, cardiac glycosides, and diuretics, enhance urinary Mg^{2+} excretion. Intracellular shifts of Mg^{2+} as a result of thyroid hormone or insulin administration can also decrease serum Mg^{2+}.

Because the Na/K-ATPase pump is Mg^{2+}-dependent, hypomagnesemia increases myocardial sensitivity to digitalis preparations and can cause hypokalemia as a result of renal potassium wasting. Attempts to correct potassium deficits with K^+ replacement therapy alone might not be successful without simultaneous Mg^{2+} therapy. Magnesium is important in the regulation of K^+ channels. The interrelationships of Mg^{2+} and K^+ in cardiac tissue have probably the greatest clinical relevance in terms of arrhythmias, digoxin toxicity, and myocardial infarction. Both severe hypomagnesemia and hypermagnesemia suppress PTH secretion and can cause hypocalcemia. Severe hypomagnesemia can also impair end-organ response to PTH.

Hypomagnesemia is associated with hypokalemia, hyponatremia, hypophosphatemia, and hypocalcemia. The reported prevalence of hypomagnesemia in hospitalized and critically ill patients varies from 11% to 61%, with the variability attributable to differences in measurement technique.[81] Recent development of a specific electrode to measure ionized Mg^{2+} has demonstrated an association between hypomagnesemia, use of diuretics, and development of sepsis.[81] Patients who develop hypomagnesemia while in intensive care have increased mortality.[81] Of alcoholic patients admitted to the hospital, 30% are hypomagnesemic.[82] Serum Mg^{2+} might not reflect intracellular Mg^{2+}. Peripheral lymphocyte Mg^{2+} correlates well with skeletal and cardiac Mg^{2+} content.

Measurement of 24-hour urinary Mg^{2+} excretion is useful in separating renal from nonrenal causes of hypomagnesemia. Normal kidneys can reduce Mg^{2+} excretion to less than 1 to 2 mEq/day in response to depletion. Hypomagnesemia accompanied by high urinary excretion (>3–4 mEq/day) suggests a renal cause. In the Mg^{2+}-loading test, urinary Mg^{2+} excretion is measured for 24 hours after an IV load.

Magnesium deficiency is treated by administration of Mg^{2+} supplements (Table 42.12). One gram of magnesium sulfate provides approximately 4 mmol (8 mEq, or 98 mg) of elemental magnesium. Mild deficiencies can be treated with diet alone. Replacement must be added to daily requirements (0.3–0.4 mEq/kg per day). Symptomatic or severe hypomagnesemia (Mg^{2+} < 1.0 mg/dL) should be treated with parenteral Mg^{2+}: 1 to 2 g (8–16 mEq) of magnesium sulfate as an IV bolus over the first hour, followed by a continuous infusion of 2 to 4 mEq/hr. Therapy should be guided subsequently by serum Mg^{2+} level. The rate of infusion should not exceed 1 mEq/min, even in emergency situations, and continuous cardiac monitoring is necessary to detect cardiotoxicity.

Because Mg^{2+} antagonizes Ca^{2+}, blood pressure and cardiac function should be monitored, although blood pressure and cardiac output usually change little during Mg^{2+} infusion. Treatment of hypomagnesemia during cardiopulmonary bypass was found to decrease the incidence of postoperative ventricular tachycardia from 30% to 7% and increase the frequency of continuous sinus rhythm from 5% to 34%.[83]

During repletion, patellar reflexes should be monitored frequently and Mg^{2+} withheld if they become suppressed. Patients with renal insufficiency have a diminished ability to excrete Mg^{2+} and require careful monitoring. Repletion of systemic Mg^{2+} stores usually requires 5 to 7 days of therapy, after which daily maintenance doses should be provided. Magnesium can be given orally, usually in a dose of 60 to 90 mEq/day of magnesium oxide. Hypocalcemic, hypomagnesemic patients should receive Mg^{2+} as the chloride salt, because sulfate can chelate Ca^{2+} and further reduce serum Ca^{2+}.

TABLE 42.12 Acute Treatment of Hypophosphatemia

Parenteral phosphate, 0.2 mM-0.68 mmol/kg (5-16 mg/kg) over 12 hr
Potassium phosphate (93 mg/mL phosphate)
Sodium phosphate (93 mg/mL phosphate)

Hypermagnesemia

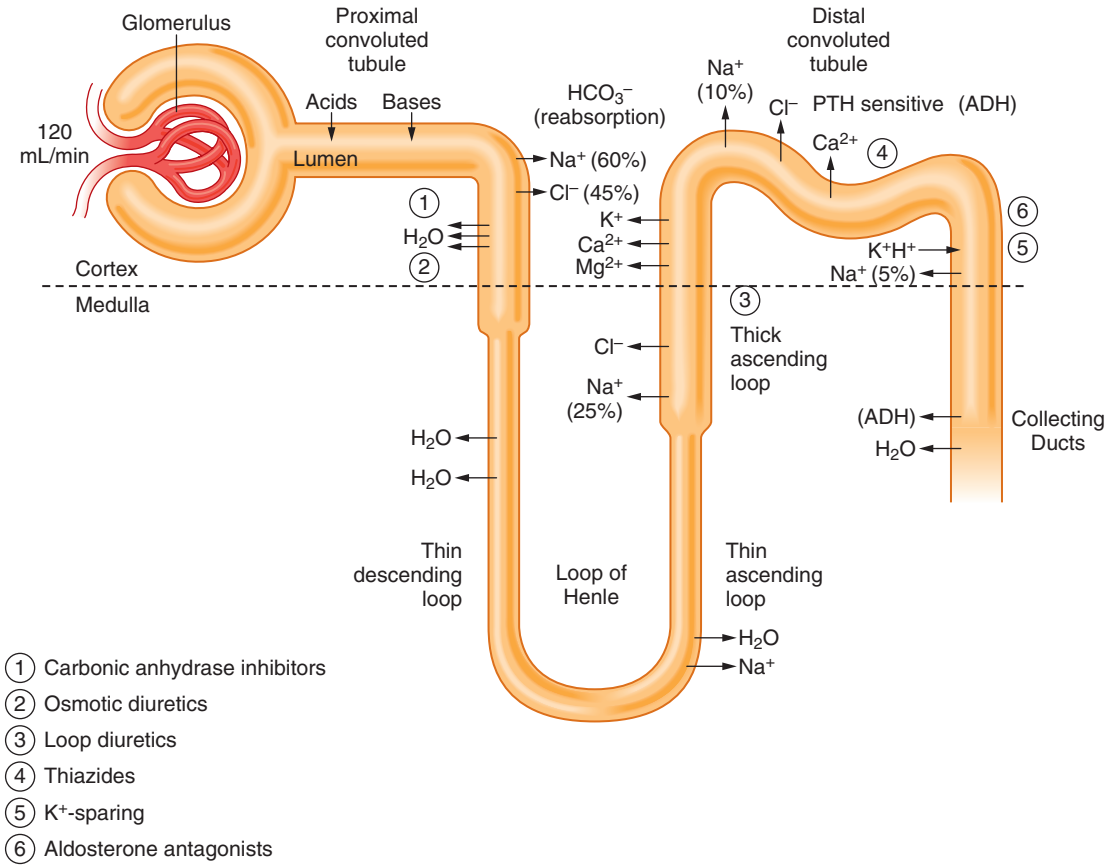
Most cases of hypermagnesemia (Mg^{2+} > 2.5 mg/dL) are iatrogenic, resulting from administration of Mg^{2+} in antacids, enemas, or parenteral nutrition, especially to patients with impaired renal function. Other rarer causes of mild hypermagnesemia are hypothyroidism, Addison disease, lithium intoxication, and familial hypocalciuric hypercalcemia. Hypermagnesemia is rarely detected in routine electrolyte determinations.[79,84,85] Hypermagnesemia antagonizes the release and effect of acetylcholine at the neuromuscular junction, depressing skeletal muscle function and enhancing neuromuscular blockade. Magnesium potentiates the action of nondepolarizing muscle relaxants and decreases K^+ release in response to succinylcholine.[79]

The neuromuscular and cardiac toxicity of hypermagnesemia can be acutely, but transiently, antagonized by IV Ca^{2+} (5–10 mEq) to buy time while more definitive therapy is instituted.[79] All Mg^{2+}-containing preparations must be stopped. Urinary excretion of Mg^{2+} can be increased by expanding ECV and inducing diuresis with a combination of saline solution and furosemide. In emergency situations and in patients with renal failure, Mg^{2+} can be removed by dialysis.

Diuretics

The most prominent property of diuretics is that they reduce reabsorption of Na^+ and Cl^- at different sites in the nephron, thereby increasing urinary Na^+ and water losses. This makes them useful in treatment of a variety of conditions, such as edematous states, hypertension, heart failure, renal dysfunction, hypercalcemia, nephrolithiasis, glaucoma, and mountain sickness. Their efficacy, safety, and optimal dosing are, however, based on small and underpowered trials.[86,87] They can be divided into three major classes depending on the site at which they impair Na^+ reabsorption. Loop diuretics act in the thick ascending limb of the loop of Henle; thiazide-type diuretics act in the distal tubule and connecting segment; and potassium-sparing diuretics act in the aldosterone-sensitive principal cells in the cortical collecting tubule.

It is important to understand the general mechanism behind Na^+ reabsorption (Fig. 42.5). The Na^+-transporting cells contain Na,K-ATPase in the basolateral membrane.[88] These pumps have two major functions. They return reabsorbed Na^+ to the systemic circulation and maintain intracellular Na^+ concentration at low levels. This is important because otherwise no Na^+ transport occurs. Each of the major nephron segments has a unique Na^+ entry mechanism; inhibition of this step is the major mechanism at which each of the different classes of diuretics acts. Approximately two-thirds of filtered Na^+ is reabsorbed in the proximal tubule by primary and secondary active transport.

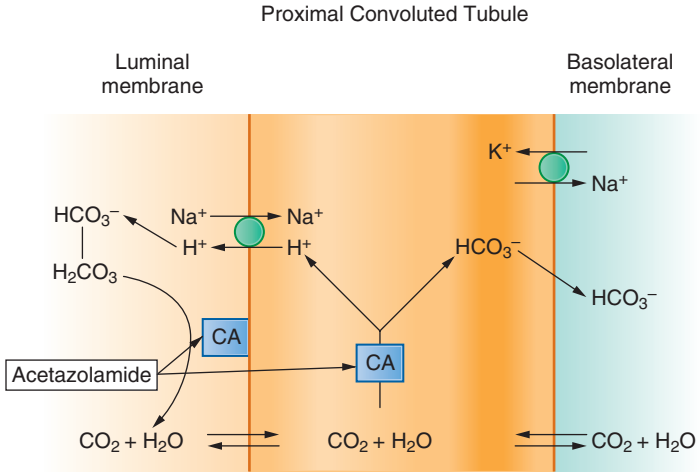


• **Fig. 42.5** Action of diuretics at various renal tubular segments. *ADH,* Antidiuretic hormone; *Ca^{2+},* calcium ion; *Cl^-*, chloride ion; *HCO_3^-*, bicarbonate; *H_2O*, water; *K^+H^+*, ——————; *Na^+*, sodium ion; *PTH,* parathyroid hormone.

Proximal Convoluted Tubule–Carbonic Anhydrase Inhibitors

Azetazolamide and dorzolamide inhibit the activity of carbonic anhydrase, which plays an important role in proximal HCO_3^-, Na^+, and Cl^- reabsorption. These agents thus produce NaCl and $NaHCO_3$ loss. The net diuresis is small because most of the excess fluid is reclaimed at more distal segments, particularly at the loop of Henle. The diuretic action is also attenuated by the metabolic acidosis that results from the loss of HCO_3^- (Fig. 42.6).

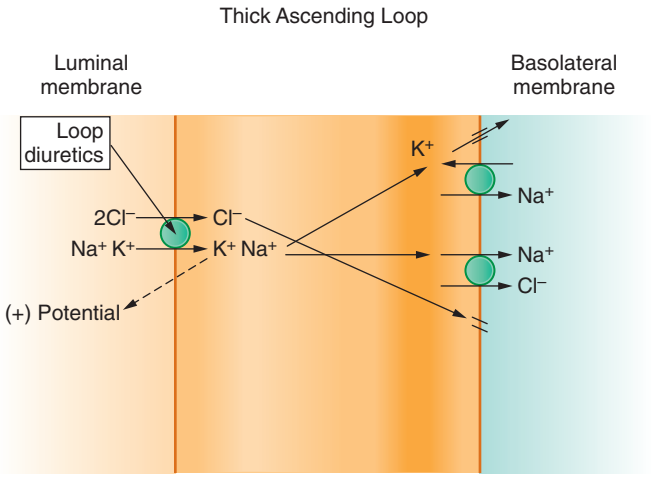
The major uses of these diuretics are for edematous states and metabolic alkalosis.[89,90] Clinical uses are glaucoma (decrease of aqueous humor, which lowers intraocular pressure), acute mountain sickness (lowers the incidence of pulmonary as well as cerebral edema), metabolic alkalosis (such as caused by thiazide diuretics), and elimination of acidic drugs (such as aspirin, uric acid). Adverse effects are acidosis, bicarbonaturia, hypokalemia, paresthesias, and renal stones (hypercalciuria, phosphaturia).



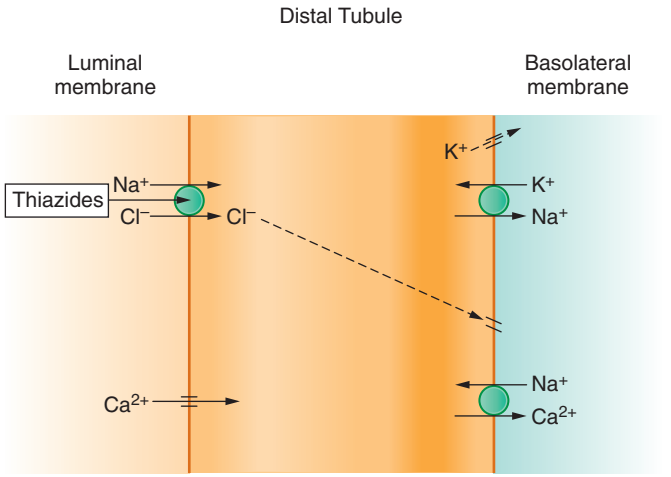
• **Fig. 42.6** Actions of carbonic anhydrase inhibitors. *CA*, Carbonic anhydrase; *Cl^-*, chloride ion; *CO_2,* carbon dioxide; *H^+,* hydrogen ion; *HCO_3^-*, bicarbonate; *H_2CO_3,* carbonic acid; *H_2O*, water; *Na^+*, sodium ion.

Ascending Loop of Henle: Loop Diuretics

Fluid entering the loop of Henle is isotonic (osmolarity 300 mOsm/L) but the volume is only a third of the volume originally filtered into Bowman capsule. The loop of Henle acts as a countercurrent multiplier (see Fig. 42.5), and as such creates a medullary interstitial osmolar gradient. The descending limb of the loop of Henle is permeable to water. Water diffuses into the hyperosmolar medullary interstitium. The osmolarity can reach a maximum of 1200 mOsm/L at the tip of the medullary interstitium in antidiuresis. The ascending limb (where loop diuretics work) is impermeable to water. NaCl is pumped from the tubule into the interstitium in the ascending limb. The tubular osmolarity decreases



• **Fig. 42.7** Actions of loop diuretics on the thick ascending loop of Henle. *Cl⁻,* Chloride ion; *K⁺,* potassium ion; *Na+,* sodium ion.



• **Fig. 42.8** Actions of thiazides on the distal convoluted tubule. *Ca^{2+},* Calcium ion; *Cl^-*, chloride ion; *K^+*, potassium ion; *Na^+*, sodium ion.

and fluid that leaves the loop is hypotonic. The collecting duct is impermeable to water without ADH.

Loop diuretics (furosemide, torsemide, bumetanide, ethacrynic acid) can lead to excretion of 20% to 25% of filtered Na^+ in large doses.[91,92] They act principally in the medullary and cortical aspects of the thick ascending limb and the macula densa cells in the early distal tubule. Loop diuretics compete for the Cl^- site, thereby diminishing net reabsorption.[93,94] Sodium reabsorbed via the $Na^+/K^+/2Cl^-$ transporter is transported back into the blood by the Na/K ATPase pump and by a Na^+/Cl^- cotransporter, the excess Cl^- returning to blood via passive diffusion. High intracellular K^+ results in its backdiffusion across the luminar membrane, providing a positive potential that drives reabsorption of both Mg^{2+} and Ca^{2+} (Fig. 42.7). Inhibition of this mechanism thus increases urinary Na^+, K^+, Ca^{2+}, Mg^+ and Cl^-.

Clinical uses of loop diuretics include acute pulmonary edema, acute renal failure, anion overdose, heart failure, hypercalcemia, hypertension, and refractory edema. Adverse effects are allergies, alkalosis, hypocalcemia, hypokalemia, hypomagnesemia, hyperuricemia, hypovolemia, and ototoxicity (ethancrynic acid > furosemide).

Thiazides

Hydrochlorothiazide, indapamide, and metolazone are organic acids that are both filtered and secreted and inhibit the Na^+/Cl^- transporter on the luminal membrane of the distal convoluted tubule. Normally, the Na^+ that is brought in by the Na^+/Cl^- cotransporter is exchanged for K^+ that returns to blood via backdiffusion. Chloride also returns to blood by such a mechanism, whereas Ca^{2+} returns by a Ca^{2+}/Na^+ antiporter. If the Na^+/Cl^- cotransporter is inhibited by thiazides, hypokalemia and alkalosis occur. Hypercalcemia can occur as the result of increased activity of the Na^+/Ca^{2+} antiporter (Fig. 42.8).

Clinical uses of thiazides are hypertension and heart failure. Their effects are improved by Na^+ restriction and attenuated by low GFR. Adverse effects are allergies, alkalosis, hypokalemia, hyperuricemia, hypovolemia, hyperglycemia, hyperlipidemia, hypercalcemia, and sexual dysfunction.

Potassium-Sparing Diuretics

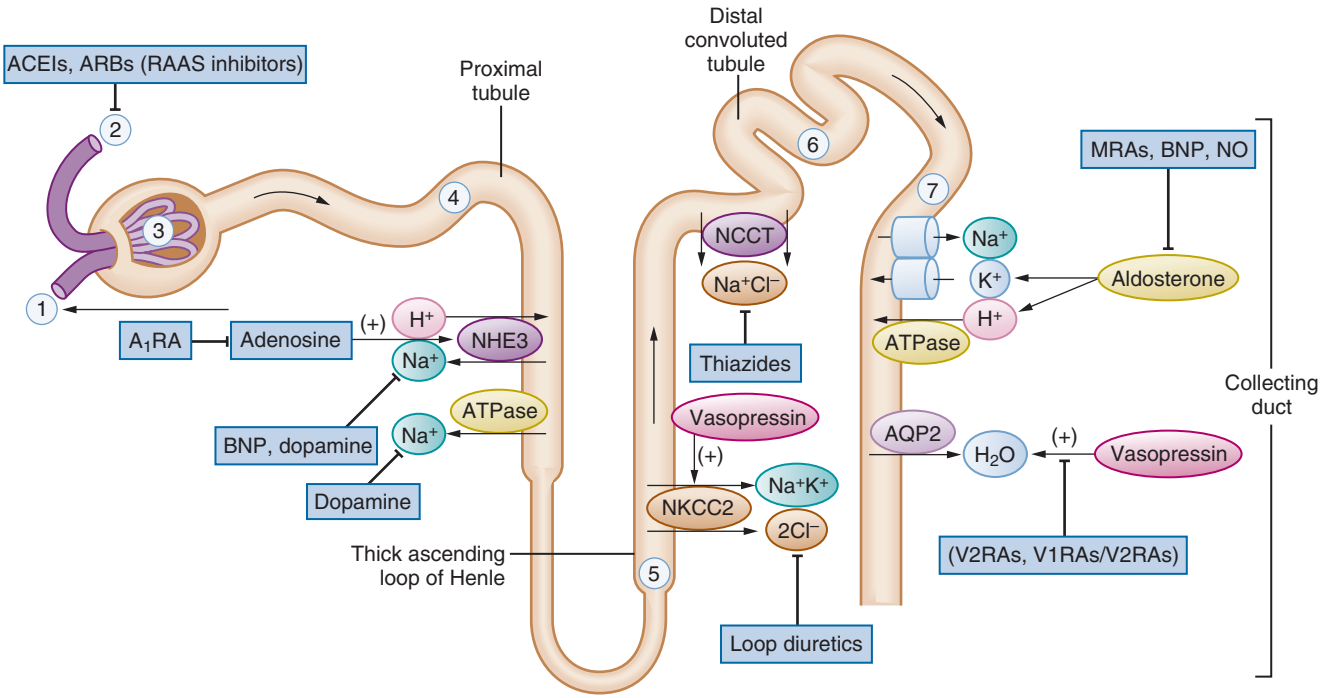
Spironolactone, amiloride, and triamterene are weak diuretics that act at the level of the collecting tubules and ducts. Most K^+ is secreted in the collecting ducts. Normally, aldosterone exerts its mineralocorticoid action via interaction with specific receptors, increasing insertion of Na^+ channels on the luminal membrane, thereby increasing activity of Na^+/K^+ and H^+ exchangers. Na^+ entering through the channels increases intracellular positive charge, and thereby extrusion of K^+ into the lumen. Potassium-sparing diuretics prevent these effects. Spironolactone is an aldosterone receptor inhibitor, whereas amiloride and triamterene block Na^+ channels. The result is a minor effect on Na^+ reabsorption but a major effect on K^+ retention. Thus they cause a minor increase in urinary Na^+ but a substantial decrease in urinary K^+ with possible hyperkalemia and acidosis. Clinical uses include hyperaldosteronism, hypertension, heart failure, and female hirsutism (spironolactone). The Na^+ channel blockers can be used as adjuncts to other diuretics. Amiloride is used for treatment of diabetes insipidus. Adverse effects include acidosis, hyperkalemia, azotemia, gynecomastia, and libido changes (spironolactone) and nephrolithiasis (triamterene).

Osmotic Diuretics

Mannitol is a non-reabsorbable sugar that acts as an osmotic diuretic, inhibiting water reabsorption in the proximal convoluted tubule (main site), thin descending loop of Henle, and the collecting ducts.[95,96] Mannitol produces a profound water diuresis in which water is lost in excess of electrolytes. However, retention of the hypertonic mannitol can induce further volume expansion. This can potentially cause pulmonary edema in patients with heart failure. Major clinical uses include early stages of oliguria, early phases of brain edema, and postischemic acute renal failure. It is also commonly used in neurosurgical anesthesia to provide good operating conditions.

Diuretics in Heart Failure

In acute decompensated heart failure, there are no differences between low and high furosemide dose strategies on outcome.



• **Fig. 42.9** Sites of action of drugs producing diuresis and natriuresis.[112] *Adenosine* produces afferent arteriolar vasoconstriction and increases Na^+ reabsorption in the proximal tubule. *Aldosterone* stimulates Na^+ and K^+ channels and Na^+,K^+-ATPase activity in the collecting tubules. *Vasopressin* stimulates activity of the $Na^+/K^+/2Cl^-$ cotransporter (*NKCC2,* also known as SLC12A1) and aquaporin 2 *(AQP2)*. Step 1 corresponds to afferent arteriolar vasodilatation. Step 2 corresponds to efferent arteriolar vasodilation. Step 3 corresponds to the increase in the glomerular filtration rate. Step 4 corresponds to inhibition of Na^+ reabsorption in the proximal tubule, and step 5 corresponds to the thick ascending loop of Henle. Step 6 corresponds to the distal tubule. Step 7 corresponds to the collecting ducts. Drugs that act at these sites are shown in colored boxes. *A_1RA,* Adenosine A_1 receptor antagonist; *ACEI*, angiotensin-converting enzyme inhibitor; *ARB,* angiotensin II type 1 receptor blocker; *ATPase,* adenosine triphosphatase; *BNP;* brain natriuretic peptide; *Cl^-,* chloride ion; *H^+,* hydrogen ion; *H_2O,* water; K^+, potassium ion; *MRA,* mineralocorticoid receptor antagonist; *Na^+,* sodium ion; *Na^+,K^+-ATPase,* sodium potassium adenosine triphosphatase; *NCCT,* Na^+/Cl^- cotransporter; *NHE3,* Na^+/H^+ exchanger 3 (also known as SLC9A3); *NO,* nitric oxide; *RAAS,* renin-angiotensin-aldosterone system; *V1RA/V2RA,* vasopressin receptor antagonist.

Because a high-dose strategy brings more relief of dyspnea, diuresis, and weight loss and a transient worsening of renal function without evidence of worse clinical outcome at 60 days, this regimen might be more beneficial.[97] The action of drugs producing diuresis and natriuresis in patients with heart failure are shown in Fig. 42.9.

Adverse Effects of Diuretics

At high doses diuretics produce adverse effects, such as hypotension, hypovolemia, electrolyte abnormalities, renal dysfunction, and neurohumoral activation. They can also contribute to longer hospitalization and higher mortality.[98] Major fluid and electrolyte disturbances can occur within the first 2 to 3 weeks of diuretic administration owing to attainment and maintenance of a new steady state.[99] Maximum diuresis always occurs with the first dose because as soon as fluid loss occurs, activation of Na^+ retaining mechanisms takes place.[100]

Volume Depletion

Although duration of Na^+ loss is limited, some patients have a large initial response of volume loss, particularly in patients with hypertension. In patients who remain edematous, the circulatory volume can be depleted and tissue perfusion reduced.

Azotemia

If circulating volume is depleted, renal perfusion can fall, which lowers GFR and elevates BUN and serum creatinine. This is called *prerenal azotemia* because the defect is in renal perfusion rather than in renal function.[101]

Hypokalemia

There is controversy whether mild hypokalemia caused by diuretics has any clinical significance. Some experts believe that hypokalemia can increase the risk of sudden death.[102,103] There is increased risk of ventricular arrhythmia.[104] A pertinent risk is when mild hypokalemia suddenly becomes profound. This can occur when epinephrine during a stress situation transfers K^+ into cells via β_2-receptor agonism.

Hyponatremia

Hyponatremia is a common side effect in edematous patients with heart failure or cirrhosis. Volume loss enhances release of ADH

and thereby causes dilution of Na^+. This is almost solely due to thiazide diuretics, which do not impair concentration ability. Other diuretics reduce the medullary osmolal gradient and concentrating ability.

Emerging Developments

In the perioperative period, maintenance IV solutions that minimize risks of deranged sodium and glucose homeostasis should be used. The fluid should have a sodium concentration close to the physiologic range to avoid perioperative hyponatremia, the most common complication of perioperative fluid therapy. The glucose content should be 1T to 2.5%, thereby avoiding hypoglycemia as well as hyperglycemia. The small amount of glucose in the solution also prevents lipolysis and the release of ketone bodies and free fatty acids.[105] Moreover, the solution should preferably have a balanced pH to avoid the hyperchloremic acidosis that occurs when larger amounts of 0.9% NaCl are given. Despite this, it is difficult to understand why 0.9% NaCl–based solutions are so frequently used worldwide.

In recent years, several studies have confirmed the safety of balanced IV solutions with physiologic sodium concentrations and 1% glucose as the preferred perioperative fluid,[106–109] which has been recommended by a European consensus statement from 2011 for intraoperative use.[110,111] Such a solution has recently been registered in Sweden for pediatric use in the treatment of isotonic dehydration; it contains glucose 10 mg/mL and is balanced and isotonic. Although fluids of this type are adequate for most pediatric patients, individual patient characteristics must, as always, be considered when choosing the type of fluid to use.

Key Points

- The major electrolytes (sodium, potassium, calcium, phosphate, and magnesium) are critical to basic physiologic functions, including action potential generation, cardiac rhythm control, muscle contraction, and energy storage, among many others.
- Hyponatremia is the most common electrolyte disorder in hospitalized patients; it is sometimes associated with severe symptoms and even death, especially when the hyponatremia is corrected too rapidly.
- New approaches differ from the previously advocated focus on separation between acute or chronic causes for hyponatremia. When seriously symptomatic, hyponatremia must be addressed expeditiously.
- Hypernatremia is categorized in terms of the adequacy of intravascular volume. It is treated first with volume resuscitation when needed followed by repletion of the free water deficit, and by addressing the underlying cause (e.g., diabetes insipidus, iatrogenic causes, and so on).
- No clear threshold has been defined for a level of hypokalemia below which safe conduct of anesthesia is compromised. There is no urgent need for K^+ replacement therapy in mild to moderate hypokalemia (3–3.5 mEq/L) in asymptomatic patients.
- Drugs are now the most common causes of hyperkalemia (e.g., nonsteroidal antiinflammatory drugs, ACE inhibitors, cyclosporin, and potassium-sparing diuretics) that occurs most commonly in patients with predisposing comorbidities (e.g., DM, renal insufficiency). In anesthesia practice, hyperkalemic cardiac toxicity is associated with the administration of succinylcholine to patients with upper motor neuron lesions or severe burns.
- Definitive treatment of hypocalcemia necessitates identification and treatment of the underlying cause. Symptomatic hypocalcemia usually occurs when serum ionized Ca^{2+} is less than 0.7 mM.
- The clinician should carefully consider whether mild, asymptomatic ionized hypocalcemia requires therapy, particularly in ischemic and septic states in which experimental evidence suggests that Ca^{2+} can increase cellular damage.
- Carbohydrate-induced hypophosphatemia (refeeding syndrome), mediated by insulin-induced cellular phosphate uptake, is the most commonly encountered type in hospitalized patients.
- Magnesium influences the release of neurotransmitters at the neuromuscular junction by competitively inhibiting the entry of Ca^{2+} into presynaptic nerve terminals.
- Diuretics reduce reabsorption of sodium chloride at different sites in the nephron, thereby increasing urinary Na^+ and water losses.
- Diuretics are useful in a variety of conditions, such as edematous states, hypertension, heart failure, renal dysfunction, hypercalcemia, nephrolithiasis, glaucoma, and mountain sickness.

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Blood and Coagulation

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CHAPTER OUTLINE

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- Reduction of Natural Anticoagulant Factors
- Fibrinolysis Modulation
- Other Inherited Conditions
- Acquired Risk Factors
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  - *Reductions in Coagulation Inhibitors*
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Hemostatic Testing
- Point-of-Care Coagulation Testing
- Transfusion Algorithms and Massive Transfusion

Blood Conservation

Hemostasis is a critical homeostatic mechanism of survival that involves vascular, cellular, and plasma components that interact to stop bleeding.[1,2] Vascular effects include vasoconstriction, expression of procoagulant factors such as tissue factor, and loss of normal anticoagulant functions of the endothelium.[2,3] Coagulation and clot formation occur by cellular and humoral factors that interact together with local and systemic factors. Surgery produces complex alterations and defects in hemostatic mechanisms, particularly in trauma, cardiac surgery with or without cardiopulmonary bypass, major orthopedic surgery, and neurosurgery. In many patients, multiple quantitative and qualitative hemostatic abnormalities develop as part of surgery, tissue injury, and complex underlying medical conditions. Additionally, the increasing use of multiple anticoagulation agents to treat cardiovascular disease contributes to preexisting perioperative hemostatic defects and increases the potential for bleeding. Furthermore, massive bleeding can produce an acquired hemostatic defect called massive transfusion coagulopathy that is characterized by tissue injury, dilutional hemostatic changes, hypothermia, acidosis, and multiorgan dysfunction.[2]

Managing hemostatic dysfunction and bleeding perioperatively requires an understanding of underlying hemostatic mechanisms. Tissue injury and the stress response activate fibrinolysis that can further contribute to coagulopathy and bleeding.[3] This chapter reviews the basis of normal hemostasis, the procoagulant and anticoagulant changes that occur in surgical patients, as well as perioperative coagulation testing and treatment of bleeding.

Normal Hemostatic Mechanisms

Complex interactions among coagulation proteins, platelets, and the vascular endothelium maintain normal hemostasis (Fig. 43.1). The vascular endothelium plays a major role in preventing clotting; it presents an important anticoagulation interface with circulating blood. Multiple substances are released to prevent activation of both cellular and humoral components of hemostasis. Understanding hemostasis, perioperative bleeding, and treatment of coagulopathy in the current era requires knowledge of the multiple interactions that occur between molecular and cellular components of the coagulation cascade.

Hemostasis, which means the "halting of blood," protects the individual from massive bleeding secondary to minor trauma. In pathologic states, however, thrombosis can occlude the microvasculature, leading to organ ischemia. Hemostasis is therefore highly regulated by a number of factors, including (1) vascular extracellular matrix and alterations in endothelial reactivity, (2) platelets, (3) coagulation proteins, (4) inhibitors of coagulation, and (5) fibrinolysis. These involve tissue factor release, generation of factor VIIa, platelet activation, and multiple cellular and humoral amplification pathways.[2–6] Prostacyclin, tissue plasminogen activator (tPA), heparan sulfate, antithrombin III, protein C, and endothelium-derived relaxing factor are normally expressed or secreted to inhibit platelet activation, fibrin formation, and to provide vascular patency.[1,2] However, if a blood vessel is cut or damaged, tissue factor and other promoters of coagulation are released or exposed to provide a thrombotic surface. Exposure of subendothelial vascular basement membrane activates platelets, and expression of tissue factor also activates thrombin generation and signals other inflammatory pathways.

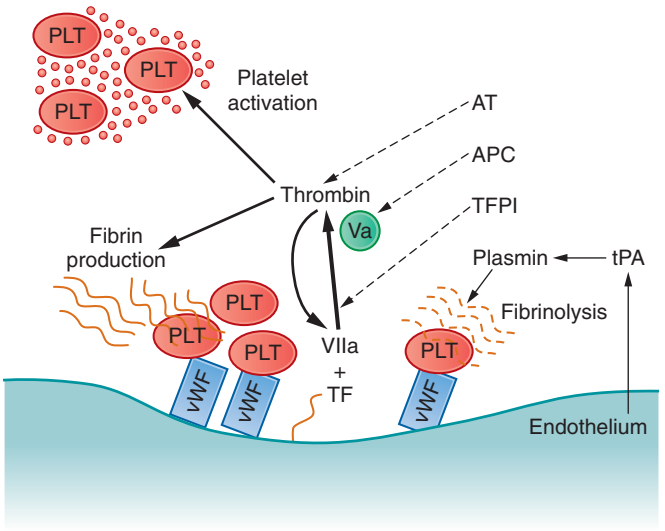
Platelet activation is an important mechanism for initiation of the coagulation cascade. Receptors on platelets bind to the damaged

Abstract

Hemostasis is a critical homeostatic mechanism of survival that involves vascular, cellular, and plasma components that interact to stop bleeding. Vascular effects include vasoconstriction, expression of procoagulant factors such as tissue factor, and loss of normal anticoagulant functions of the endothelium. Coagulation and clot formation occur by cellular and humoral factors that interact together with local and systemic factors. Surgery produces complex alterations and defects in hemostatic mechanisms, particularly in trauma, cardiac surgery with or without cardiopulmonary bypass, major orthopedic surgery, and neurosurgery. In many patients, multiple quantitative and qualitative hemostatic abnormalities develop as part of surgery, tissue injury, and complex underlying medical conditions. Additionally, the increasing use of multiple anticoagulation agents to treat cardiovascular disease contributes to preexisting perioperative hemostatic defects and increases the potential for bleeding. Furthermore, massive bleeding can produce an acquired hemostatic defect called massive transfusion coagulopathy that is characterized by tissue injury, dilutional hemostatic changes, hypothermia, acidosis, and multiorgan dysfunction.

Keywords

bleeding
blood conservation
coagulation testing
coagulopathy
disseminated intravascular coagulation
hemostasis
hypercoagulability



• **Fig. 43.1** Schematic summary of procoagulant and anticoagulant processes. Initial plug formation begins with von Willebrand factor *(vWF)* binding to collagen at the site of injury, which acts as a bridge for platelets to adhere. At the same time, exposed tissue factor *(TF)* at the site of injury binds with small amounts of circulating activated factor VII *(FVIIa)* to produce thrombin via the tissue factor (extrinsic) pathway. Thrombin activates a positive feedback loop by producing more of itself, cleaves fibrinogen to insoluble fibrin, and activates platelets that release more procoagulant and inflammatory factors. The process is kept in check by anticoagulant forces. Away from the site of injury, antithrombin *(AT)* inhibits thrombin. Additionally, activated protein C *(APC)* destroys factor V (*Va*—needed for the tissue factor pathway), and tissue factor pathway inhibitor *(TFPI)* destroys TF-FVIIa complexes. The endothelium releases tissue plasminogen activator *(tPA)* that cleaves plasminogen into plasmin to initiate fibrinolysis. *PLT,* Platelet.

blood vessel by forming a bridge with von Willebrand factor (vWF) to initiate platelet adhesion. Once platelets adhere, they undergo surface receptor changes that cause platelets to aggregate. Once platelets aggregate, they expose factors on their surface that provides a substrate for activation of the coagulation cascade and formation of the early hemostatic plug. Platelets play vital roles in maintaining vascular hemostasis. Any abnormality in platelet number or function poses a significant risk for perioperative coagulopathy.

Hypercoagulability

Normal hemostasis is a balance between procoagulant and anticoagulant mechanisms. The coagulation system ensures that bleeding does not continue indefinitely after vascular injury. This is balanced by thromboresistant forces involving anticoagulant proteins to control clot formation and fibrinolytic proteins to remove clot once vascular injury has been repaired. A proper balance between these systems must be maintained to ensure the fluid nature of blood, yet be readily activated when pathologic activation occurs.[6]

In surgical patients, especially postoperatively, there is potential for a hypercoagulable state. Hypercoagulability, also known as *thrombophilia* or a *prothrombotic state*, is a condition in which blood clots more readily than normal. It results from a shift of the normal equilibrium of procoagulant and anticoagulant forces in favor of coagulation.[6,7] Although arterial and venous thrombi were once thought to represent distinct problems, patients with hypercoagulability can be at risk for both, and it has been suggested that hypercoagulability represents a spectrum of disease rather than separate clinical entities.[8-10] In the perioperative environment, clinicians are usually aware and concerned about the risk of bleeding; however, hypercoagulability is also a potential cause of postoperative adverse outcomes that is often overlooked.[6,11,12]

Risk factors for hypercoagulability can be inherited or acquired, and are caused by either increasing procoagulant activity and/or decreasing anticoagulant or fibrinolytic activity.[6,13] About 80% of patients with venous thromboembolism (VTE) have at least one underlying risk factor.[14] Because of this increased risk, hypercoagulable patients often receive prophylactic anticoagulation therapy.[15,16]

Inherited Risk Factors

Most patients with inherited risk factors for hypercoagulability are at risk to develop venous thromboembolic events early in life.[17] One of the most common risk factors is inherited antithrombin deficiency.[7] Other conditions, for example, the prothrombin G20210A mutation, are continually being discovered.[2,7,18] Inherited risk factors can enhance procoagulant effects, reduce natural anticoagulation, impair fibrinolysis, or have other potential effects.[7] Fig. 43.2 presents an overview of the interaction of coagulation and fibrinolytic pathways and illustrates how different inherited risk factors modify hemostasis.

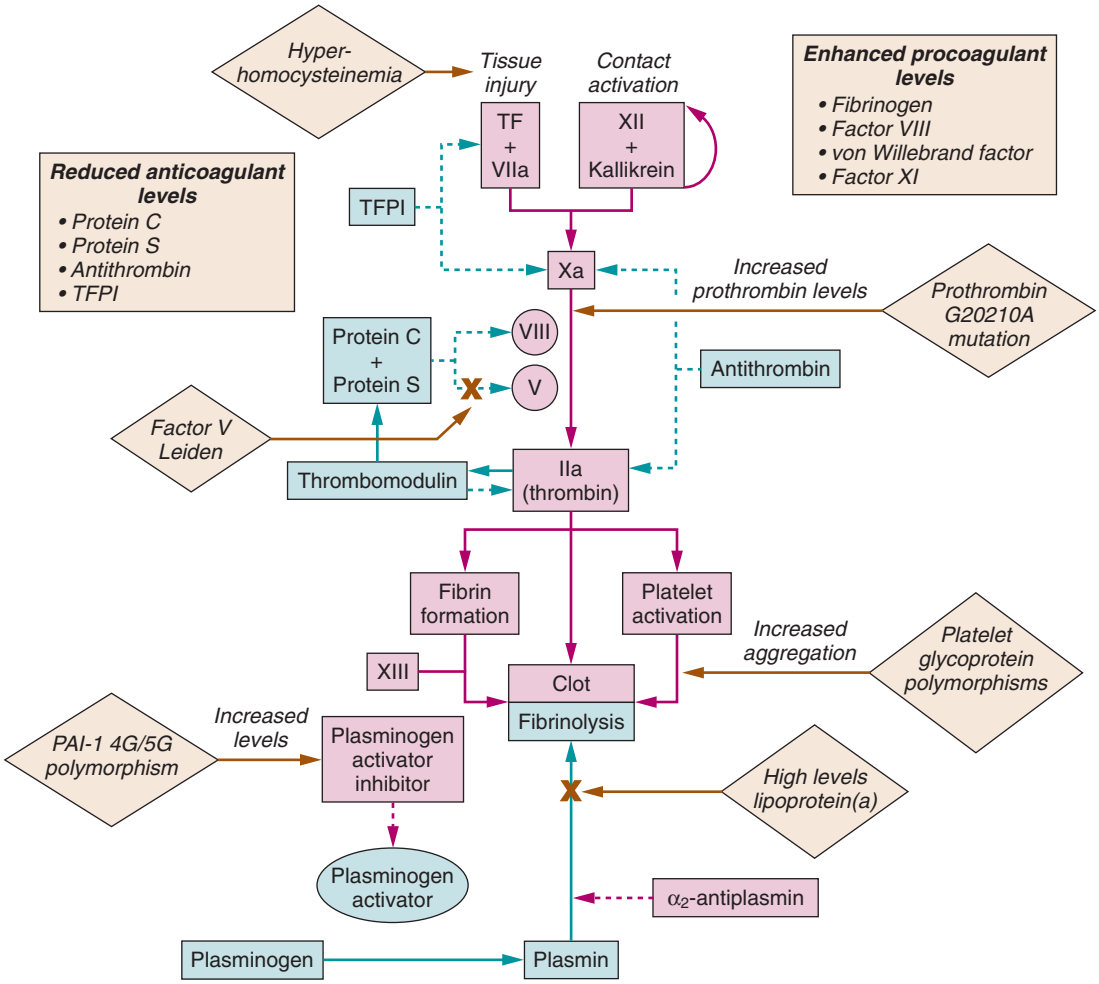
Increased Procoagulant Effects

The most common inherited risk factors for VTE are factor V (FV) Leiden, present in approximately 5% of the population, and the prothrombin G20210A mutation, present in approximately 2% of Caucasians.[19,20] In the FV Leiden mutation, an amino acid replacement modifies activated procoagulant FV so that it is no longer inactivated or inhibited by activated protein C. In patients with FV Leiden, thrombotic risk is increased approximately 3-fold in heterozygotes, 18-fold in homozygotes, and 9-fold overall compared with individuals without the mutation.[6] Patients heterozygous for the prothrombin G20210A mutation have higher plasma levels of prothrombin, the precursor for thrombin, and an approximately threefold greater risk for VTE; homozygous individuals for the G20210A mutation are rare.[6,21,22] Whether FV Leiden and prothrombin G20210A carriers have increased risk for arterial thrombosis is less clear.[23]

Other common procoagulant effects include fibrinogen abnormalities caused by increased levels or structural variants that are either more or less susceptible to clot formation, known as *dysfibrinogenemia*. Fibrinogen is an increasingly important target for therapeutic interventions in bleeding and coagulopathy. Similarly, patients with the highest plasma fibrinogen concentration have an approximately twofold increased risk for arterial thrombosis, and stroke patients with fibrinogen levels of 450 mg/dL or greater have poorer functional outcomes.[24,25] Hyperfibrinogenemia also increases the risk for VTE.[26,27] Dysfibrinogenemias can also cause hypercoagulability if the resulting fibrin molecules fail to inhibit thrombin or are less susceptible to cleavage by plasmin.[28,29] Elevated coagulation factor levels, including vWF and FVIII, can occur in patients with unexplained VTE, and increased FVIII levels are a risk factor for arterial vascular events.[30–32]

Reduction of Natural Anticoagulant Factors

Two important circulating anticoagulants are protein C and protein S. These are vitamin K–dependent proteins that inhibit the activated



• **Fig. 43.2** Inherited risk factors for hypercoagulability. Procoagulant forces *(red)* and natural anticoagulant/fibrinolytic forces *(blue)* are shown. *Dashed lines* indicated an inhibitory effect. Inherited risk factors are presented in diamond shapes with lettering and arrows indicating the mechanism for the hypercoagulable effect. "X" denotes a specific block in a pathway. See text for full details. *PAI,* Plasminogen activator inhibitor; *TF,* tissue factor; *TFPI,* tissue factor pathway inhibitor. (Modified with permission from Sniecinski RM, Hursting MJ, Paidas MJ, et al. Etiology and assessment of hypercoagulability with lessons from heparin-induced thrombocytopenia. *Anesth Analg*. 2010;112:46–58.)

procoagulant FV and FVIII.[6] Inherited qualitative or quantitative deficiencies of protein C and protein S increase the risk for VTE by 5- to 10-fold.[33] Importantly, large loading doses of the vitamin K antagonist warfarin, without concomitant heparin therapy, can result in a transient procoagulant state by depleting proteins C and S. This most commonly manifests as microthrombi within cutaneous vessels, a condition known as "warfarin skin necrosis."

Antithrombin (formerly called antithrombin III) is a serine protease inhibitor that avidly binds to thrombin; this interaction is facilitated by heparin and, along with its inhibition of FXa, the primary mechanism for heparin's anticoagulant action. Heparin and related glycosaminoglycans are normally present on endothelial surfaces or administered therapeutically. Heterozygous antithrombin deficiency is associated with approximately 50% of normal levels, whereas homozygous antithrombin deficiency is likely always fatal in the newborn or in utero, and is exceedingly rare.[34] Acquired antithrombin deficiency can also occur after prolonged heparin administration, or in patients with sepsis or disseminated intravascular coagulation (DIC).[35] Patients with antithrombin deficiency are at an increased risk for thrombotic events.[36] Whether antithrombin should be replaced in prolonged cardiopulmonary bypass operations remains an area of active investigation.

Fibrinolysis Modulation

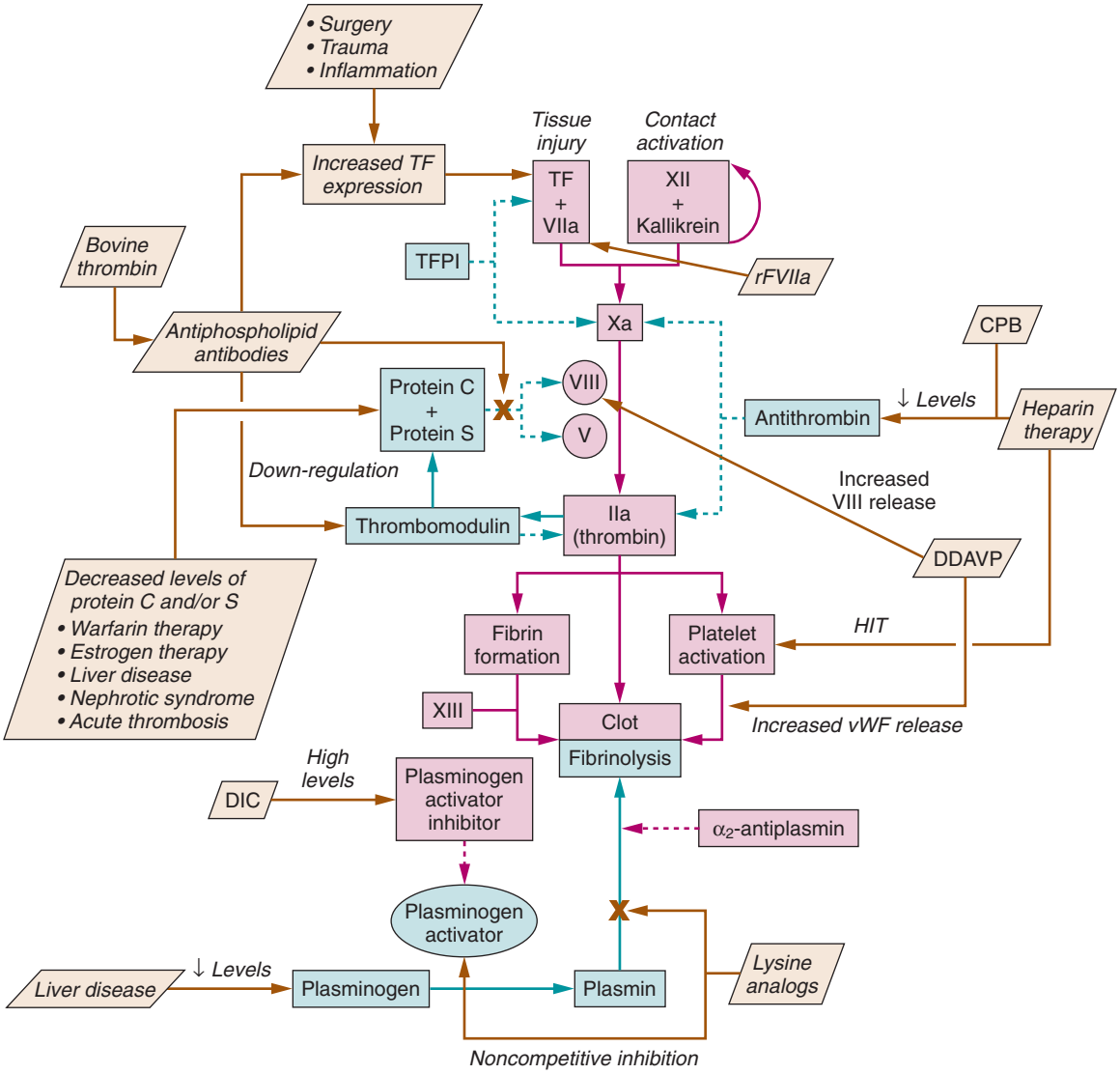
Fibrinolysis regulates the extent of clot formation and vascular patency as part of hemostatic regulation. After tissue and vascular injury, multiple hemostatic mechanisms are initiated to modulate fibrinolysis. An important circulating serine protease inhibitor that regulates fibrinolysis is plasminogen activator inhibitor-1 (PAI-1) and a specific polymorphism (4G/5G) correlates with higher plasma levels.[37] The 4G allele is associated with an increased risk of VTE but only when combined with another genetic risk factor for thromboembolic complications.[38] Abnormalities in tPA, another important regulator of fibrinolysis, are associated with a twofold to threefold increased risk of myocardial infarction and thrombotic stroke.[6] Inherited deficiencies of plasminogen and polymorphisms affecting plasma levels of thrombin-activatable fibrinolysis inhibitor are reported, but their associations with thrombotic risk remain unclear.[6]

Other Inherited Conditions

Increased levels of homocysteine are thought to produce endothelial dysfunction and could have variable effects on arterial or venous thrombosis and potentially other vascular ischemic events.[6] Hyperhomocystinemia can also be acquired in individuals with folic acid deficiency, and folate therapy was once thought to reduce ischemic cardiovascular disease. Other important polymorphisms exist for regulatory glycoproteins on platelets. Lack of the glycoprotein Ib/IX complex or vWF receptor results in Bernard-Soulier disease. Common deficiencies include abnormalities of the IIb/IIIa receptor that binds fibrinogen and allows platelet cross-linking, known as Glanzmann thrombasthenia. Patients with these platelet glycoprotein genetic variants can still have ischemic cardiovascular disease despite their relative platelet dysfunction, although some reports suggest reduced cardiovascular risk.[11,39]

Acquired Risk Factors

Acquired risk factors are usually transient, yet can confer higher thrombotic risk than genetic disorders. Like inherited factors, some acquired conditions enhance procoagulant effects (e.g., heparin-induced thrombocytopenia), whereas others decrease levels of natural anticoagulants (e.g., antiphospholipid antibodies). However, most acquired risk factors are multifactorial and have mechanisms that remain to be fully characterized. We have grouped the acquired risk factors into three broad categories: disease states, patient-related causes, and pharmacologic causes (Fig. 43.3).



• **Fig. 43.3** Acquired risk factors for hypercoagulability. Procoagulant forces *(red)* and natural anticoagulant/fibrinolytic forces *(blue)* are diagrammed. Dashed lines indicate an inhibitory effect. Acquired risk factors are presented in diamond shapes with lettering and arrows indicating the mechanism for the hypercoagulable effect. "X" denotes a specific block in a pathway. Note that some acquired risk factors have multiple effects; see text for full details. *CPB,* Cardiopulmonary bypass; *DDAVP,* desmopressin; *DIC,* disseminated intravascular coagulation; HIT, heparin-induced thrombocytopenia; *rFVIIa,* recombinant factor VIIa; *TF,* tissue factor; *TFPI,* tissue factor pathway inhibitor. (Modified with permission from Sniecinski RM, Hursting MJ, Paidas MJ, et al. Etiology and assessment of hypercoagulability with lessons from heparin-induced thrombocytopenia. *Anesth Analg*. 2010;112:46–58.)

Disease States Associated With Hypercoagulability

Antiphospholipid antibodies, including lupus anticoagulants, anticardiolipin antibody, and anti–β_2-glycoprotein 1 antibody are associated with increased risk of thrombosis.[6] Patients with lupus anticoagulants are actually hypercoagulable despite increased prothrombin times, and have increased risk for both arterial and venous thrombosis and miscarriage.[6] Multiple mechanisms are responsible for increased thrombotic risk with antiphospholipid antibodies and are thought to be due to decreased thrombomodulin expression, increased tissue factor expression, and impairment of the protein C anticoagulant pathway.[40] Patients with thrombosis (arterial or venous) or repeated pregnancy loss plus antiphospholipid antibody detected on at least two occasions at least 12 weeks apart meet diagnostic criteria for antiphospholipid syndrome.[41] Patients with known antiphospholipid antibodies are at risk for recurrent thrombotic events and require ongoing anticoagulation, usually with warfarin.[6]

Other important factors that contribute to hypercoagulability include renal and hepatic dysfunction, although these are commonly considered risks for bleeding. Severe hepatic dysfunction and cirrhosis lead to decreased synthetic capabilities and decreased levels of anticoagulant factors, including antithrombin, protein C, protein S, and plasminogen.[6] Endothelial dysfunction, especially with renal failure and often pulmonary and portal vascular dysfunction, also occur. This, in turn, increases platelet activation and is an important cause of hypercoagulability.[6] In nephrotic syndrome, fibrinogen levels are increased and antithrombin levels are low, increasing the potential for thrombosis.[6]

Another important clinical setting is blood stasis, which commonly occurs with postoperative immobility or low cardiac output associated with heart failure—important risk factors for hypercoagulability. Although a low-flow state is a component of the Virchow triad, it alone does not create thrombosis. The importance of the other two Virchow factors— vessel wall abnormalities and dysfunctional blood constituents—is now becoming clear at the molecular level.[6] Metabolic syndrome characterized by abdominal obesity, hypertension, elevated glucose, and increased cholesterol levels is associated with endothelial dysfunction and increased platelet aggregation.[42] Cancer can have multiple causes for hypercoagulability, including cells that release microparticles to promote fibrin deposition.[43] Advanced age is associated with procoagulant changes, including vascular dysfunction, increased fibrinogen levels, increased FVII, impaired fibrinolytic activity, and increased platelet aggregation.[6] Many of these factors can be additive with complex interactions that are not well understood. Routine VTE prophylaxis is therefore an important part of perioperative management.

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is an important antibody-mediated prothrombotic complication of heparin therapy that occurs in 0.5% to 5% of patients treated with heparin for at least 5 days (see Chapter 45).[16,44] HIT is characterized by an otherwise unexplained drop in platelet count by 50% or more, often to less than 150,000/μL and frequently accompanied by thrombosis, plus the presence of HIT antibodies.[44] When HIT is suspected, heparin, including low-molecular-weight heparin treatment, should be discontinued, and alternative anticoagulation therapy initiated even before laboratory confirmation.[16,44]

HIT is mediated by antibodies to a complex of heparin and platelet factor 4 (PF4). Antibodies recognize antigenic sites newly exposed on PF4 when it is conformationally modified by binding to heparin. Platelets are activated by the Fc domain of the immunoglobulin G (IgG) in the heparin-PF4 immune complexes, and release microparticles that promote thrombin formation and thrombosis. Thrombocytopenia, excessive thrombin generation, and a prothrombotic state ensue. Antibody-mediated endothelial injury and tissue factor production further increase the prothrombotic state.[44]

Up to 7% to 50% of heparin-treated patients generate heparin-PF4 antibodies, especially after cardiovascular surgery. HIT antibodies circulate with a median half-life of approximately 90 days. The presence and level of HIT antibodies, regardless of thrombocytopenia, are associated with increased morbidity or mortality in various clinical settings. Clinical HIT occurs in 1% to 5% of patients administered unfractionated heparin and less than 1% of patients administered low-molecular-weight heparin. Cardiac transplant and neurosurgery patients (11% and 15%, respectively), as well as orthopedic patients, are at increased risk of HIT.[44]

HIT increases the risk of thrombosis, including deep VTE, pulmonary embolism, myocardial infarction, stroke, and limb artery occlusion requiring amputation. The overall risk for thrombosis in patients with HIT is 38% to 76%. Other risk factors for HIT-related thrombosis include female gender, malignancy, higher-titer heparin-PF4 antibodies, and more severe thrombocytopenia. Other complications include skin lesions at heparin injection sites, DIC, warfarin-associated venous limb ischemia, and acute systemic reactions after heparin bolus. Although counterintuitive, bleeding is rare even in the presence of severe thrombocytopenia.[44]

HIT should be suspected whenever the platelet count drops by 50%, or new thrombosis occurs in a patient 5 to 14 days after the start of heparin therapy. Other causes of thrombocytopenia (e.g., sepsis, mechanical destruction with an intraaortic balloon pump or with extracorporeal circulation, or another drug-induced thrombocytopenia) should be excluded. In "rapid-onset" HIT, the platelet count begins to drop minutes to hours after heparin exposure, usually owing to heparin-PF4 antibodies from a previous heparin exposure within the prior 3 months. HIT should also be suspected if acute systemic reactions, such as hypotension, pulmonary hypertension, and/or tachycardia, occur 2 to 30 minutes after intravenous heparin bolus. This can be observed intraoperatively and can present as anaphylaxis, usually accompanied by acute thrombocytopenia.[16,44,45] HIT can also occur days to weeks after stopping heparin ("delayed-onset HIT"), and should be considered if a recently hospitalized, heparin-treated patient presents with thrombosis.[44] For suspected HIT, laboratory testing for heparin-PF4 antibody is recommended. Because of the high thrombotic risk early in HIT, treatment should not be withheld while awaiting laboratory results.[44]

The recommended treatment for strongly suspected or confirmed HIT, with or without complicating thrombosis, is stopping heparin and initiating a nonheparin alternative anticoagulant. The mainstay agents include intravenous administration of a direct thrombin inhibitor, either argatroban or bivalirudin.[46] Other heparin sources such as catheter flushes and heparin-coated devices should be eliminated. Different direct thrombin inhibitors are approved in the United States for use in HIT patients without initial thrombosis (argatroban), in HIT patients with thrombosis (argatroban), and in patients with or at risk of HIT undergoing percutaneous coronary intervention (argatroban, bivalirudin). Previously used agents that were derivatives of the leech protein hirudin are no longer available (desirudin, lepirudin). The more recently approved direct oral anticoagulants (apixaban, dabigatran, edoxaban, rivaroxaban) provide potential alternatives for venous thromboembolic prophylaxis in

patients but not as immediate therapies for HIT therapy. Recent evidence-based guidelines from the American College of Chest Physicians for the use of these alternative anticoagulants in patients with HIT in noninterventional and interventional settings have been reported.[16] Alternative nonheparin anticoagulant strategies are required in HIT patients who need intraoperative anticoagulation. If heparin use is unavoidable or planned, the heparin exposure should be limited to the surgery itself, with alternative anticoagulation used preoperatively and postoperatively. If cardiac surgery is required, prospective studies have evaluated bivalirudin as the most investigated and useful alternative, although plasmapheresis has also been reported.[16]

Hypocoagulability: Perioperative Bleeding

Bleeding in surgical patients is a common and multifactorial problem. Surgery-induced tissue injury with both large vessel bleeding and microvascular bleeding can occur. Patients often have acquired defects that can be complicated by the surgical insult, or coagulation abnormalities that occur owing to antiplatelet or anticoagulant drug use or massive blood loss. Major coagulation abnormalities occur perioperatively and are influenced by multiple factors, including type of surgery, cardiopulmonary bypass, and preexisting abnormalities. Coagulopathic states and risk factors predisposing to surgical bleeding are listed in Tables 43.1 and 43.2.

Patients with atherosclerotic cardiovascular disease often receive anticoagulation and/or antiplatelet therapies that interfere with hemostasis (see Chapter 45).[47-50] Patients can also receive prophylactic anticoagulation therapy for atrial fibrillation, VTE prophylaxis, or prosthetic cardiac valves. Surgical patients have acquired changes in hemostasis that contribute to postoperative bleeding, including activation of coagulation, fibrinolytic, and inflammatory pathways.[46,47,51–53] Trauma and obstetric patients can also develop massive hemorrhage.[4,53,54] Therapies that prevent clot from forming in pathologic states also interfere with normal hemostasis, an important mechanism protecting patients from exsanguination during surgery.

TABLE 43.1 Coagulopathic States Associated With Increased Risk for Bleeding

Hemophilia
Inherited platelet disorders
von Willebrand disease
Liver failure
Renal failure (uremia)
Disseminated intravascular coagulation
Dilutional coagulopathy
Anticoagulant and antiplatelet therapy
Other coagulation disorders (factor deficiencies)

TABLE 43.2 Risk Factors for Bleeding in Surgical Patients

Advanced age
Small body size or preoperative anemia (low red cell volume)
Antiplatelet or antithrombotic drugs
Preexisting coagulopathy
Prolonged operation including prolonged cardiopulmonary bypass time
Emergency operation
Comorbidities: heart failure, chronic obstructive pulmonary disease, hypertension, peripheral vascular disease, renal failure, liver failure

Risk Factors for Bleeding

Perioperative bleeding with increased transfusion requirements is caused by patient-related, procedure-related, and process-related factors.[55] However, most studies do not distinguish between red blood cell (RBC) and hemostatic factor transfusion. Important indicators of high risk for bleeding and transfusion requirements include (1) advanced age, (2) low preoperative RBC volume (preoperative anemia or small body size), (3) preoperative antiplatelet or antithrombotic treatment, (4) reoperation or complex procedures, (5) emergency operations, and (6) noncardiac patient comorbidities (see Table 43.2).[55]

Patient-Related Causes of Bleeding

Risk for bleeding is increased by acquired or congenital coagulopathies, including hemophilia, complex procedures (e.g., multilevel spine surgery, combined valve/coronary revascularization, aortic dissection, and major aortic surgery), repeat cardiac and orthopedic procedures, and sepsis with thrombocytopenia. Certain patients have an accentuated response to antiplatelet drugs. Thrombocytopenia from whatever cause (defined as platelet count <50,000/μL) leads to a high risk of excessive bleeding; however, this also depends on platelet function, which is variable and difficult to measure. Anemia also contributes to bleeding in complex ways. Congenital or acquired qualitative platelet defects increase bleeding risk (see earlier text).

Common Inherited Hemostatic Disorders

There are multiple disorders of hemostasis not involving platelets that are classified by whether they increase or decrease coagulation. Procoagulant disorders (see earlier) are complex, in that some disorders may have both hemorrhagic and thrombotic manifestations. Other disorders also produce bleeding disorders (see Table 43.1). Hemophilia and von Willebrand disease (vWD) are the most common.

Hemophilia A is X-linked coagulopathy owing to FVIII deficiency. It represents the most common form of hemophilia, present in about 1 in 5000 to 10,000 men; hemophilia B, a FIX deficiency, occurs in approximately 20,000 to 34,000 men. Hemophilia is a recessive, sex-linked X chromosome disorder that occurs more commonly in men than women because men have a single X chromosome. There has been significant progress in hemostatic therapy with the development of highly purified, virally inactive plasma-derived and recombinant factors VIII and IX (see Chapter 44). These products have also facilitated perioperative management of these patients when they require surgery. Patients with hemophilia who are treated with factors can develop antibody inhibitors, and the advent of factor concentrates and the activated factors (e.g., recombinant FVIIa) has greatly facilitated management. The perioperative management of these patients requires involvement of a hematologist familiar with the specific guidelines established for these patients. Guidelines for the management of hemophilia are available at www.wfh.org.

vWD and its acquired form are rare bleeding disorders that can lead to unforeseen bleeding in surgical patients.[56] The diseases related to defects in vWF, a critical circulating macromolecular protein necessary for platelet function, are classified as (1) partial quantitative deficiency (type I), (2) qualitative deficiency (type II), or (3) total deficiency (type III). Qualitative vWD type II is further

divided into four variants based on the characteristics of the involved vWF. Each form of vWD corresponds to specific mechanisms, with corresponding clinical features and therapeutic requirements. Type I often has variable presentations and may be responsive to desmopressin therapy, whereas qualitative and quantitative deficiencies might require replacement therapy. vWF facilitates platelet adhesion to subendothelial vascular basement membrane and platelet aggregation under high shear stress associated with arterial flow, and also functions as a carrier for coagulation FVIII in the plasma.[56]

There is also an acquired form of vWD that can present as a result of reduced synthesis, increased removal, or generation of subunits/multimers with reduced activity. With inherited vWD, patients have a lifelong history of bleeding episodes, whereas the acquired form can present with acute or refractory bleeding episodes perioperatively. Patients with aortic stenosis and ventricular assist devices often develop acquired forms of vWD. Typically, no family history of bleeding is noted; however, acquired vWD presents as the hereditary form with mucocutaneous and increased perioperative bleeding.[57]

Laboratory evaluation of vWD is based on measurement of vWF activity and antigens as well as multimeric analysis of vWF. Treatment options include desmopressin, cryoprecipitate, factor VIII/vWF concentrates, intravenous immunoglobulin, and plasma exchange. Because the half-life of vWF is reduced in acquired forms, high doses of FVIII/vWF concentrate administered at frequent intervals can be necessary during bleeding episodes. In cases unresponsive to standard therapy, recombinant activated FVII (rFVIIa) might be an alternative option. The most effective therapy is treating the underlying disease.[57]

Physician-Related Factors

Surgical technique is an important factor influencing perioperative bleeding and blood transfusion.[58] Multiple factors influence perioperative bleeding risk, including differences in surgical technique and operating time. Differences in the threshold for transfusion therapy and surgical reexploration of excessive postoperative hemorrhage also contribute to variability in transfusion practices. Transfusion algorithms and practices vary regionally and between centers.[54,59,60]

Procedure-Related Factors

Procedure-related factors increase the risk for both bleeding and perioperative morbidity and mortality. Repeat procedures have higher transfusion rates, and the type and urgency of operation are independent predictors for transfusion. Cardiopulmonary bypass impairs platelet function and coagulation. Complex, long procedures, including aortic surgery, major oncologic surgery, bilateral internal mammary artery grafts, aortic valve replacement with pulmonary autograft (Ross procedure), and ventricular assist devices, are examples of complex surgeries associated with a high risk of bleeding.[55] Although off-pump cardiac surgery can be associated with an overall reduction in transfusion requirements, with extensive surgery, blood loss, and hemodilution, these patients are also at risk for bleeding.[61,62] Repeat procedures and long operating times because of surgical complexity increase the risk of bleeding from multiple causes, including hypothermia.

Pharmacologic Factors

Preoperative prophylactic antiplatelet and anticoagulant treatment is associated with increased perioperative bleeding and transfusion (see Chapter 45). Preoperative antiplatelet regimens must be managed for the maximum cardioprotective benefit while minimizing the risk of hemorrhage.[55,63] Dual-antiplatelet therapy with $P2Y_{12}$ receptor inhibitors (clopidogrel, prasugrel, ticagrelor) and aspirin therapy result in higher postoperative bleeding, more transfused blood products, and a higher rate of reexploration for mediastinal hemorrhage during emergency coronary artery bypass grafting.[64–66] Current guidelines recommend stopping $P2Y_{12}$ receptor inhibitors 5 to 7 days before cardiac operations if possible.[63,67] Newer anticoagulation agents, including dabigatran, rivaroxaban, and apixaban, should be stopped as recommended by prescribing information.[68]

Disorders of Hemostasis: Disseminated Intravascular Coagulation

DIC occurs after pathologic inflammatory states such as sepsis or tissue injury.[35,69] Excessive activation known as DIC occurs when normal anticoagulation mechanisms both in plasma and on vascular endothelium are incapable of modulating or inhibiting the excessive thrombin formation. The pathologic hallmark of DIC is microvascular fibrin deposition and thrombotic microangiopathy. Platelet activation and sequestration and a consumptive coagulopathy deplete platelets and hemostatic factors. Patients with DIC have a complex coagulopathic state characterized by thrombocytopenia, consumptive coagulopathy, and hypofibrinogenemia.

Thrombocytopenia

Thrombocytopenia is a diagnostic feature of DIC. Platelet counts of less than 100,000/μL occur in 50% to 60% of patients and of less than 50,000/μL in 10% to 15% of patients. However, there are multiple perioperative causes of thrombocytopenia. Dilutional thrombocytopenia is common following resuscitation of major bleeding after trauma and surgery. Intracranial bleeding in DIC occurs in only 0.3% to 0.5% of patients. Thrombocytopenia is also an independent predictor of intensive care unit (ICU) mortality (relative risk 1.9–4.2).[69] Thrombocytopenia lasting more than 4 days in the ICU or a 50% reduction of platelet counts during an ICU stay is associated with a fourfold to sixfold increase in mortality. HIT can also contribute.

Coagulopathy

Reduction in coagulation factor is another hallmark of DIC. Impaired synthesis owing to hepatic dysfunction or vitamin K deficiency, and consumption of coagulation proteins with bleeding can also contribute to DIC. Coagulation factor levels correlate with DIC severity. This manifests by prolonged prothrombin time (PT) or activated partial thromboplastin time (aPTT). Increased PT or aPTT occurs in 14% to 28% of ICU patients but is part of the diagnostic criteria in DIC. FVIII levels can be increased in patients with DIC. In DIC and similar syndromes, insufficiency of the von Willebrand cleaving protease ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) can occur. This enzyme normally cleaves the prothrombotic ultralarge vWF multimers in plasma that facilitate platelet–vessel wall interactions and contribute to development of thrombotic microangiopathy and organ dysfunction.[35]

Fibrinogen Consumption

Fibrinogen levels have been suggested for the diagnosis of DIC. However, fibrinogen is an acute-phase reactant, and levels can vary depending on the starting level. Despite consumption, plasma levels can remain normal, in part depending on the starting level that often is not available. Low fibrinogen levels indicate severe

DIC.[35,69] After plasmin-mediated lysis of the cross-linked γ-chain of fibrinogen, a fragment called D-dimer is liberated, the measurement of which reflects degradation of cross-linked fibrin. D-dimer levels are increased in DIC, but also after VTE, recent trauma or surgery, and commonly in ICU patients. Other assays for fibrin degradation products have also been used in evaluating DIC. D-dimer levels are also influenced by hepatic and renal function.[35]

Reductions in Coagulation Inhibitors

Plasma levels of antithrombin, protein C, and other circulating coagulation inhibitors can be useful in evaluating DIC. These are commonly abnormal after cardiac surgery, in critically ill patients, and in 90% of patients with DIC. Antithrombin might be an important predictor for outcomes in sepsis and DIC. Protein C levels can also decrease in DIC and are a therapeutic target with activated protein C (Xigris), an agent withdrawn from the market owing to lack of efficacy. Protein C is activated by thrombin. The endothelial protein thrombomodulin binds to thrombin to modulate its effect but also activates protein C. Protein C has pleiotropic effects, but inhibits FV and FVIII, and functions as an anticoagulant. Thrombomodulin also activates thrombin activatable fibrinolysis inhibitor. In sepsis and DIC, the protein C system is defective owing to multiple causes and represents a therapeutic target.[35] Tissue factor pathway inhibitor (TFPI), another serine protease inhibitor, inhibits the TF-FVIIa complex and FXa, a key initiator of hemostasis. TFPI is reduced in DIC, and TFPI has been studied as a therapeutic target in sepsis.[35]

Fibrinolysis Indicators

The release of tPA and urokinase-type plasminogen activator occurs in DIC. These plasminogen activators generate plasmin, which is balanced by increases in plasminogen activator inhibitor 1 (PAI-1). In DIC increased D-dimer levels occur as a manifestation of increased fibrinolytic activity. However, fibrinolysis is unable to counteract the concomitant coagulation activation. Fibrin degradation products including D-dimers suggest both clot formation and fibrinolytic activity. Other methods to monitor fibrinolytic activity include measuring plasminogen and α_2-antiplasmin levels. However, in DIC these proteins can also be consumed. Plasmin generation can be determined in part by measuring plasmin–α_2-antiplasmin complexes that can be increased in DIC.[35]

Hemostatic Testing

Hemostatic testing is often used preoperatively to identify patients at risk for bleeding and to better define the specific defect producing bleeding. Platelet dysfunction owing to dilutional coagulopathy is a major cause of bleeding after massive transfusion, after cardiac surgery, or because of concurrent use of antiplatelet agents. Hemostatic testing facilitates a rational approach to pharmacologic and transfusion-based therapy. However, most platelet function tests available for point-of-care (POC) testing or as laboratory-based testing have not been suitably validated in surgical patients and non-POC testing is not readily available. Dilutional thrombocytopenia can also affect test results. Better tests of platelet dysfunction are needed to allow more accurate diagnosis of the underlying disorder, particularly in high-risk surgical patients.

Standard hemostatic testing is routinely used in surgical patients to evaluate hemostasis (PT, aPTT, platelet count, fibrinogen level, and platelet function testing). Despite the lack of studies supporting the absolute utility of hemostatic function tests in the perioperative management of surgical patients, multiple studies have shown that using algorithms based on POC coagulation tests can reduce bleeding and transfusion requirements after cardiac surgery. Transfusion algorithms can prevent or reduce the empirical administration of hemostatic factors to guide intraoperative transfusion.[70] A summary of the standard hemostatic tests and their utility is provided in Tables 43.3 through 43.6.

Point-of-Care Coagulation Testing

POC coagulation monitors that evaluate viscoelastic properties of whole blood include thrombelastography, rotation thromboelastometry (ROTEM, Pentapharm GmbH, Munich, Germany), and Sonoclot (Sienco, Inc., Arvada, CO) analysis (see Chapter 44).[71]

TABLE 43.3 Perioperative Coagulation Tests for Surgical Patients: Prothrombin Time

Typical normal range is 11–13 seconds

International normalized ratio (INR) = $(PT_{test}/PT_{normal})^{ISI}$, where ISI is the International Sensitivity Index (a quality control measure for the tissue factor used)

Overview

Assesses the extrinsic and common coagulation pathways

Primarily used to monitor long-term use of anticoagulant therapy through the INR, evaluate liver function, evaluate coagulation disorders

Method

Prothombin time (PT) is the time it takes for clot to form after recalcification and thromboplastin is added to citrated plasma.

Important Notes

The normal range for the laboratory in which PT is tested should be used in the interpretation.

TABLE 43.4 Perioperative Coagulation Tests for Surgical Patients: Activated Partial Thromboplastin Time

Typical normal range is 25–38 seconds

Overview

Assesses the intrinsic and common coagulation pathways

The best single screening test for coagulation disorders; when properly performed, activated partial thromboplastin time (aPTT) is abnormal in 90% of patients with coagulation disorders.

Used to monitor heparin therapy, screen for hemophilia A and B, detect clotting inhibitors.

Method

aPTT is the time it takes for clot to form after recalcification and addition of phospholipid and an activator of the intrinsic coagulation system to citrated plasma.

Important Notes

The normal range for each laboratory should be used in the interpretation.

Reagents are variably sensitive to the effects of lupus anticoagulant. If sensitive, a false-positive aPTT elevation can result from this cross-reactivity rather than from a bleeding tendency.

TABLE 43.5 Perioperative Coagulation Tests for Surgical Patients: Fibrinogen

Typical normal range is 2–4 g/L (200–400 mg/dL)

Overview

Fibrinogen, or factor I, is a glycoprotein synthesized in the liver. It is cleaved by thrombin to produce fibrin monomer, the basis of clot formation.

Decreased levels of fibrinogen can indicate disseminated intravascular coagulation, liver disease, or dilutional coagulopathy.

Method

Fibrinogen can be assessed both quantitatively, using immunologic methods, and qualitatively, with clotting assays similar to one-stage assay methods used for other clotting factors.

TABLE 43.6 Perioperative Coagulation Tests for Surgical Patients: Platelet Aggregation Studies

Typical normal range is >65% aggregation in response to the platelet activators adenosine diphosphate, epinephrine, collagen, ristocetin, and arachidonic acid.

Overview

Platelet aggregation studies are used to classify qualitative platelet abnormalities.

Abnormalities can be in adhesion, release, or aggregation.

Method

Platelet aggregation is stimulated by introducing activators in vitro.

Aggregation is measured using a turbidimeter and expressed graphically by wave patterns.

Important Notes

Platelet aggregation studies are rarely useful in evaluating acquired bleeding disorders.

These systems measure multiple aspects of the clotting process, including hemostatic factor and platelet interactions, fibrin formation, clot retraction, and fibrinolysis. The tests are routinely evaluated in whole blood, allowing potential evaluation of platelet function, although fibrinogen highly influences these tests. This type of hemostatic testing is increasingly used in managing patients after trauma and massive hemorrhage or other major surgery. When viscoelastic testing is normal, surgical bleeding should be considered; however, these tests can also be used to guide transfusion of procoagulant therapies.

Transfusion Algorithms and Massive Transfusion

Most studies demonstrate that transfusion algorithms based on coagulation testing reduce the need for platelets, fresh frozen plasma, or cryoprecipitate. Indeed, any test that prevents empirical administration likely will reduce transfusions. Most transfusion algorithms suggest transfusion when bleeding is accompanied by a PT or aPTT greater than 1.5 times the normal value, thrombocytopenia with a platelet count less than 50,000 to 100,000/μL, or fibrinogen concentration less than 100 mg/dL (or 1 g/L). Because most laboratory testing is slow, POC viscoelastic testing has become the focus of most transfusion algorithms.[72] Prospective algorithms using platelet function data have also been reported. However, platelet function testing is problematic in that most tests need a relatively higher number of platelets to work and it is unclear whether they are applicable to the platelet dysfunction encountered after cardiopulmonary bypass.

Battlefield trauma can cause massive bleeding, and extensive information on massive transfusion has come from experience in the Iraq War. Massive transfusion is commonly defined as 10 or more units of RBC transfusions in a 24-hour period, but use of 4 or more red cell units within 1 hour when the ongoing need is foreseeable; or replacing 50% of the total blood volume within 3 hours might also be appropriate in the acute clinical setting.[73,74] Blood transfusion is the main therapeutic option for treating acute hemorrhage, and in trauma patients the ideal solution is fresh whole blood, although this is not widely available.[6] With life-threatening bleeding, multiple blood volumes may be transfused, leading to coagulopathy if sufficient factors are not replaced. The etiology of coagulopathy during massive transfusion is complex, involving dilution of factors, hypothermia, tissue hypoperfusion/ischemia, acidosis, and potential DIC.[75]

Because coagulation test results are not often available, massive transfusion protocols often use fixed doses of component therapies that include fresh frozen plasma and platelets after transfusion of a defined number of RBCs, often in an attempt to mimic the transfusion of fresh whole blood. In addition to fixed ratios, antifibrinolytic agents are also considered if fibrinolysis is present and are an important consideration of multimodal therapy as demonstrated in surgical patients and trauma. The role of factor concentrates to manage bleeding is increasingly evolving in clinical algorithms.[76–78]

Blood Conservation

Blood conservation is often discussed in many perioperative settings, but not actively practiced, in part because of the additional work involved. Pharmacologic management of hemostasis in patients undergoing surgery represents an important therapeutic approach in the management of complex surgical patients and for blood conservation. Because surgery represents a major consumer of blood products and because agents can be administered prophylactically, pharmacologic approaches are an important aspect of blood conservation. Unfortunately, many studies have reviewed issues related to RBC use and not hemostatic factor use.

Of the major preoperative patient risk factors for transfusion, low RBC mass owing to small body size or from preoperative anemia is important. Additional important considerations for perioperative blood conservation are the preoperative treatment of anemia, especially for elective surgery. A low starting RBC volume, calculated by hematocrit multiplied by estimated blood volume, correlates with bleeding and the need for allogeneic RBC transfusion. Blood conservation guidelines should reduce hemodilution and conserve red cells. The judicious use of preoperative erythropoietin and supplemental iron can increase RBC mass, but this requires interventions weeks before surgery. Minimizing extracorporeal circuits with circuits that require reduced priming volumes may be useful in cardiopulmonary bypass. Additional strategies before surgical intervention include normovolemic hemodilution, salvage of RBCs from the operative field, and use of pharmacologic agents that reduce bleeding. In cardiac surgical patients, additional considerations include modified ultrafiltration.

Multimodal interventions provide the best opportunity to reduce bleeding and the need for allogenic transfusion.

An important aspect of preoperative risk evaluation is the management of preoperative therapies that interfere with normal hemostasis. Surgical patients are increasingly receiving both antiplatelet agents and anticoagulation for perioperative thromboprophylaxis and as therapy for ischemic cardiovascular disease (see Chapter 45). As a result, patients often present for surgery with an acquired hemostatic imbalance because of preexisting anticoagulation. These agents should be discontinued before surgery, including the thienopyridines, drugs that inhibit $P2Y_{12}$ receptor binding. For drugs like clopidogrel, there is variability in patient response to their use; however, newer P2Y12 inhibitors such as prasugrel are more potent than clopidogrel and have a much lower incidence of resistance. Specific laboratory assays that include POC testing, such as VerifyNow (Accriva Diagnostics, San Diego, CA), might help identify patients who can safely undergo urgent operations.

Managing blood resources with a multidisciplinary team of anesthesiologists, blood bankers, surgeons, and intensivists should be considered when developing blood conservation strategies.[46] Patients with known coagulopathies or hereditary deficiencies should be optimized preoperatively as illustrated in Table 43.7. Most studies suggest that developing a transfusion algorithm that all team members agree with, and the use of laboratory and/or POC testing to guide transfusion decisions, are important aspects of blood conservation.

Treatment of the coagulopathy includes volume replacement, normothermia, resolution of acid-base abnormalities, and blood component therapy. Because of fibrinolysis, antifibrinolytic drugs should be considered for dosing.

TABLE 43.7 Management of Patients With Hemophilia for Elective Surgery

- Surgical procedures should be performed in coordination with a team experienced in the management of hemophilia.
- Procedures should take place in a center with adequate laboratory support for reliable monitoring of clotting factor levels.
- Preoperative assessment should include inhibitor screening.
- Surgery should be scheduled early in the week and early in the day for optimal laboratory and blood bank support, if needed.
- Availability of sufficient quantities of clotting factor concentrates should be ensured before undertaking major surgery.
- The dosage and duration of clotting factor concentrate coverage depends on the type of surgery performed.

Modified from Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19:e1–e47.

Key Points

- Hemostasis is a complex process that involves interactions between vascular components with blood cellular and plasma components.
- Coagulopathy in surgical patients can result from consumption/loss of coagulation components, drug effects, surgical trauma, and preexisting hemostatic defects.
- The growing use of anticoagulants and antiplatelet agents poses potential problems in the perioperative period.
- Both congenital and acquired forms of hypercoagulability can occur in surgical patients.
- Heparin-induced thrombocytopenia is a hypercoagulable state complicating anticoagulation therapy and is a major risk factor for adverse events.
- Acquired hemostatic disorders related to anticoagulation agents are common perioperative considerations requiring factor therapy.
- Inherited bleeding disorders such as hemophilia and von Willebrand disease require specific perioperative management.
- Disseminated intravascular coagulation is a severe consumptive hemostatic disorder that can occur in diverse settings.
- The etiology of coagulopathy associated with massive transfusion is complex and involves dilution of factors, hypothermia, tissue hypoperfusion, acidosis, and possible disseminated intravascular coagulation.
- Although transfusion therapies remain important, blood conservation has gained priority to minimize adverse effects.
- Laboratory testing and objective algorithms are important approaches to reduce transfusion of banked blood products.

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44

Transfusion and Coagulation Therapy

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Hemoglobin and Volume Replacement Therapies

Historical Aspects of Transfusion

The observation by Harvey in 1628 that blood circulates in a closed vascular system was pivotal in the practice of blood transfusion.[1] As blood was recognized as vital to sustain life, Denis in Paris and Lower in Oxford attempted xeno-transfusion (animal blood to humans) with little success in the 17th century. The first documented transfusion of human blood was made in 1818 by Blundell, an obstetrician in London, who recognized the need for transfusion in women suffering from postpartum hemorrhage. His results were not reproducible owing to the lack of knowledge of blood types and anticoagulants.

Major advances were made in the beginning of 20th century when Landsteiner identified blood groups A, B, and C (later renamed *group O*). Transfusion of fresh whole blood was reported as a treatment for epistaxis due to thrombocytopenia in 1910. Storage and distribution of donated blood became possible after sodium citrate was developed as an anticoagulant during World War I. The infrastructure of the modern blood banking system was established by World War II; use of fresh whole blood transfusion saved many wounded soldiers. However, the risk of pathogen transmission, including hepatitis via blood transfusion, was recognized later.

During World War II, Cohn and colleagues developed the cold ethanol method to separate albumin, γ-globulin, and fibrinogen from plasma, which became the basic principle for commercial plasma fractionation. Pooling of random donor plasma to manufacture factor (F) VIII concentrates without effective donor screening or virus inactivation steps in the late 1970s and early 1980s led to transfusion-related transmission of viruses, particularly human immunodeficiency virus (HIV) and hepatitis C to a large number of hemophiliac patients worldwide. Many precautions for blood-borne pathogens have been implemented, including vapor heat treatment and nanofiltration, since the mid-1980s; recombinant coagulation factors became available in the 1990s. The risk of infectious transmission also fueled efforts to develop synthetic oxygen carriers.[2,3]

Over the years, clinicians have recognized the importance and potential harms of blood component therapies, fostering the creation of patient blood management programs.[4] Preoperative anemia management is a critical part of patient blood management; iron supplementation and/or erythropoietin therapy can be used in appropriate patient groups.[5,6] Perioperative cessation of antithrombotic agents, intraoperative blood salvage, and antifibrinolytic therapy are also utilized to minimize the need for allogeneic blood

TABLE 44.1 Characteristics of Allogeneic Blood Components

Component	Volume	Shelf Life	Storage Temperature
Red blood cells	220–340 mL	42 days	1–6°C
Apheresis platelets	250–300 mL	5 days	20–24°C
Random donor platelets	50–70 mL	5 days	20–24°C
Plasma	200–250 mL	1 y	< –18°C
Cryoprecipitate	10–15 mL	1 y	< –18°C

Note: Plasma frozen within 8 hours is called FFP and plasma frozen between 8–24 hours of collection is called FP24.

transfusion along with point-of-care coagulation monitors.[7] The rational and cost-effective uses of blood components are now the subject of published transfusion guidelines.[7–12]

Packed Red Blood Cells

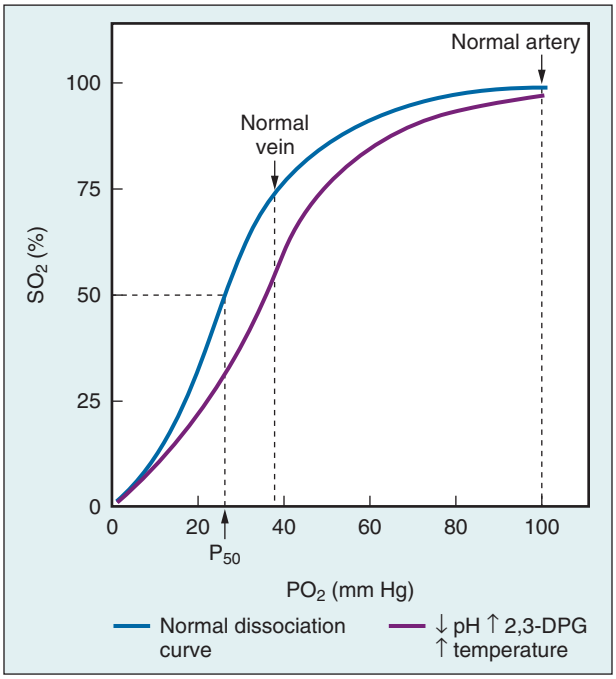
Circulating red blood cells (RBCs) are anuclear, hemoglobin-carrying cells of about 7 to 8 µm in diameter. The biconcave and discoid shape of RBCs confers advantages in increasing surface area for gas exchange and flexibility in passing through capillaries. On average, RBCs remain in the circulation for 120 days. Senescent or abnormal RBCs are eliminated by the spleen. The synthesis of RBCs (erythropoiesis) is regulated by erythropoietin, which is elevated in anemia and hypoxia. Erythropoiesis is also affected by the availability of iron, an integral component of hemoglobin.

Packed RBCs (PRBCs) are prepared by separating most plasma components of donated whole blood by centrifugation. One unit of RBCs collected in anticoagulant-preservative solution is about 300 mL with a hematocrit of 50% to 70%. Dextrose is added to maintain glucose metabolism, and adenine and phosphate allow synthesis of adenosine triphosphate (ATP; Table 44.1). Additive solutions (adenine, glucose, mannitol, sodium chloride) are also used to extend shelf life up to 42 days.[13] Depending on the storage solution, RBCs have a shelf life of 28 to 42 days at 1°C to 6°C. During storage, intracellular 2,3-diphosphoglycerate (DPG) is reduced to < 10% of normal at 5 weeks such that release of oxygen from hemoglobin is significantly impaired (Fig. 44.1). Nonetheless, no differences in morbidity and mortality were detected between short-term storage (6–11 days) and long-term storage (21–28 days) in prospective randomized studies in premature infants, adult cardiac surgical patients, and critically ill adult subjects.[14–17]

Clinical Uses

Transfusion of RBCs is indicated to restore the oxygen-carrying capacity in patients with severe anemia or major blood loss. There is no absolute level of hemoglobin that indicates a threshold for transfusion ("transfusion trigger"); underlying clinical conditions and laboratory data for each patient should be considered. Acute anemia is less well tolerated compared to chronic anemia, in which peripheral oxygen delivery is compensated by elevated 2,3-DPG levels in RBCs and higher cardiac output (see Fig. 44.1). In patients with moderate to severe cardiovascular dysfunction, anemia might not be well tolerated. The extent and duration of clinical bleeding are also important criteria for transfusion in major trauma and surgery. According to the American Society of Anesthesiologists (ASA) guidelines for blood component therapy, transfusion of RBCs is almost always indicated for hemoglobin less than 6 g/dL, whereas it is rarely indicated for hemoglobin greater than 10 g/dL. For hemoglobin between 6 g/dL and 10 g/dL, transfusion should be considered if complications due to inadequate oxygenation are anticipated.[8] It remains controversial as to whether liberal or restrictive transfusion strategy is preferable in various surgical and medical settings.[18] Restrictive transfusion (hemoglobin triggers < 7–8 g/dL) appears to increase mortality and ischemic events relative to a liberal strategy (triggers < 9–10 g/dL) in cardiovascular surgery patients[19] and elderly orthopedic surgical patients.[20] There was no difference in adverse event rates between liberal and restrictive strategies in nonsurgical critically ill patients.[18]

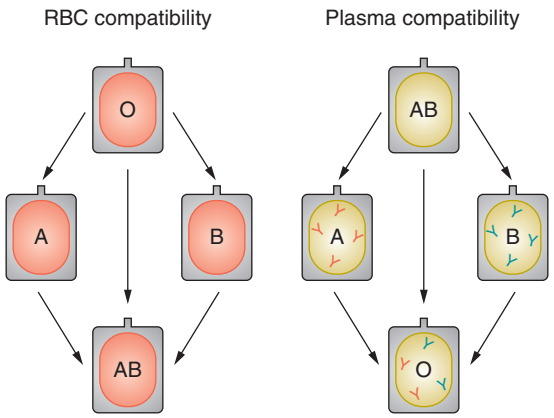
ABO and Rh blood group–specific packed RBCs should be administered whenever possible (Fig. 44.2). In the case of life-threatening hemorrhage without time for formal cross-matching, either Rh-positive or Rh-negative group O RBCs can be transfused in principle. In Rh-negative women of childbearing age, Rh-negative group O RBCs should be preferred for reducing the risk of alloantibody (anti-D) development, which can cause anemia in an Rh-positive fetus. Transfusion of mismatched RBCs, typically related to ABO, can induce immunoglobulin M (IgM) antibody–mediated acute hemolysis, but in less serious mismatches of minor antigens such as Rh, Kell, and Duffy, survival of transfused RBCs is shortened.



• **Fig. 44.1 Oxygen-dissociation curve.** The oxygen-dissociation curve of hemoglobin at normal pH is shown in blue. The dissociation of oxygen from hemoglobin can be increased *(red)* by acidosis, elevated 2,3-DPG (2,3-diphosphoglycerate), or higher temperature. Conversely, the curve can be shifted to the left by alkalosis, low 2,3-DPG, or hypothermia. The partial pressure of oxygen (PO_2) when hemoglobin is 50% saturated (P_{50}) is about 26.6 mm Hg.

Side Effects

Acute hemolytic transfusion reactions are usually caused by ABO incompatibility. This potentially fatal complication occurs in about



• **Fig. 44.2 ABO compatibility.** For RBC transfusion, the recipient can receive the same blood type or blood group(s) specified by the arrow(s). Blood group O recipients can be transfused only with group O blood whereas group AB recipient can be transfused with O, A, B, or AB group RBCs. Rh-positive or Rh-negative RBCs can be transfused in an Rh-positive recipient, and Rh-negative RBCs should be given to an Rh-negative recipient. For plasma product transfusion, the recipient can receive the same plasma type or plasma group(s) specified by the arrow(s). Blood group AB recipients can be transfused only with group AB plasma whereas type O recipients can be transfused with O, A, B, or AB group plasma. Rh types are not considered for plasma product transfusion. Orange arrow, anti-B antibody; green arrow=anti-A antibody.

1 in 30,000 transfusions. As little as 20 to 30 mL of incompatible RBCs can cause agitation, nausea/vomiting, dyspnea, fever, flushing, hypotension, tachycardia, and hemoglobinuria. Two major complications of intravascular hemolysis include renal failure from acute tubular necrosis and disseminated intravascular coagulation (DIC).

Febrile nonhemolytic transfusion reaction is relatively common (0.1–1% of RBC transfusions). Other immunologic complications of transfusion include human leukocyte antigen (HLA) alloimmunization, graft-versus-host disease, and immunosuppression triggered by donor leukocytes.[21] The risk of these complications can be partially reduced by use of leukocyte adsorption (leukoreduction) filters at blood collection and γ-irradiation after collection to prevent lymphocyte proliferation. The leukoreduction process presumably reduces virologic risks associated with leukocytes, including cytomegalovirus, Epstein-Barr virus, and human T-cell leukemia virus I and II. Transmission of emerging virus (e.g., Zika) through transfusion is possible; thus, careful donor screening and implementation of available pathogen reduction techniques are recommended.[22] Although transfusion-related variant Creutzfeldt-Jakob diseases (vCJDs) and bovine spongiform encephalopathy (BSE) are rare, there is a theoretical advantage in leukodepletion to prevent prion transmission.[23]

Erythropoietin

Erythropoietin is a hormone produced in the kidney in response to hypoxemia, such as in chronic pulmonary disease and at high altitudes. Recombinant human erythropoietin products are available for intravenous (IV) or subcutaneous (SC) injection. The primary indication for recombinant erythropoietin is anemia associated with chronic renal insufficiency. Other indications for erythropoietin include treatment of anemia related to the antiviral zidovudine in HIV-infected patients and treatment of chemotherapy-induced anemia in patients with metastatic, nonmyeloid malignancies. Preoperative erythropoietin treatment of anemia has been shown to reduce allogeneic RBC transfusion,[24] but its high cost hinders easy access for perioperative anemic patients. There are a variety of perioperative dosing regimens in conjunction with iron supplementation.[24] One example is a weekly dose of 600 units/kg SC started 3 weeks before surgery and the 4th dose given on the day of surgery. A single dose of 80,000 IU SC dose 2 days before cardiovascular surgery reduced the overall transfusion rate from 39% to 17% in a prospective randomized placebo-controlled study involving 600 patients.[25]

Side Effects

Erythropoietin therapy induces a marked expansion of erythroid cells, which can result in iron deficiency; thus, iron should be supplemented as appropriate. Target hemoglobin levels should not be set above 13 g/dL because the risk for cardiovascular events and stroke is increased. Hypertension can be worsened by erythropoietin, especially in patients with chronic renal failure. Erythropoietin therapy can adversely affect the survival of cancer patients, with progression or recurrence of certain tumors.

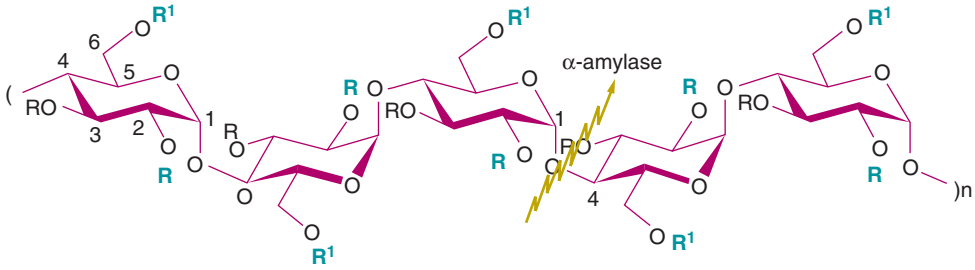
Blood Substitutes

The limited availability of blood and infection risks are the driving forces in developing oxygen-carrying blood substitutes. Two major classes of substitutes are hemoglobin-based oxygen carriers (HBOC) and perfluorocarbon (PFC) emulsions. Bovine-derived hemoglobin glutamer-200 (Oxyglobin, Biopure, Cambridge, MA) is currently approved for canine anemia in the United States. In South Africa, bovine hemoglobin glutamer-250 (Hemopure, Biopure, Cambridge, MA) is approved for treatment of human anemia. Free hemoglobin solutions have a higher affinity for oxygen compared to RBCs (P_{50} of 12–14 mm Hg for HBOC vs. 27 mm Hg for RBCs).[26,27] The modification of hemoglobin by pyridoxal phosphate increases P_{50} to 32 mm Hg, improving release of oxygen.[3] Potential benefits of HBOCs include sparing allogeneic RBC transfusion in anemia, trauma, and major surgery, and reduction of transfusion-related infection and other complications. Compassionate use of HBOC has been reported in a Jehovah's Witness patient with acute lymphoblastic leukemia who survived severe anemia (lowest hemoglobin, 3.1 g/dL).[28] However, vasoconstrictive properties of HBOC remain a major concern for further clinical development.[2,3]

PFC emulsions consist of halogen-substituted hydrocarbons that enhance plasma oxygen solubility. Hydrophobic PFC molecules are dissolved in plasma using emulsifiers. Unlike hemoglobin, the oxygen-carrying capacity of PFC is directly proportional to oxygen partial pressure.[2] Febrile reactions or flu-like symptoms can occur as PFC emulsion is taken up by the reticuloendothelial system. PFC is not clinically available at present, but potential perioperative uses include acute lung injury and acute normovolemic hemodilution to spare RBCs from extracorporeal circuits.

Albumin

Albumin is a 69-kDa plasma protein synthesized in the liver and present in plasma at 3 to 5 g/dL (~60% of plasma protein). Plasma-derived, pasteurized (60°C for 10 hours) fractions are available in iso-oncotic (5%) or hyper-oncotic (25%) solutions. Albumin exerts oncotic activity (colloid osmotic pressure) to retain intravascular water. The oncotic pressure of 5% albumin is equivalent to plasma. Albumin also serves to carry poorly



• **Fig. 44.3 Hydroxyethyl substitution of hydroxyethyl starch (HES).** The structural formula of HES poly(O-2-hydroxyethyl)starch. R = –H, $–CH_2CH_2OH$. R^1 = –H, CH_2CH_2OH, or glucose unit. Enzymatic cleavage site of α-amylase *(yellow arrow)* is at C1 and C4 atoms. Hydroxyethyl groups at position C2 inhibit the access of α-amylase to the substrate more effectively than those at C6. HES products with high C2/C6 ratios are more slowly degraded. (From Kozek-Langenecker SA: Effects of hydroxyethyl starch solutions on hemostasis. Anesthesiology 2005; 103: 654-660.)

water-soluble molecules (apoprotein, bilirubin, transferrin, and so on) and can bind a number of drugs. In hypovolemic patients, there is no evidence that albumin reduces mortality compared with crystalloid or colloid solutions.[29] There are a few indications for albumin use, including fluid replacement for hypovolemic shock with lack of response to crystalloids or colloids, priming for extracorporeal circuits, and plasma exchange therapy. In acute liver failure, albumin can be used to restore oncotic pressure. The intravascular retention of albumin is affected by increased vascular permeability (e.g., first 24 hours of thermal injury) and excretion (e.g., nephrotic syndrome). Albumin does not affect hepatic or renal function.

Synthetic Colloids

Synthetic colloid solutions include hydroxyethylstarches (HESs), in which rapid degradation by α-amylase is prevented by hydroxyethylation of glucose subunits (Fig. 44.3). The molar replacement ratio indicates the proportion of glucose molecules replaced with hydroxyethyl units (e.g., 0.4 = 40% replacement). The C2/C6 ratio indicates the number of hydroxyethyl units at the C2 relative to the C6 position. HES with higher molar replacement and C2/C6 ratios is retained longer owing to slower metabolism (Table 44.2). HES is excreted by the kidneys after degradation.

Differences between albumin and HES in efficacy and safety are controversial. HES products are available in iso-oncotic (6%) or hyper-oncotic (10%) solutions. The most commonly used are 6% HES solutions, with an average molecular weight of 600 to 670 kDa (Hespan, Hextend, B. Braun, Bethlehem, PA), but low-molecular-weight HES (130 kDa, Voluven, Fresenius Kabi, Halden, Norway) has recently become available in the United States.[30] HES products are as effective as albumin as fluid replacements, but large doses of HES (particularly, Hespan) can adversely affect coagulation (fibrin polymerization)[31] and exacerbate renal dysfunction in sepsis.[32] Excess HES can falsely elevate turbidometric fibrinogen measurements.[33]Recently, the European Medical Association has recommended suspending marketing authorization for HES colloids in patients with sepsis or at risk for renal insufficiency. Colloid replacement therapy might still be indicated in early volume resuscitation after acute blood loss (e.g., trauma).

TABLE 44.2 Synthetic Hydroxyethyl Starch Colloid Solutions

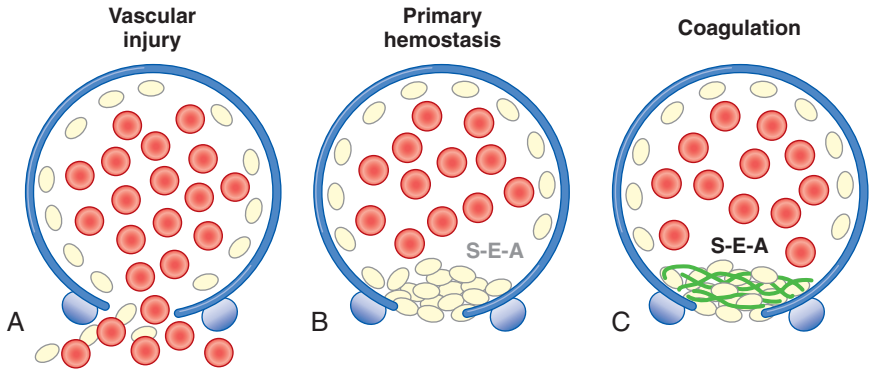
Type of HES	600/0.7	670/0.75	260/0.45	130/0.4
Product name	Hespan	Hextend	Pentaspan	Voluven
Concentration	6%	6%	10%	6%
Solvent	Saline	LR	Saline	Saline
Oncotic pressure (mm Hg)	25–30	25–30	55–60	36
Mean molecular mass (kDa)	600	670	260	130
Molar substitution	0.7	0.75	0.45	0.4
C2/C6 ratio	5	4.5	6	9
Maximum daily dose (mL/kg)	20	20	20	33

LR, Lactated Ringer's Solution.

Hemostatic Interventions and Coagulation Therapies

Platelet Concentrates

Platelets are anuclear, granulated cells 2 to 4 μm in diameter derived from bone marrow megakaryocytes. The normal half-life of platelets is 7 to 10 days. There are 150 to 350×10^9/L platelets in the circulation, but their concentration near arterial vessel walls is significantly higher owing to the margination of platelets by larger RBCs.[34] Platelets rapidly respond to disruption of normal endothelium, contributing to the initial arrest of bleeding (primary hemostasis), and support of localized thrombin generation and fibrin formation (secondary hemostasis or coagulation; Fig. 44.4).[35]



Event	Vascular injury Bleeding	Primary hemostasis Localization of factors	Thrombin generation Fibrin polymerization
Elements	Collagen Tissue factor	Platelets ADP, Thromboxane vWF, Fibrinogen FVII, FX, FII	Platelets (S) Fibrinogen (E) FII, FIX, FX, FXI, FXII (A) FV, FVIII
Interventions	Erythrocytes	Platelets Cryoprecipitate vWF concentrate Desmopressin	Plasma, PCC Cryoprecipitate Fibrinogen FXIII concentrate rFVIIa

• **Fig. 44.4 Hemostatic processes and phase-specific interventions**. (A) Hemorrhage occurs after vascular injury. Extravascular (subendothelial) collagen and tissue factor are exposed to the flowing blood. Transfusion of erythrocytes/red blood cells is the initial intervention. The intact vascular wall *(blue)*, platelets *(white ovals)*, erythrocytes *(red circles)*, and fibrin *(green)* are depicted. (B) Platelets adhere to the vascular injury site by interacting with von Willebrand factor (vWF) by glycoprotein Ib/IX receptors. Mural platelets are activated by collagen and trace thrombin (by the extrinsic pathway involving factors VII [FVII], X [FX], and II [FII]). They release adenosine-5-diphosphate (ADP) and thromboxane, stabilizing platelet–platelet interactions with fibrinogen. Thus, the primary (hemostatic) plug is established. Platelet transfusion and measures to increase von Willebrand factor can augment this process. (C) Activated platelet aggregates serve as a catalytic surface and binding sites for coagulation responses. Substrates (S; fibrinogen), pro-enzymatic factors (E; factors II, IX [FIX], X, XI [FXI], and XIII [FXIII]), and accelerators (A; factors V [FV] and VIII [FVIII]) are congregated. These factors can be replaced using plasma transfusion or specific factor concentrates (see text for details). *PCC,* Prothrombin complex concentrate; rFVIIa, recombinant factor VIIa. (From Tanaka KA, Bolliger D, Vadlamudi R, Nimmo A. Rotational thromboelastometry (ROTEM)-based coagulation management in cardiac surgery and major trauma. *J Cardiothorac Vasc Anesth*. 2012;26: 1083–1093.)

Since the first platelet transfusion in the 1950s, platelet concentrate remains the mainstay therapy for thrombocytopenia.[36] Platelet concentrates are prepared by centrifugation of citrated whole blood within 8 hours of collection. After separating RBCs from platelet-rich plasma, further centrifugation yields 1 unit of platelet concentrate and plasma. Each unit of platelets, referred to as *random-donor platelets*, contains 5.5×10^{10} platelets in 50 to 70 mL of plasma. Four to 8 random-donor units are pooled to increase platelet count by 5 to 10×10^9/L in the adult. In order to decrease multiple donor exposures, single-donor platelet apheresis is increasingly used. During the apheresis procedure, donor blood is placed in the extracorporeal circuit and centrifuged to separate platelets. One platelet apheresis unit contains 30 to 50×10^{10} platelets in 250 to 300 mL of plasma. Platelet concentrates are agitated and stored at room temperature (20–24°C) for up to 5 days (see Table 44.1).

Clinical Uses

Platelet transfusion is used to prevent or treat bleeding due to platelet dysfunction or thrombocytopenia. Hereditary platelet dysfunction is rare, but adhesion defects in Bernard-Soulier syndrome (GPIb/IX deficiency), aggregation defects in Glanzmann thrombasthenia (GPIIb/IIIa deficiency), and a secretion defect in Hermansky–Pudlak syndrome (lack of dense granules) are prototypical hemorrhagic conditions resulting from decreased primary hemostasis.[37] Platelet dysfunction in perioperative patients is usually due to antiplatelet therapy (see Chapter 45). Platelet transfusion can be required even with a normal platelet count if platelet dysfunction is clinically suspected or identified by platelet function testing.[38,39]

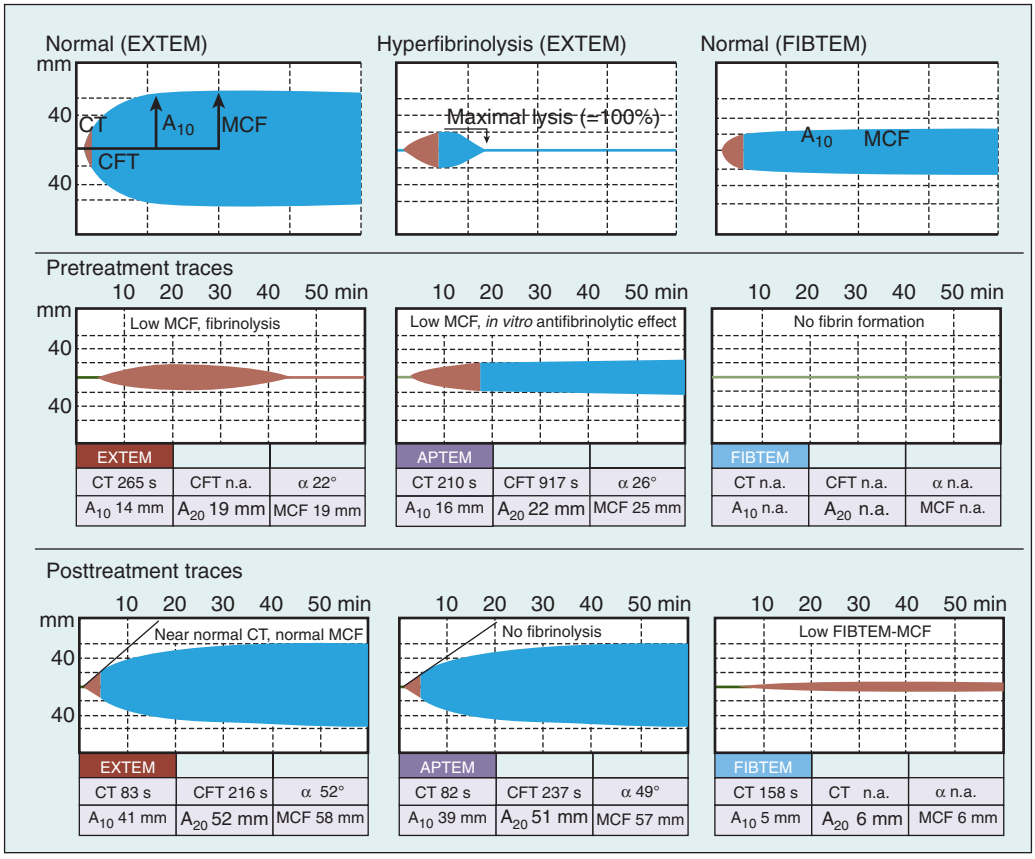
Perioperative platelet dysfunction is most commonly caused by acetylsalicylic acid (aspirin), thienopyridines, or GPIIb/IIIa

inhibitors.[40] For thrombocytopenia associated with bone marrow disorders, prophylactic platelet transfusion for a threshold below 10×10^9/L appears to reduce the risk of serious bleeding events.[41,42] The recommended thresholds for platelet transfusion for nonbleeding, critically ill patients are also in the similar range ($10–20 \times 10^9$/L).[43] The trigger platelet count usually falls in the range of $50–100 \times 10^9$/L in trauma or major surgery.[8-11] The trigger values are generally higher for neurosurgical and cardiovascular procedures ($> 100 \times 10^9$/L).[44] For other procedures, such as lumber puncture or central venous catheterization, a threshold of platelet count between 20 and 50×10^9/L is used, but supporting evidence is rather weak.[45]

Platelet transfusion is administered to mitigate microvascular bleeding due to thrombocytopenia or platelet dysfunction, but hypofibrinogenemia and hyperfibrinolysis need to be addressed separately as the latter are important causes of perioperative bleeding.[46–48] It is often difficult to quantify hemostatic efficacy of platelet transfusion in the presence of multifactorial factor deficiency after major trauma or surgery.[49] Platelet count does not reliably reflect functional recovery in the presence of platelet inhibitors and other pathologic conditions (e.g., extracorporeal circuit) that adversely affect platelet function.[39,50] The timing and amount of platelet transfusion can be individualized using platelet function testing[39,51] and/or thromboelastometry/thromboelastography (Fig. 44.5).[52,53] Modified thromboelastometry/thromboelastography assays suitable for monitoring antiplatelet agents have been developed, but further clinical validations are warranted for the standardization and optimal thresholds for transfusion.[38,39]

Side Effects

The risk of bacterial contamination is higher with platelet concentrates than other blood components since they are stored at room temperature. An immunoassay kit is available to test for aerobic or anaerobic gram-positive and gram-negative bacteria



• **Fig. 44.5** Examples of rotational thromboelastometric tracings. Tissue factor–activated whole blood thromboelastometry (EXTEM) reflects the pattern of whole blood clotting, which is triggered by tissue factor. On the fibrin-specific (FIBTEM) test, fibrin-specific clotting after tissue factor activation is demonstrated by inhibiting platelet–fibrin interactions with the platelet inhibitor cytochalasin D. Normal ranges for EXTEM and FIBTEM are as follows: EXTEM-CT, 35 to 80 s; clot formation time (CFT), 35 to 160 s, angle, 63 to 818; A_{10}, 50–71 mm; maximum clot firmness (MCF), 53 to 72 mm; FIBTEM-A_{10}, 7–23 mm; MCF, 9 to 25 mm. Pretreatment: traces obtained from a bleeding patient with major blunt trauma. Prolonged computed tomography (CT) and early clot breakdown are notable on EXTEM. Fibrinolysis is corrected in vitro on APTEM, but CT and amplitude remain abnormal. Severe hypofibrinogenemia and fibrin breakdown are also observed on FIBTEM. Posttreatment: CT is nearly normal and MCF is within normal range on EXTEM after treatment with 2 g of intravenous tranexamic acid, and transfusion of 20 U cryoprecipitate and a unit of apheresis platelets. Hyperfibrinolysis is no longer detected (EXTEM = APTEM). Fibrin polymerization is improving, but FIBTEM-MCF remains below normal. (From Tanaka KA, Esper S, Bolliger D. Perioperative factor concentrate therapy. *Br J Anaesth*. 2013;111 Suppl 1:i35–i49.)

(sensitivity, 10^3–10^5 colony formation units/mL). The lack of virus reduction procedures for platelet concentrates has been a major concern, and transmissions of Zika virus via platelet transfusion were recently reported.[54] A recently US Food and Drug Administration (FDA)–approved pathogen- reduction system (Intercept Blood System, Cerus Corp., Concord, CA) uses the combination of amotosalen and ultraviolet A light to block DNA and RNA replication of various pathogens in plasma and platelet concentrates. Further clinical validations are needed as to its indications and efficacies against emerging pathogens.[55]

Alloimmunizations after platelet transfusion can result in antibodies against HLA class I antigens and platelet-specific antigens. Problems due to platelet alloimmunization include refractoriness to platelet transfusion and post-transfusion purpura. For those who require frequent platelet transfusions, the use of leukoreduced, HLA-matched, and ABO-compatible platelet units should be considered to reduce the risk of platelet alloimmunization.[56] Hemolysis of RBCs can be caused by anti-A or anti-B antibody present in donor plasma of platelet concentrates. This typically occurs after group O platelet transfusion in non-group O recipients.[57] The incidence of severe hemolysis is estimated to be in the range of 1 in 6600 (apheresis platelet transfusion) to 1 in 9000 (non–ABO-identical platelet transfusions).

Other potential complications of platelet transfusion in surgical patients include transfusion-associated lung injury (TRALI) and thrombotic complications.[58] Last, it is unclear whether there is a clinical difference in hemostatic efficacy and safety between pooled platelet concentrates and apheresis platelets. The increment in platelet count was higher after apheresis platelets compared to pooled concentrates, but without impacting clinical bleeding in hemato-oncology–related thrombocytopenia.[59] Similarly, the clinical relevance of platelet preparation for bacterial contamination and donor exposure remains unclear.[60]

Plasma

Plasma transfusion has been traditionally performed using fresh frozen plasma (FFP). FFP is prepared from whole blood (~500 mL) or apheresis donations and frozen at –18°C within 8 hours of collection. However, other plasma products have been increasingly used to make up the shortfall in plasma supply in the United States. Plasma frozen between 8–24 hours of phlebotomy (FP24) is a unit of plasma containing similar factor levels to FFP except for factor VIII (FVIII, up to 20% reduction).[61,62] Each unit of FFP or FP24 is approximately 200 to 250 mL, and contains all components of donor plasma, including procoagulant and anticoagulant factors, albumin, and immunoglobulins. The recovery of coagulation factors after each plasma unit is about 2% to 3% in the adult but can vary with donors, clinical hemorrhage, and/or ongoing consumption. Plasma products can be stored frozen up to 12 months. Thawed plasma (FFP and FP24) are maintained in the liquid state for up to 5 days at 1°C to 6°C for clinical use, but some degradations of plasma factors do occur, particularly for FV and FVIII.[63,64] Donor plasma should be compatible with recipients' ABO types (see Fig. 44.2), but Rh types do not need to be considered. Blood group AB and A plasma have been used as universal donors for emergency.[48]

Solvent-Detergent (S/D) Plasma

Octaplas LG (Octapharma AG, Lachen, Switzerland) is a commercial S/D plasma licensed in many countries, including the United States. Large pools of donor plasma are collected in a blood type–specific batch (280 L from ~1500 donors) from countries at low risk for vCJD.[65] The plasma pool is subsequently treated for 1 to 1.5 hours at 30°C (previously 4–4.5 hours) with a combination of solvent, 1% tri(n-butyl)phosphate (TNBP), and a detergent (1% Octoxynol-9), inactivating enveloped viruses.[66] After extraction of S/D reagents, the product solution is passed through an affinity ligand column for intended removal of prions. The processes are presumed to remove emerging virus (e.g., Zika).[22] The filtered plasma is aliquoted in 200-mL bags, and frozen to below –65°C. Octaplas LG is stored at < 18°C, and a specific type (A, B, AB, O) of bag is thawed before transfusion. The production steps decrease the levels of protein S and α_2-plasmin inhibitor in the final plasma batch, but the duration of S/D treatment has recently been reduced,[66] resulting in less significant deviations of protein S and α_2-plasmin inhibitor from normal ranges in Octaplas LG compared to the older products.

In a study comparing cryosupernatant (250 mL/bag) and Octaplas (200 mL/bag) in therapeutic plasma exchange (TPE) for thrombotic thrombocytopenic purpura (TTP), there was no statistical difference in the number of TPE treatments from admission to clinical remission between products.[67] Citrate reactions (paresthesia, muscle cramps) were less frequent with Octaplas (6.9% vs. 18%) than with cryosupernant and, more important, allergic reactions were less common with Octaplas (3.1% vs. 9.3%).[67] The risk of transfusion-related acute lung injury is also reduced with S/D plasma because anti-HLA/anti-granulocyte antibodies in donor units are significantly diluted by pooling of donor plasma.[68]

Third-generation S/D plasma is not blood-type specific (Uniplas LG, Octapharma). Uniplas/UniplasLG can be transfused universally in any recipient because anti-A and anti-B antibodies are removed. Other features of Uniplas LG are similar to Octaplas LG.

Lyophilized Plasma

Lyophilized (freeze-dried) plasma (LyoPlas N-w) is available in several countries. This blood type–specific, single-donor plasma is produced by the German Red Cross (DRK-Blutspendedienst West). Donor plasma is tested for viral hepatitis and parvovirus B19, and type-specific plasma (A, B, AB, O) is kept frozen in quarantine until the donor is retested negative after a minimum of 4 months. After the quarantine, frozen single plasma units are thawed and filtered to eliminate blood cells and cell debris, reducing the risk of leukocyte-associated cytomegalovirus (CMV) transmission. The bottles of plasma are sealed and refrozen (< –30°C) and subsequently dehydrated under vacuum and gradually rising temperature.

The French Military Blood Institute (FMBI) has manufactured French lyophilized plasma (FLyP) since 1994.[69] For the production of FLyP, apheresis plasma is collected from male/female donors who fulfill rigorous medical criteria. Leukoreduced plasma undergoes pathogen reduction steps, including amotosalen and ultraviolet light (Intercept Blood System). Mixing of 3000 mL of pathogen-inactivated plasma from a maximum of 10 donors (mixture of A, B, and AB blood types) results in neutralization of anti-A and anti-B hemagglutinins). The plasma is subsequently aliquoted in an individual flask and freeze-dried over 4 days.

The major advantage of this lyophilized plasma is that it can be kept at room temperature (range, 2–25°C) for 15 months (LyoPlas N-w) or 2 years (FLyP). Each bottle of powdered plasma is reconstituted with 200 mL of sterile water before transfusion. These plasma products can be transported to locations where a

TABLE 44.3 Plasma Concentrations and Half-Lives of Coagulation Factors

	Concentration (μM)	Half-Life (h)	Available Concentrate(s)
Fibrinogen	7.6	72–120	pd-fibrinogen, cryoprecipitate
Prothrombin	1.4	72	PCC, FEIBA
Factor V	0.03	36	None
Factor VII	0.01	3–6	pd-FVII, r-FVIIa, PCC, FEIBA
Factor VIII	0.00003	12	pd-FVIII, r-FVIII
Factor IX	0.09	24	pd-FIX, r-FIX, FEIBA
FX	0.17	40	pd-FX, PCC, FEIBA
Factor XI	0.03	80	pd-FXI
Factor XIII	0.03	120–200	pd-FXIII, r-FXIII, cryoprecipitate
vWF	0.03	10–24	pd-vWF, r-vWF, cryoprecipitate
Protein C	0.08	10	pd-Protein C, PCC
Protein S	0.14	42.5	PCC
Antithrombin	2.6	48–72	pd-antithrombin, r-antithrombin

Adapted from Bolliger D, Gorlinger K, Tanaka KA: Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. Anesthesiology 2010; 113: 1205-1219.
FEIBA, Factor eight inhibitor bypassing activity; *PCC,* prothrombin complex concentrate (some PCC products contain minimal levels of FVII, protein C, and protein S; see Table 44.3); *pd,* plasma-derived; *r,* recombinant; *vWF,* von Willebrand factor.

steady supply of safe plasma is not feasible. Type AB or universal lyophilized plasma can be stocked for emergencies. One study reported that FV and FVIII are 25% and 20% lower in FLyP than in FFP, respectively, but other factor levels, endogenous thrombin generation potential, and thromboelastometry profile are comparable between the two.[70]

Clinical Uses

Plasma transfusion is mainly indicated for treatment of complex coagulopathies in which multiple coagulation factors and inhibitors are depleted. For congenital factor deficiency, plasma transfusion should be considered only if recombinant or plasma-derived factor concentrate is not available (Table 44.3). Plasma products are sometimes transfused prophylactically before invasive procedures when risk of bleeding is high, but there is limited evidence and no cut-off level for any coagulation test that clearly indicates the need for plasma.[44] When the international normalized ratio (INR) is < 1.5, excessive bleeding is unlikely.[71,72] Plasma transfusion is frequently used to treat bleeding conditions when prothrombin time (PT) is greater than 1.5 times the midpoint of the normal range or activated partial thromboplastin time (aPTT) is greater than 1.5 times the upper limit of normal.[73]

The most commonly used plasma dose is 2 units for adults, which amounts to 5 to 8 mL/kg.[74,75] However, factor increments are generally 10% even after 12 mL/kg of plasma transfusion, and 15 to 30 mL/kg might be necessary to keep coagulation factors above 50% of normal.[76,77] Plasma products need to be administered early rather than late to avoid fluid overload in cases of massive hemorrhage.[78,79] However, larger plasma and platelet doses relative to RBCs (1:1:1 ratio) failed to improve the survival of major civilian trauma victims (n = 338) compared to lower doses (n = 342).[49]

It is feasible to implement targeted coagulation therapy after the first round of blood products in major trauma patients when rapid viscoelastic coagulation tests are used (see Fig. 44.5).[48,80,81] Guidelines of the American Association of Blood Banks and the European task force recommend early plasma transfusion without a specific FFP:RBC ratio.[11,73] For acute reversal of vitamin K antagonist (e.g., warfarin) therapy, FFP is used in conjunction with vitamin K, but plasma-derived, virus-inactivated prothrombin complex concentrate (PCC) is more effective for this indication, as described later.[10,82]

For congenital factor deficiencies, plasma-derived or recombinant factor concentrates are often available and are preferable to plasma transfusion in terms of safety and efficacy (Table 44.4). Plasma can be used as a replacement fluid (plasma exchange) in patients undergoing therapeutic plasma exchange (apheresis).[83] It is the first-line therapy to reduce mortality from thrombotic thrombocytopenia purpura (TTP) by providing metalloprotease (ADAMTS13) that cleaves high-molecular von Willebrand factor (vWF).[84] Plasma exchange has also been used to remove antibodies relating to ABO-incompatible or donor-specific HLA antibodies in pretransplant patients and heparin-induced thrombocytopenia before cardiac surgery.[85] Large amounts of plasma are required to achieve sufficient antibody removal, and 5% albumin is used as an exchange fluid to reduce unnecessary donor exposures and the risk of allergic reaction.[86,87]

Side Effects

Allergic reactions to plasma are the most common complications, occurring in 1% to 3% of all transfusions. The risk of fluid overload owing to a large volume of plasma transfusion should be considered in patients with limited cardiovascular reserve.

TABLE 44.4 Factor Contents of Commercially Available Prothrombin Complex Concentrates (PCCs)

	FII IU/mL	FVII IU/mL	FIX IU/mL	FX IU/mL	PC IU/mL	PS IU/mL	Heparin U/mL
4-Factor PCC							
Beriplex/Kcentra (CSL Behring, Germany)	20–48	10–25	20–31	22–60	15–45	13–26	0.4–2
Octaplex (Octapharma, Austria)	11–38	9–24	25	18–30	7–31	7–32	<15
Prothromplex Total (Baxter, Austria)	24–45	25	30	30	>20	NQ	<15
Cofact (Sanquin, Netherlands)	14–35	7–20	25	11–39	11–39	1–8	None
3-Factor PCC							
Bebulin (Baxter, USA)	30	3–5	25	35	N.Q.	N.Q.	3.75
Profilnine (Octapharma, Austria)	37	3	25	16	N.Q.	N.Q.	None
Uman Complex DI (Kedrion, Italy)	25	N.Q.	25	20	N.Q.	N.Q.	N.Q

Note: Other PCC products are also available in different countries.
PC/PS, Protein C/protein S; *AT*, antithrombin, *NQ*, not quantified.
The percent (%) activity of each factor is shown relative to FIX activity (based on the prescribing information for each product; actual factor contents may vary for each vial).

Hypocalcemia can result from citrate accumulation after plasma transfusion, and is treated with calcium chloride or gluconate. Risk of viral transmission has been reduced significantly since the 1990s by implementing nucleic acid testing for human immunodeficiency virus and hepatitis C virus. Use of pathogen-inactivated plasma (S/D or methylene blue–treated plasma) might further reduce viral transmission risks.[88]

TRALI is a serious complication of plasma transfusion. It is causally associated with anti-HLA antibodies. Multiparous females are often sensitized to HLA antigens; thus, the incidence of TRALI has gone down after many blood centers started to produce the majority of plasma products from male donors.[89]

Cryoprecipitate

Cryoprecipitate is prepared from thawing FFP at 1°C to 6°C. The cold-insoluble precipitate containing FVIII, vWF, FXIII, fibrinogen, and fibronectin is resuspended in a small amount of plasma (~15 mL), and stored at −18°C up to 12 months. Cryoprecipitate was the first concentrated source of FVIII and used to be called *cryoprecipitated antihemophilic factor*. Plasma-derived or recombinant factor concentrate has largely replaced the use of cryoprecipitate in congenital deficiency of FVIII, vWF, FXIII, or fibrinogen.[90]

Clinical Uses

Cryoprecipitate is used to manage bleeding due to acquired hypofibrinogenemia (< 100–150 mg/dL). Each unit contains 150 to 250 mg of fibrinogen; 5 to 10 units are thawed and pooled before infusion (Table 44.5). Each unit of cryoprecipitate increases plasma fibrinogen by approximately 100 mg/dL per 5 kg body weight. The volume of cryoprecipitate required to increase fibrinogen levels is far less than that of FFP. However, it takes longer to thaw and pool multiple units of cryoprecipitate, whereas thawed FFP is more readily available for transfusion. In many European countries, cryoprecipitate is no longer available. Plasma-derived, pasteurized fibrinogen concentrate is used, as described later.

The minimal level of plasma fibrinogen to minimize perioperative bleeding has not been established.[91] International guidelines previously recommended a minimal fibrinogen of 80 to 100 mg/dL,[9,92] similar to management of congenital afibrinogenemia. More recently, higher fibrinogen levels (150 to 200 mg/dL) have been recommended in European guidelines for perioperative transfusion[10,11] based on clinical data supporting fibrinogen greater than 200 mg/dL in postpartum hemorrhage,[93] coronary bypass grafting surgery,[46,94–96] and cystectomy.[97] Plasma fibrinogen levels are measured in plasma (commonly by the von Clauss method), but there is variability among different test reagents and detection methods.[98] Viscoelastic coagulation tests can be used to assess fibrinogen levels in a timely manner (15- to 30-minute turnaround),[81] but there is also variability between 2 commercially available fibrin-specific tests by thromboelastography/thromboelastometry.[99,100]

Side Effects

Exposure to multiple donors from pooled cryoprecipitate units is a major concern since no viral inactivation procedure is clinically available.[101] Use of pasteurized plasma-derived fibrinogen concentrates is strongly recommended for patients with congenital afibrinogenemia or dysfibrinogenemia. Cryoprecipitate contains some plasma, but the risk of TRALI is unclear. Risk of thrombotic complications is unknown, but potentially of concern since cryoprecipitate rapidly increases plasma fibrinogen, FVIII, FXIII, and vWF (ADAMTS13 is minimal in cryoprecipitate units).[102]

TABLE 44.5 Fibrinogen-Rich Products

	Cryoprecipitate		Fibrinogen Concentrate	
How supplied	15 mL/U		50 mL vial	
Contents	Fibrinogen FXIII FVIII/vWF	1500 mg/dL 2.8 IU/mL 6–8 IU/mL	Fibrinogen FXIII	2000 mg/dL 1 IU/mL
Pretransfusion procedures	Thawing and blood type compatibility required		Reconstituted with H_2O No thawing, blood-type free	
Other considerations	Immunoglobulins, anaphylaxis No virus inactivation		Filtration and vapor-heat for viral removal/inactivation No cell debris, minimal Immunoglobulins	

Note: Fibrinogen level in plasma is approximately 200 mg/dL.
FXIII, factor XIII; *FVIII,* factor VIII; *vWF,* von Willebrand factor.

Fibrinogen Concentrate

Fibrinogen concentrate is a lyophilized product prepared from plasma. It can be stored at room temperature for up to 30 months. Pasteurization and sterile filtration are applied to fibrinogen concentrate, thereby reducing the risk of pathogen transmission and of TRALI. It can be rapidly reconstituted and administered intravenously because no thawing or blood type matching is required.[103] In contrast to cryoprecipitate or plasma, in which fibrinogen concentration varies, fibrinogen content is standardized in each vial of fibrinogen concentrate (900–1300 mg/g vial).

Clinical Use

Fibrinogen is licensed for hereditary hypofibrinogenemia and afibrinogenemia in the United States, but it is also indicated for acquired hypofibrinogenemia as an alternative to cryoprecipitate in many European countries. Several small retrospective clinical studies have demonstrated hemostatic effects of fibrinogen replacement after complex cardiac surgical cases,[104,105] but the results of recent prospective randomized trials for fibrinogen replacement in cardiac surgery are mixed (Table 44.6).[106–110] Fibrinogen replacement can be effective if hypofibrinogenemia (< 150–200 mg/dL) is the main cause of bleeding, but thrombin generation is not extensively impaired after loss of 100% to 150% of circulating blood volume.[78] However, impaired thrombin generation is not uncommon in complex cardiopulmonary bypass procedures and after major trauma with hypothermia and acidosis.[51,80,107,110] Therefore, fibrinogen replacement per se may be insufficient to achieve effective hemostasis. The combination of tissue factor–activated whole blood thromboelastometry (EXTEM) and the fibrin-specific test (FIBTEM) can be used to assess impaired thrombin generation and fibrin polymerization. Fibrinogen replacement as part of a point-of-care guided transfusion algorithm appears to be effective in reducing the transfusion requirement for RBCs and plasma.[51,80,105,111]

Side Effects

Elevated fibrinogen levels before surgery are associated with proinflammatory state, but therapeutic fibrinogen replacement (target, 200–350 mg/dL) has not been associated with thromboembolic events in surgical and nonsurgical patients.[106-110,112]

Recombinant Factor VIIa

Recombinant activated factor VIIa (rFVIIa) is an activated form of human FVII produced in hamster kidney cells. Its hemostatic activity is mainly mediated by tissue factor–dependent activation of FX and subsequent thrombin generation. Use of rFVIIa is clinically indicated for prophylaxis or treatment of bleeding in hemophiliacs who develop neutralizing antibodies to FVIII or FIX and with congenital FVII deficiency.

Off-label use of rFVIIa has been reported after major bleeding in trauma and surgery, but multifactorial coagulopathy in addition to hypothermia and acidosis can make its activity unpredictable and potentially dangerous. The incidence of thromboembolic complications appears to be nearly 7-fold higher in those without congenital factor deficiency.[113] The use of rFVIIa should be considered only after replenishing plasma proteins (particularly prothrombin and fibrinogen), and optimizing body temperature and pH. Use of rFVIIa is decreased when a transfusion algorithm guided by point-of-care principles is implemented.[51,111]

Clinical Uses

The recommended initial dose of rFVIIa for hemophiliacs with inhibitors is 90 to 120 μg/kg, but higher doses of 200 to 400 μg/kg have been used without major thrombosis. In refractory bleeding, combination therapy with factor eight inhibitor bypassing activity (FEIBA), an activated PCC, has been suggested.[114] In nonhemophiliacs, the initial dose of rFVIIa is lower (20–70 μg/kg).[115] In randomized trauma trials, the efficacy of higher initial doses (200 μg/kg) was limited to a small reduction in RBC use with no effect on 30-day mortality.[116,117] In a randomized trial in intracerebral hemorrhage, rFVIIa at 80 μg/kg reduced hematoma expansion but led to increased arterial thrombosis.[118] Similarly, in a study of bleeding after cardiac surgery, there were fewer reoperations and decreased allogeneic blood use with rFVIIa at 40 μg/kg and 80 μg/kg but with increased adverse events, including stroke.[119]

Side Effects

Thrombotic complications after rFVIIa are infrequent in hemophilia, but these risks appear to be increased in nonhemophiliacs undergoing surgery.[120] In this setting, the incidence of thromboembolic complications appears to be nearly 7-fold higher than in patients

TABLE 44.6 Prospective Randomized Trials of Fibrinogen Replacement in Cardiac Surgery

	Study Setting	Fibrinogen	Control	Fibrinogen Levels After Fibrinogen Vs. Placebo	Efficacy of Fibrinogen; Key Findings
Rahe-Meyer et al.[106]	61 thoracic aortic replacement	8 g if FIBTEM-MCF < 22 mm and clinical bleed (n = 29)	Placebo (n = 32)	260 vs. 189 mg/dL	Yes; Reduced allogeneic product usage with fibrinogen
Tanaka et al.[107]	20 valve replacement or repair	4 g if clinical bleed (n = 10)	1 U apheresis platelet if clinical bleed (n = 10)	209 vs. 165 mg/dL	No; similar postoperative blood loss
Ranucci et al.[109]	116 mixed cardiac cases with CPB over 90 min	4 g if FIBTEM-MCF < 22 mm (n = 58)	Placebo (n=58)	367 vs. 242 mg/dL	Yes; Reduced allogeneic product usage with fibrinogen
Jeppsson et al.[108]	48 coronary bypass grafting surgery	2 g before surgery if fibrinogen < 380 mg/dL (n = 24)	Placebo (n=24)	230 vs. 200 mg/dL	No; similar postoperative blood loss
Rahe-Meyer et al.[110]	152 thoracic aortic replacement	8 g if FIBTEM-MCF < 22 mm and clinical bleed (n = 78)	Placebo (n = 74)	~300 vs. ~150 mg/dL[a]	No; More platelet transfusion with fibrinogen

CPB, Cardiopulmonary bypass; *MCF*, maximum clot firmness.
[a]FIBTEM-MCF 21.5 mm vs. 9 mm.

treated for bleeding due to congenital factor deficiency.[113] In an analysis of 35 published randomized clinical studies, the incidence of arterial thromboembolic events, but not venous thrombosis, was increased by 1.7-fold with rFVIIa therapy.[121] Higher rFVIIa dose (> 80 µg/kg), age, and coronary artery disease were contributing factors to thrombosis.

Prothrombin Complex Concentrate

PCC is a sterile, lyophilized concentrate of factors II, VII, IX, and X and protein C and S. Prior to development of FIX concentrates, PCC with low amounts of FVII (3-factor PCC) was used to treat hemophilia B. There is a variety of commercial PCCs available in different countries, but the content of PCC is standardized to the amount of FIX in each vial (each vial contains at least 500 IU of FIX; see Table 44.4). Advantages of PCC include rapid availability (no need for blood typing, thawing), small volume of infusion, and avoidance of complications such as ABO incompatibility and TRALI associated with plasma. PCC containing clinically relevant FVII levels (4-factor PCC) has been approved by the FDA for acute reversal of vitamin K antagonists in the treatment of major bleeding[122] and for prevention of bleeding prior to urgent surgery.[82] PCCs increase thrombin generation by interacting with negatively charged phospholipids on activated platelets at the vascular injury site.[123] Commercial PCCs are fractionated from pooled plasma and undergo multiple pathogen reduction steps, such as vapor heating, S/D treatment, and nano-filtration.

Clinical Uses

PCC can be rapidly reconstituted with sterile water (20 mL per 500 IU) without the need for thawing and blood type matching. Dosing depends on the extent of anticoagulation. A high initial dose of 30 to 50 IU/kg (daily maximum, 5000 IU) is used in life-threatening bleeding associated with anticoagulation, including intracranial hemorrhage and retroperitoneal bleeding. A lower dose of 20 to 25 IU/kg is used for soft tissue bleeding, epistaxis, and hematuria. Subsequent doses are based on PT/INR measurements. In acute bleeding, the major advantage of PCC is that procoagulant FII, FVII, FIX, and FX can be rapidly (< 30 minutes, Fig. 44.6) increased by 40% to 80% without dilution of RBCs and platelets.[82,122,124] The vicious cycle of hematoma formation, tissue edema, and rebleeding can be prevented by prompt reestablishment of hemostasis.[125] Adjunctive vitamin K is recommended to sustain PT/INR because plasma FVII falls quickly after a dose of PCC owing to its short half-life.[124]

There is a paucity of data on PCC for treatment of coagulopathy in trauma, major surgery, and hepatic dysfunction. There have been a number of retrospective studies on PCC in trauma and surgical patients who had suffered from major bleeds[51,80,105,126,127] or those who were refractory to standard transfusion, including platelets, plasma, and cryoprecipitate.[128,129] There are insufficient data regarding the optimal timing and dose of PCC outside the setting of acute reversal of vitamin K antagonists.

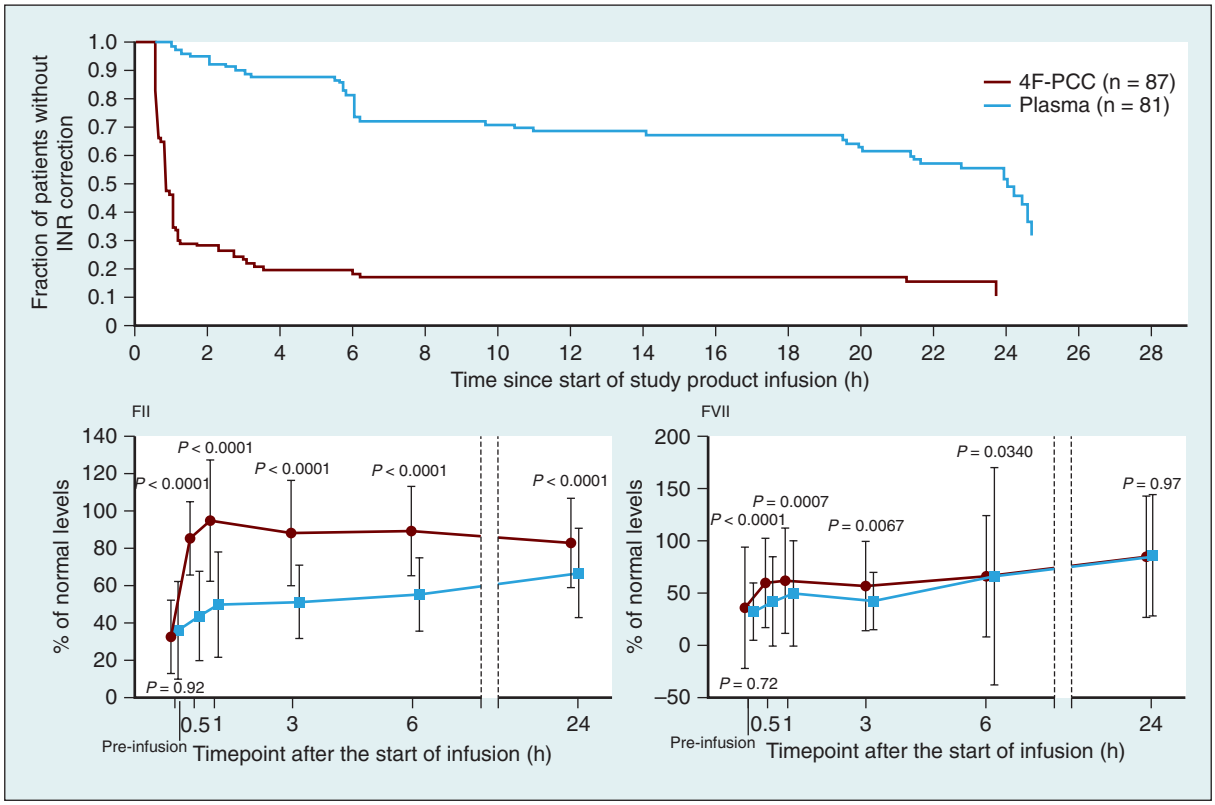
Side Effects

Use of PCC is generally safe for acute reversal of anticoagulation and the incidence of thrombotic complications is about 0.9% to 2%.[130,131] Thrombogenicity is still a concern in the case of blood stasis associated with congestive heart failure.[132] PCC is contraindicated in patients with DIC,[10] but the use of PCC is often considered in bleeding associated with hepatic cirrhosis and severe hemodilution.[126,129,133] Thrombotic complications appear to be more commonly associated with off-label indications.[113]

Current antiviral protocols for factor concentrates are not effective against prions (e.g., vCJD) or nonlipid-enveloped, heat-resistant viruses (e.g., parvovirus B19), but these risks are considered low.[134]

Antithrombin Concentrate

Antithrombin (AT) is a serine protease inhibitor with a molecular weight of 58 kDa. Normal plasma AT is about 150 µg/ml (2.6 µM).



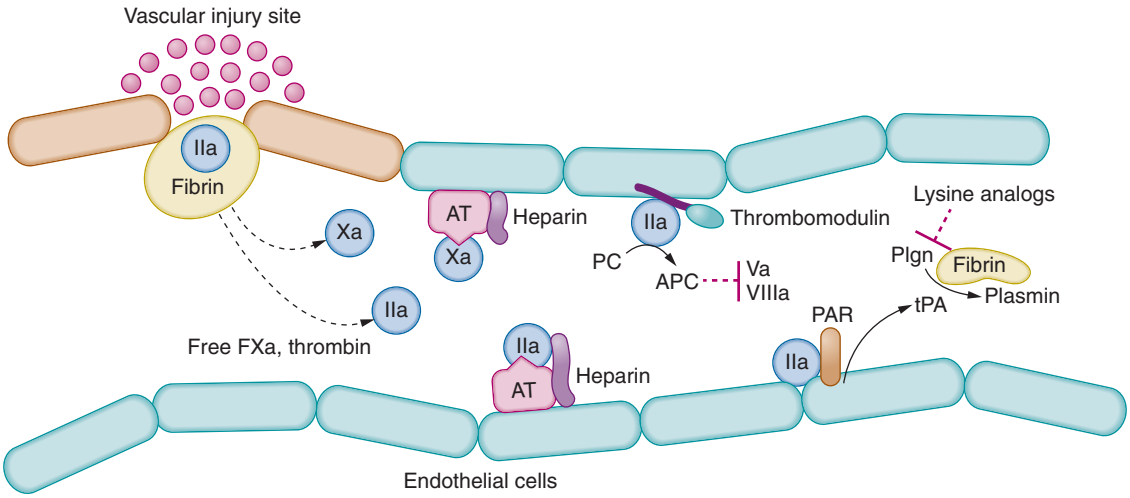
• **Fig. 44.6 INR correction and coagulation factor levels in warfarin-treated patients who received 4-factor PCC or plasma transfusion.** The mean plasma coagulation factor levels [% of normal activity (SD)] for FII (prothrombin) and FVII over 24 hours after injection of four-factor PCC (4F-PCC) or plasma transfusion. The elapsed time (h) from the treatment is indicated on the horizontal axis. *Pre,* Baseline; *F,* factor. *P* values indicate the significant difference in protein levels between groups. (From Goldstein JN, Refaai MA, Milling TJ, Jr., et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. *Lancet*. 2015;385:2077–2087.)

Anticoagulant activity of AT is potentiated by endothelial surface heparan sulfate or exogenously administered heparin. In congenital AT deficiency, AT is 40% to 60% of normal, resulting in prolonged half-life of FXa and thrombin (Fig. 44.7).[135] The incidence of venous thromboembolism is increased in congenital AT deficiency during pregnancy and after major trauma or surgery. Replacement of AT using plasma-derived (Thrombate III, Grifols, Los Angeles, CA) and recombinant AT concentrate (ATryn, GTC Biotherapeutics, Framingham, MA) are indicated to prevent thrombotic complications in congenital deficiency. Recombinant AT is produced in transgenic goats and has different glycosylation and a shorter half-life (11 hours vs. 2.5 days). Whether the cost of higher doses is justified by the improved viral safety of recombinant AT is unknown.

Acquired AT deficiency is frequently observed following treatment with intravenous heparin for more than 4 to 5 days. In cardiac surgical patients with heparin insensitivity (activated clotting time < 400 sec), plasma-derived or recombinant AT concentrates restore plasma AT activity effectively without the need for additional heparin or FFP.[136,137] AT concentrates are less likely to decrease hematocrit and platelet count compared to FFP. Both plasma-derived and recombinant AT concentrates contain trace amounts of heparin; thus, they should not be used in patients with heparin-induced thrombocytopenia (HIT).[10]

Protein C Concentrate

Protein C is a vitamin K-dependent factor similar to prothrombin, FVII, FIX, and FX. Protein C activation by thrombin is limited in the presence of fibrinogen, FV, FVIII, and platelets at a vascular injury site, but is more efficiently activated by thrombin bound to thrombomodulin expressed on the endothelium (see Fig. 44.7). Elevated systemic thrombin activity thus increases protein C activation as observed in thrombophilia,[138] sepsis,[139] and traumatic injury.[140] Activated protein C with protein S downregulates activated FV and FVIII and exerts antiinflammatory and cytoprotective functions by modulating endothelial protein C receptor and protease-activated receptor-1 (PAR-1, thrombin receptor).[141] Antiinflammatory effects of activated protein C (recombinant) might be beneficial in patients with severe sepsis (Acute Physiologic Assessment and Chronic Health Evaluation [APACHE] score > 25), but serious bleeding is the major side effect.[142] Homozygous



• **Fig. 44.7 Regulation of procoagulant responses.** Local and systemic regulation of coagulation and fibrinolysis at a site of vascular injury are shown. Hemostasis is established as fibrin is polymerized by thrombin (FIIa) and activated FXIII. When thrombin or FXa is released (i.e., free thrombin) into the systemic circulation during hemostatic activation, antithrombin (AT) and thrombomodulin of intact endothelium bind to thrombin and reduce its procoagulant activity. Thrombomodulin-bound thrombin activates protein C (APC), which inactivates FVa and FVIIIa. Thrombin also causes the release of tissue plasminogen activator (tPA) from endothelium, which promotes plasminogen (Plgn) conversion to plasmin on the fibrin surface. Broken lines indicated inhibitory action of respective protease inhibitors. *PAR,* Protease-activated receptor (thrombin receptor on endothelium). (Adapted from Ide M, Bolliger D, Taketomi T, Tanaka KA. Lessons from the aprotinin saga: current perspective on antifibrinolytic therapy in cardiac surgery. *J Anesth.* 2010;24:96–106.)

protein C deficiency in newborns manifests as purpura fulminans with thrombosis in small vessels causing skin necrosis.[143] Incidence of venous thromboembolism is 8- to 10-fold higher in individuals with heterozygous protein C deficiency.[144]

Lyophilized protein C concentrate (Ceprotin, Shire, Lexington, MA) is available for prevention and treatment of purpura fulminans and venous thrombosis in the North America. The initial dose for acute thrombosis is 100 to 120 IU/kg, followed by maintenance doses of 45 to 60 IU/kg every 6 to 12 hours. The infectious risk of plasma-derived protein C is low owing to viral inactivation steps, including polysorbate-80, vapor-heat, and ion exchange chromatography. Precautions for use include bleeding, sodium overload, rare allergic reactions and heparin-induced thrombocytopenia due to trace amounts of heparin.

Antifibrinolytic Agents

The lysine analogs ε-aminocaproic acid (EACA) and tranexamic acid (TXA) are widely popular antifibrinolytic agents with hemostatic properties in many clinical areas.[145] Both drugs prevent plasminogen from binding to fibrin by occupying the plasminogen lysine-binding site (see Fig. 44.7). Plasmin activation and subsequent fibrin degradation are inhibited because tissue plasminogen activator (tPA) and plasminogen can no longer co-localize on the surface of fibrin. Most clinical studies have been done with TXA because it is more potent and universally available. EACA and TXA have a low molecular weight (131 Da and 157 Da, respectively); thus, they are less antigenic compared to the bovine plasmin inhibitor aprotinin (6512 Da), which acts as a direct plasmin inhibitor. Clinical use of aprotinin has been resumed but is limited to coronary bypass grafting surgery in Canada and Europe after its suspension from 2007 to 2012 owing to safety concerns.[146,147]

Clinical Uses

Lysine analogs have been conventionally used to reduce bleeding in patients with hemophilia and von Willebrand disease.[148] EACA is administered orally or intravenously for bleeding associated with fibrinolysis, with an initial dose of 5 g in adults. In hemophiliacs having dental extraction, TXA is given at a dose of 10 mg/kg 3 to 4 times a day. Antifibrinolytic therapy appears to be useful in bleeding associated with menorrhagia[149] and chronic thrombocytopenia.

Reduced perioperative blood loss and decreased usage of PRBCs has been reported in cardiac, hepatic, and orthopedic surgeries without increased rate of thromboembolic events with the use of TXA. Multiple TXA regimens have been clinically used and the optimal dosage and route for any specific indication are unclear. The reported studies are largely underpowered for safety issues.[150,151]

In cardiac surgery with cardiopulmonary bypass, the typical loading dose of intravenous EACA and TXA is 50 mg/kg and 10 to 15 mg/kg, respectively, after systemic anticoagulation. Continuous infusion of EACA and TXA is commonly used at 15 mg/kg/hr for EACA and 7.5 mg/kg/hr for TXA until the end of surgery. A single high-dose of TXA (100 mg/kg) was used in a large randomized

controlled trial (Aspirin and Tranexamic Acid for Coronary Artery Surgery [ATACAS]) involving 4631 patients undergoing coronary artery bypass grafting surgery.[152] The incidence of surgical revision owing to major hemorrhage or cardiac tamponade and the total number of transfused allogeneic blood products were reduced by nearly 50%. In the trauma setting, TXA (1 g loading, followed by 1 g over 8 hours) improved mortality without increasing cardiovascular complications.[153]

Side Effects

Systemic thrombosis is uncommon with EACA or TXA, but they should not be used in patients with DIC.[10] Lysine analogs are mainly excreted by the kidneys, and dosage should be reduced based on serum creatinine level. EACA and TXA are eliminated by hemofiltration or dialysis. With renal or ureteral bleeding, lysine analogs can increase the risk of ureteral obstruction due to clot formation. Prolonged infusion of TXA is associated with seizures presumably owing to TXA crossing the blood–brain barrier and antagonizing GABA and glycine receptors.[154] In the ATACAS trial, the incidence of seizures was 0.7% in cardiac surgery patients treated with TXA (100 mg/kg bolus) compared to 0.1% in the placebo control. Lowering the total TXA dose to 30 mg/kg or use of alternative agents (EACA) might reduce seizure risk in susceptible patients (e.g., valve replacement).[155]

Desmopressin

Desmopressin (1-deamino-8-D-arginine vasopressin) is a synthetic vasopressin analog with antidiuretic activity. In mild to moderate von Willebrand disease and hemophilia A, intravenous desmopressin (0.3–0.4 μg/kg) increases plasma vWF and FVIII by 2- to 3-fold within 60 to 90 minutes. Increased vWF might improve platelet adhesion to sites of vascular injury. Desmopressin is often administered to patients with preexisting platelet dysfunction related to antiplatelet drugs and uremia. Desmopressin appears to reduce blood loss, but most studies failed to demonstrate reduced RBC transfusion in nonhemophilic surgical patients.[156] Inconsistent efficacy could be related to simultaneous release of tissue plasminogen activator and tachyphylaxis or exhaustion of stored vWF-FVIII in high-stress situations.

Side Effects

Rapid intravenous administration of desmopressin causes flushing and mild hypotension via vasopressin V_2 receptor stimulation. Vascular occlusion due to elevated vWF is rare in von Willebrand disease and hemophilia A but could be a concern in surgical patients with preexisting cardiovascular disease.[156]

Topical Hemostatic Agents

Topical hemostatic agents are useful in controlling minor bleeding from bone (bone wax, Ostene, Baxter, Round Lake, IL) or small capillaries and venules (e.g., topical thrombin).[157] Bovine thrombin has been clinically used for a long time but is associated with major immunologic reactions, including immunization against endogenous prothrombin, thrombin, FV, and cardiolipin. Acquired FV deficiency due to bovine thrombin exposure can result in serious bleeding.[158] Plasma-derived thrombin (Evithrom, Ethicon, Somerville, NJ) or recombinant thrombin (Recothrom, Mallinckrodt, Hazelwood, MO) are preferred to bovine thrombin (Thrombin–JMI, Pfizer, New York, NY) as a topical agent.

Oxidized cellulose (Surgicel, Ethicon) induces local hemolysis of RBCs by lowering pH and provides a physical matrix for coagulation. Disadvantages include inactivation of natural clotting enzymes, such as thrombin, and potential for inflammation and delayed wound healing. Microfibrillar collagen (Avitene, Bard) increases local platelet adhesion and activation, leading to hemostasis within 5 minutes. The collagen particles do not cause much swelling and are reabsorbed within 8 weeks. It should be cautioned that microfibrillar collagen can pass through RBC salvage system filters. Platelet gel (Vitagel, Stryker) combines microfibrillar collagen and thrombin with the patient's own platelet and plasma (fibrinogen) but requires centrifugation for preparation.

Fibrin sealants (TISSEEL, Baxter; Crosseal, OMRIX Biopharmaceuticals, Ltd, Brussels; Evicel, Ethicon) are effective for venous oozing from raw surfaces. They are supplied with separate vials of fibrinogen, thrombin, and calcium chloride that are mixed at the wound by a dual-syringe applicator. Hemostasis results from topical fibrin formation. A patch sponge (TachoSil, Baxter) impregnated with lyophilized human fibrinogen and thrombin is also available for treatment of raw surface bleeding. To prevent viral transmission from the human plasma, fibrinogen and thrombin are treated with solvent-detergent, nanofiltration or vapor-heat. Recombinant aprotinin (TISSEEL) and tranexamic acid (Crosseal) are added for improved clot stability.

Gelatin forms (Gelfoam, Pfizer; Gelfilm, Pfizer; Surgiform, Surgiform Technology, Ltd., Kershaw County, SC) provide a physical matrix for clot formation, and are effective in bleeding from small capillaries and venules. Another gelatin-based sealant (FloSeal, Baxter) is a mixture of human thrombin and bovine-derived gelatin-based matrix. Thrombin generates fibrin from blood fibrinogen and the gelatin particles expand to tamponade bleeding. Gelatin matrix is reabsorbed after 6 to 8 weeks.

These topical agents are generally safe and useful adjuncts for hemostasis when used for appropriate indications and anatomic sites.[157]

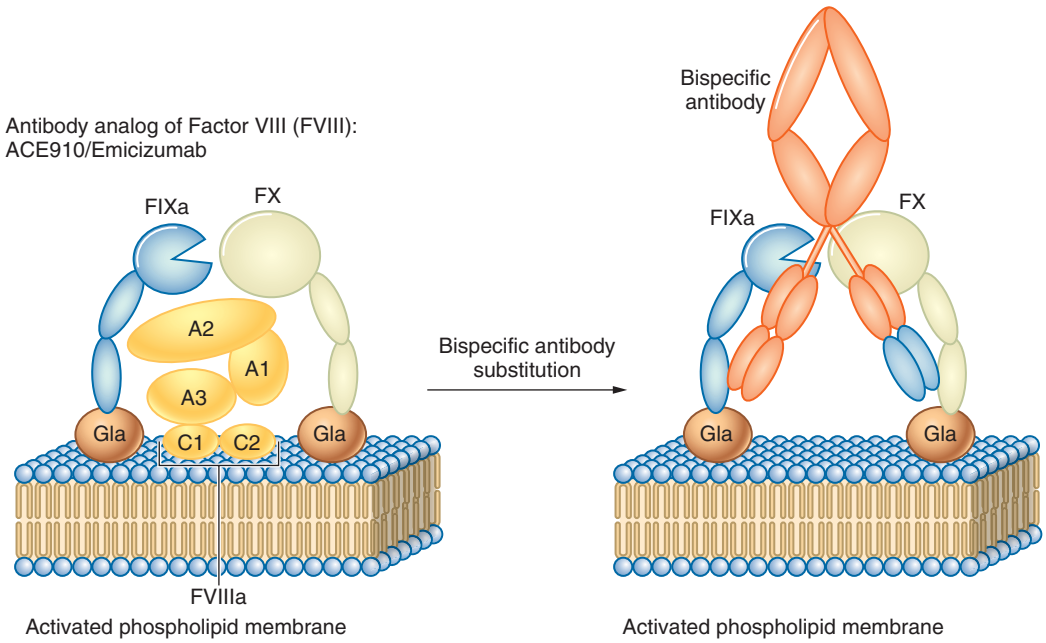
Special Considerations

Liver Failure

Patients with liver failure often develop abnormal hemostasis since most coagulation factors and inhibitors are synthesized by hepatocytes. Hemophilia A and B can be cured by liver transplantation.[159] The liver is also the major site for clearance of activated coagulation factors and plasminogen activators. The extent of coagulopathy varies with the type and stage of liver and biliary tract disease.[160,161] PT/INR has been part of the outcome assessment for liver disease.[162] Coagulopathy in end-stage liver disease is often viewed as a hemorrhagic condition, but recent clinical data indicate that the hypocoagulable state coexists with a potentially prothrombotic state due to generalized decreases in both procoagulant and anticoagulant proteins.[160,161]

Jehovah's Witnesses

Devout Jehovah's Witnesses (JWs) do not accept transfusion of "primary components" including RBCs, white blood cells, platelets, and plasma. The use of immunoglobulins, albumin, and plasma-derived FVIII and FIX ("hemophiliac preparations" per religious leaders) have been allowed since 1978. The policy on blood transfusion was changed recently—acceptance of fractionated products of "primary components" was left to the individual believer (Table 44.7).



• **Fig. 44.8** Schematic illustration of the FVIII-mimetic cofactor action of emicizumab (ACE910), an anti-FIXa/X bispecific antibody. *Left:* Activated FVIII (FVIIIa) supports the interaction between activated factor IX (FIXa) and factor FX (FX) through its binding to both factors on the activated phospholipid membrane at a coagulation site. *Right:* Emicizumab binds to FIXa and FX, promoting the interaction between FIXa and FX, enhancing the generation of activated FX (FXa) and exerting FVIII-mimetic cofactor activity. (Adapted from Muto A, Yoshihashi K, Takeda M, et al. Anti-factor IXa/X bispecific antibody ACE910 prevents joint bleeds in a long-term primate model of acquired hemophilia A. *Blood*. 2014;124:3165–3171.)

TABLE 44.7 Primary Components and Fractionated Products for Jehovah's Witnesses

Primary Components	Fractionated Products of Primary Components
Not Acceptable	**Up to the Individual Believer**
Red blood cells	Hemoglobin-based oxygen carrier
White blood cells	Interleukins, Interferons
Platelets	Platelet gels
Plasma	Albumin, immunoglobulins, coagulation factor/inhibitor concentrates, recombinant human proteins, topical hemostatics

Many strategies for blood conservation for JW patients have been described, including preoperative administration of iron and erythropoietin, intraoperative use of normovolemic hemodilution and cell scavenging, and use of desmopressin, antifibrinolytics, and recombinant proteins, such as rFVIIa or other plasma-derived factor concentrates (see Table 44.3).[163] Using such techniques, even complex cardiac surgical procedures can be successfully performed in JW patients. A recent meta-analysis in adult JW patients undergoing cardiac surgery showed a nonsignificant trend to better early outcomes—including mortality, reoperation owing to bleeding, and thromboembolic complications—than in controls with and without blood transfusion.[164]

Emerging Developments

Special focus on patient blood management (PBM) to reduce inappropriate blood component use has reduced the plasma usage in the United States. Improved pathogen detection in donors and pathogen reduction treatments should allow increasingly safer supplies of allogeneic blood products.[55]

There are continuing efforts to improve techniques to utilize hematopoietic progenitors, embryonic stem cells, and pluripotent stem cells to achieve in vitro mass production of functional RBCs and platelets.[165,166] In time, cultured autologous RBCs and platelets might become valid transfusion resources for those with rare antigens and multiple alloantibodies. Cultured RBCs and platelets might also be used as a carrier for the delivery of therapeutic agents to certain cells (e.g., cancer) or organs.[167,168]

A bispecific antibody targeting FIXa and FX has been developed to bypass FVIII activity in hemophilia patients who develop FVIII neutralizing antibody.[169] The anti-FIXa/FX immunoglobulin G antibody (emicizumab; ACE910) aligns FIXa and FX into spatially appropriate positions, thus eliminating the need for FVIII (Fig. 44.8). Once-weekly subcutaneous injection of emicizumab was effective in reducing bleeding episodes in 18 Japanese hemophilia patients with or without anti-FVIII antibody.[170]

There is increasing interest in abrogating contact activation (intrinsic coagulation pathway) to reduce pathologic thrombosis associated with DIC and extracorporeal circulation.[171] Two main targets are factor XI[172,173] and factor XII.[174] These pathways are hypothesized to cause minimal bleeding complications because normal tissue factor triggered hemostasis is maintained.

Key Points

- Transfusion of blood components can be lifesaving, but there are potentially serious complications. ABO-incompatible transfusion—transfusion-associated circulatory overload (TACO) and TRALI—are two of the most common causes of death after blood transfusion. Proper identifications of the donor unit and patient and careful risk–benefit assessments are essential prior to each component transfusion.
- Transfusion of RBC concentrates should be determined not only by threshold hemoglobin values but also by the rate/extent of hemorrhage, clinical conditions (e.g., reduced cardiovascular reserve), and the risk–benefit ratio.
- Hemodilution can be extensive in major trauma and surgery, affecting both procoagulant and anticoagulant factors. Reduced plasma levels of fibrinogen and factor XIII early during hemodilution result in fragile clot formation, which is susceptible to fibrinolysis. Fibrinogen can be replaced more efficiently by cryoprecipitate (or plasma-derived fibrinogen) than by FFP.
- Plasma-based PT and aPTT are frequently used to evaluate coagulopathy but are not predictive of perioperative bleeding risks. Thromboelastography/thromboelastometry of whole blood is a useful adjunct to PT/aPTT and platelet count because the stability of fibrin polymerization (i.e., activity of thrombin, fibrinogen, and FXIII) can be assessed.
- Early plasma and platelet administration, along with RBCs, is indicated in major hemorrhage associated with severe trauma. Expedited surgical control of bleeding is crucial in improving morbidity and mortality, and there does not appear to be any specific ratio of blood products that can be recommended. The use of thromboelastography/thromboelastometry can be helpful in the selection of hemostatic product(s).
- For certain hereditary deficiencies of coagulation factors or inhibitors, plasma-derived or recombinant concentrates are available and are preferable for safety (e.g., reduced risk of viral transmission) and efficacy. Use of factor concentrates in acquired factor deficiency is generally considered to be off-label, but there are some supportive data available for certain indications (e.g., PCC for vitamin K antagonist reversal and fibrinogen for dilutional coagulopathy).
- Topical hemostatic agents are frequently used by surgeons, and can be potentially useful to reduce blood loss. The proper indication(s) and site(s) should be considered to reduce untoward complications (e.g., tissue swelling, necrosis, intravascular absorption).

Key References

Goldstein JN, Refaai MA, Milling TJ Jr, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. *Lancet*. 2015;385:2077–2087. The authors compared the efficacies of 4-factor PCC or plasma in a multicenter, open-label, phase 3b randomized trial involving 181 patients undergoing an urgent surgical or invasive procedure. The intention-to-treat efficacy population comprised 168 patients (PCC, n = 87; plasma, n = 81). Rapid INR reduction (≤ 1·3 at 0·5 hr after therapy) was achieved in 48 (55%) patients in the PCC group compared with 8 (10%) patients in the plasma group. Effective hemostasis was achieved in 78 (90%) patients in the PCC group compared with 61 (75%) patients in the plasma group. Both endpoints demonstrated noninferiority and superiority of PCC over plasma. The safety profile of 4F-PCC was generally similar to that of plasma; 49 (56%) patients receiving PCC had adverse events compared with 53 (60%) patients receiving plasma. Notably, fluid overload or similar cardiac events were more frequent in the plasma group (3% vs. 13% with PCC). (Ref. 82).

Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*. 2015;313:471–482. The authors conducted a prospective randomized trial of 1:1:1 versus 1:1:2 ratio of plasma, platelets, and RBC administration (n = 338 vs. 342) in the early resuscitation of major civilian trauma victims. Improved hemostasis was more frequently observed in the 1:1:1 group than in the 1:1:2 group (86.1% vs. 78.1%). The increased donor exposure was evident in the 1:1:1 group (median 19 U plasma plus platelets vs. 11 U in the 1:1:2 group). This study failed to point to the optimal ratio (or volume) of plasma and platelet transfusion. Fibrinogen or fibrin polymerization was not continuously monitored and cryoprecipitate was seldom used in either group of patients (median, 0 unit). (Ref. 49).

Myles PS, Smith JA, Forbes A, et al. Tranexamic acid in patients undergoing coronary-artery surgery. *N Engl J Med*. 2017;376:136–148. The authors compared the safety and efficacy of a single high-dose TXA regimen (100 mg/kg prior to cardiopulmonary bypass) in a multicenter randomized controlled trial in patients undergoing coronary artery bypass grafting surgery. There was no difference between TXA (n = 2311) and placebo (n = 2320) in the primary outcomes consisting of death and thromboembolic complications (nonfatal myocardial infarction, stroke, pulmonary embolism, renal failure, or bowel infarction) within 30 days after surgery. Total number of units of blood products was reduced from 7994 with placebo to 4331 with TXA (P < 0.001). In addition, the incidences of major hemorrhage or cardiac tamponade leading to reoperation were reduced by 50% (P = 0.001). Seizures occurred in 0.7% and 0.1% in patients treated with and without TXA, respectively (P = 0.002). TXA seems to be safe and effective in reducing perioperative blood loss in cardiac surgery. However, caution should be exercised for postoperative seizures in some patients receiving high-dose TXA. (Ref. 152).

Nakayama Y, Nakajima Y, Tanaka KA, et al. Thromboelastometry-guided intraoperative haemostatic management reduces bleeding and red cell transfusion after paediatric cardiac surgery. *Br J Anaesth*. 2015;114:91–102. The authors reported a prospective randomized study (n = 100) of conventional versus thromboelastometry (ROTEM)–guided hemostatic intervention in cardiac surgery for infants (median age, 10–13 months). Platelets and plasma were the only 2 products available for hemostatic therapy during the study. In the conventional group, platelets and plasma were transfused when platelet count was below 80 × 109/L, and activated clotting time (ACT) was over 150 seconds. Corresponding indications in the ROTEM group were platelets for EXTEM-A10 (10-minute amplitude) below 30 mm and plasma for FIBTEM-A10 below 5 mm. The amount of intraoperative plasma transfusion was higher in the ROTEM group than the conventional group (median, 21 mL/kg vs. 14 mL/kg; P < 0.005). This resulted in higher fibrinogen levels in the ROTEM group immediately after surgery (165 vs. 125 mg/dL; P < 0.001). Reduced postoperative blood loss, RBC transfusion, and duration of ICU stay in the ROTEM group suggest that early plasma transfusion to maintain fibrin polymerization may be more effective than conventional management focused on clotting time (e.g., PT/INR, aPTT, or ACT). (Ref. 79).

Raza I, Davenport R, Rourke C, et al. The incidence and magnitude of fibrinolytic activation in trauma patients. *J Thromb Haemost*. 2013;11:307–314. The authors investigated the incidence and extent of hyperfibrinolysis in 303 consecutive trauma patients using thromboelastometry (maximum lysis of > 15%) and fibrinolytic markers

(plasmin–antiplasmin complex and D-dimer levels). Hyperfibrinolysis was evident on thromboelastometry in only 5% of patients, while plasma fibrinolysis markers were elevated in 57% of patients in proportion to the base deficit and hypotension on admission. The 28-day mortality of patients with hyperfibrinolysis on thromboelastometry was 40%, whereas it was 12% in those with elevated plasma fibrinolysis markers. These data suggest that hyperfibrinolysis on thromboelastometry represents a marker of worse prognosis and that antifibrinolytic therapy should be considered according to the injury severity regardless of the thromboelastometry findings. (Ref. 47).

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Anticoagulant and Antiplatelet Therapy

DAVID ROYSTON

CHAPTER OUTLINE

Normal Platelet Function and Hemostasis

Mechanisms of Thrombin and Fibrin Generation

Indirect Inhibitors of Thrombin Generation
- Historical Considerations
- Heparins
- Low-Molecular-Weight Heparin
- Pentasaccharide
- Vitamin K Antagonists

Direct Thrombin Inhibitors
- Intravenous Direct Thrombin Inhibitors
- Oral Direct Thrombin Inhibitors
- Inhibitors of Activated Factor X

Antiplatelet Agents
- Oral Agents
- Platelet Receptor Inhibitors
- Adenosine Diphosphate Analogs
- Glycoprotein IIb/IIIa Antagonists
- Protease Activated Receptor-1 (Thrombin Receptor)

Emerging Developments
- Reversal of Novel Anticoagulants

Arterial and venous thrombosis are major causes of morbidity and mortality. Venous thromboembolism (VTE) is the leading cause of preventable in-hospital mortality. Deep vein thrombosis (DVT) leading to VTE causes as many as 300,000 deaths annually in the United States and approximately 300,000 within the European Union as well.[1,2]

Arterial thrombosis is the most common cause of myocardial infarction (MI), ischemic stroke, and limb gangrene. Arterial thrombi, which typically form under high shear conditions, consist of platelet aggregates held together by small amounts of fibrin. Because of the predominance of platelets, strategies to inhibit arterial thrombogenesis focus mainly on drugs that block platelet function, but include anticoagulants for prevention of cardioembolic events in patients with atrial fibrillation or mechanical heart valves.

DVT can lead to pulmonary thromboembolism (PE), which can be fatal, and to postphlebitic syndrome. Venous thrombi, which form under low shear, are composed mainly of fibrin and trapped red blood cells, with relatively few platelets. With the predominance of fibrin in venous thrombi, anticoagulants are the agents of choice for the prevention and treatment of DVT and VTE.

The incidence of VTE is about 20% higher in men than in women and increases with age in both sexes. Asian and Hispanic populations have a lower risk of VTE, whereas Caucasians and African Americans have a 2.5-fold higher risk.

Agents such as vitamin K antagonists or dual antiplatelet therapy with aspirin and clopidogrel have addressed inappropriate thrombosis. Administration of these drugs significantly reduces the risk of thrombotic events but also increases bleeding. They also suffer from inconsistency in efficacy associated with pharmacogenetic factors and drug interactions. Recently there have been a number of additional anticoagulant and antiplatelet drugs[3] based on a greater understanding of hemostasis mechanisms that are outlined in the following text.

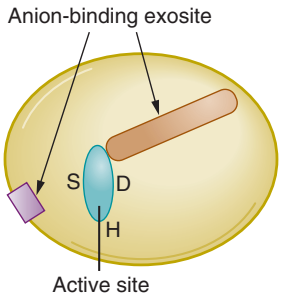
Normal Platelet Function and Hemostasis

A brief overview of the hemostatic system is provided as background for consideration of antiplatelet and anticoagulant drugs; further detail is provided in Chapters 43 and 44. The initial response of the hemostatic system to tissue or endothelial injury is to produce a platelet plug (primary hemostasis). Platelets have multiple surface receptors that, when stimulated, produce a shape change involving the energy-dependent actin-myosin system. Principal among these is the glycoprotein Ib (GpIb) receptor, which binds to von Willebrand factor (vWF), a large protein expressed on the abluminal side of endothelial cells that is exposed when there is endothelial injury. The glycoprotein Ib receptor is expressed at all times. There are also receptors for adenosine diphosphate (ADP), thrombin, and thromboxane A_2. These receptors principally allow feedback amplification to enhance generation of the primary hemostatic plug.

With the platelet shape change, the surface of the platelet also changes with expression of a second binding site, the glycoprotein IIb/IIIa (GpIIb/IIIa) receptor. The GpIIb/IIIa receptor binds fibrinogen to provide bridging between adjacent platelets. The surface of the platelet also becomes electronegatively charged and expresses binding sites for factor V, an essential cofactor in the generation of thrombin.

Mechanisms of Thrombin and Fibrin Generation

The coagulation phase of hemostasis involves thrombin-catalyzed cleavage of fibrinogen to fibrin, which binds and stabilizes the



• **Fig. 45.1** Thrombin structure. The thrombin active site (shown in *aqua*) is surrounded by a ring of negative charge and contains three conserved amino acid residues (serine 195 *[S]*, aspartic acid 102 *[D]*, and histidine 57 *[H]*). Fibrinogen interacts with the negatively charged ring around the active site as well as with the active site itself. Fibrinogen also interacts with the positively charged exosite shown on the right *(Anion-binding exosite)*, which is likely important in both orienting fibrinogen correctly within the active site and maintaining a strong bond between enzyme and substrate. Upon recognition of the correct substrate sequence, the hydroxyl of Ser195 cleaves the postarginine peptide bond. The anion-binding site on the right will also bind hirudin-like proteins. The anion-binding exosite to the left binds to glycosaminoglycans (heparan and chondroitin) and to heparin.

weak platelet hemostatic plug. Thrombin is highly specific in cleaving fibrinogen at only two arginine sites. The active site of thrombin is surrounded by negatively charged amino acid residues and away from this are positively charged exosites. This arrangement allows the very specific alignment and cleavage of fibrinogen (Fig. 45.1).

There are no covalent bonds holding platelets together during formation of the primary hemostatic plug. If left in this state, the platelet plug disintegrates in a few hours, resulting in late bleeding. The process of blood coagulation, with soluble factors in the blood entering into a cascade of protease activation that leads to the formation of fibrin, is localized to the site where the original platelet plug was formed. This localization is achieved by two mechanisms. First, the chain of reactions that leads to cleavage of fibrinogen to fibrin is restricted to a surface, such as platelet phospholipids. Second, a series of inhibitors constrains the reaction to the site of injury and platelet deposition.

Historically the blood coagulation system is separated into two initiating pathways: the tissue factor (extrinsic) pathway and the contact factor (intrinsic) pathway. These pathways meet in a final common pathway in which factor Xa converts prothrombin to thrombin, which then cleaves fibrinogen to fibrin. The prothrombin time (PT) is a plasma and test tube test of the integrity of the extrinsic pathway, and the activated clotting time or activated partial thromboplastin time (aPTT) are tests of the intrinsic system for blood and plasma, respectively.

This model based on the concept of a waterfall or cascade is an oversimplification of the coagulation system, as proteins from each pathway influence one another. It is probably more correct to think of the coagulation system as an interactive network with carefully placed amplifiers and restraints.

Fibrin formation involves a process of initiation and amplification. The specific properties of platelets and the coagulation system cooperate to ensure that fibrin formation occurs only at the localized site where it is required to initiate wound repair. This is achieved by the following physicochemical means. First, the surface of resting platelets contains acidic phospholipids such as phosphatidylserine that have their negatively charged pole directed inward. During irreversible shape change, this pole is flipped to the outside of the platelet to provide a negatively charged outer surface to anchor coagulation. Second, the coagulation system relies primarily on soluble factors synthesized in the liver that circulate in the plasma as inactive zymogen forms and become active after proteolytic cleavage. Apart from factor XIII, which is a transglutaminase, all active factors are serine proteases related to the digestive enzyme trypsin. Other factors in the coagulation process, such as tissue factor, factor V, factor VIII, and high-molecular-weight kininogen act as cofactors. Factors VII, IX, X, and prothrombin contain carboxylated glutamic acid residues at their N-terminal regions. Vitamin K acts as a cofactor for the enzyme that carboxylates glutamic acid, forming gamma-carboxy glutamic acid, with a resultant higher density of negative charges. This charged area interacts at the organizing surface of the platelet with ionized calcium ions (Ca^{2+}), acting as a bridge with the negative surface charge on the activated platelet.

Indirect Inhibitors of Thrombin Generation

Historical Considerations

Heparin, one of the oldest anticoagulant drugs currently still in widespread clinical use, was discovered in 1916 by a second-year medical student, Jay McLean, and Professor Howell at Johns Hopkins University. McLean was investigating procoagulant preparations when he isolated a fat-soluble phosphatide anticoagulant in canine liver for which Howell coined the term *heparin* (from *hepar*, Greek for liver). In the early 1920s, Howell isolated a water-soluble polysaccharide anticoagulant, which was also termed *heparin*, although it was distinct from the phosphatide preparations previously isolated.

Research on heparin continued into the 1930s. Jorpes described the structure of heparin in 1935, and the first heparin product for intravenous use was launched in 1936. Best perfected a technique for producing safe, nontoxic heparin that could be administered in a salt solution. The first human trials of heparin began in 1935, and by 1937 it was clear that heparin was a safe, easily available, and effective anticoagulant.

Heparins

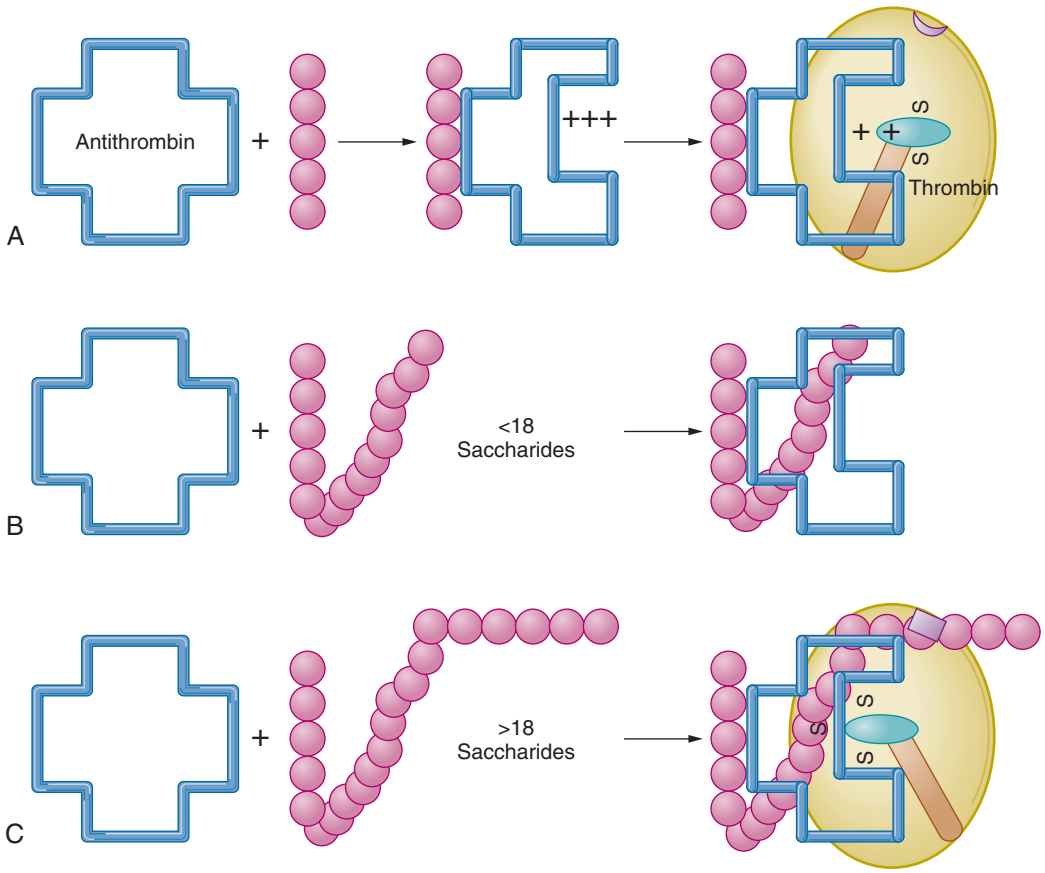
Heparins are available as unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs), which are chemical modifications of unfractionated heparin. The pharmacology of both has been extensively reviewed.[4–8]

Unfractionated Heparin

UFH is a naturally occurring glycosaminoglycan. It is a negatively charged sulfated polysaccharide formed from alternating residues of D-glucosamine and L-iduronic acid. Heparin is mostly located in lung, intestine, and liver in mammals. Standard preparations are derived from porcine intestine and prepared as calcium or sodium salts. The number and sequence of the saccharides are variable, producing a heterogeneous collection of polysaccharides. Molecular weights range from 3000 to 30,000 Da, with a mean of 15,000 Da representing 40 to 50 saccharides in length. There is no apparent difference between any of the available forms of UFH with respect to pharmacology or anticoagulant profile.[6]

Mechanism of Action

Numerous physiologic actions have been proposed for heparin. Heparin has a direct antiinflammatory action in humans and a



• **Fig. 45.2** Effects of heparin chain length on antithrombin (AT) and its binding to thrombin. A, The pentasaccharide binds to AT to induce a conformational change, but the arginine-derived electropositivity (+++) remains to reduce affinity for thrombin. With increasing saccharide chain length contributing more anionic charge, this effect is reduced, as shown in B. The most avid reaction with thrombin requires heparin binding, not only to AT but also to thrombin itself, at the anionic binding site that normally binds glycosaminoglycans (shown as a *lavender box*) to form a ternary complex. Only heparin moieties with more than 18 saccharides are able to do this, as shown in C.

wide spectrum of interactions with various enzymes, hormones, biogenic amines, and plasma proteins. The role of heparin as an antiinflammatory agent is strengthened when one considers that heparin alone has no effects on coagulation and is found in lower orders of the animal kingdom, such as mollusks, which lack a coagulation system. Heparin alone has no anticoagulant activity but requires a plasma cofactor, originally designated antithrombin III, and now simply called *antithrombin* or *AT*. AT has a low level of intrinsic anticoagulant activity mediated by a positively charged arginine center that binds to the catalytic serine of proteases of the coagulation cascade.

Binding of heparin to AT is highly specific via a pentasaccharide sequence found in about one-third of molecules and is reversible. Binding of heparin and subsequent anticoagulant activity depend on saccharide chain length (Fig. 45.2). The binding of AT to thrombin is suicidal to the thrombin-antithrombin complex, but the heparin molecule is able to dissociate from this complex unchanged. Inhibition of thrombin activation also prevents feedback by thrombin on factors V and VIII, which normally amplifies the clotting cascade. In contrast, inhibition of factors IXa, Xa, and XIIa requires only that heparin bind AT to form the heparin-AT complex.[6] This explains why LMWHs and the synthetic pentasaccharide fondaparinux act as inhibitors of factor Xa but not necessarily of thrombin.

Heparin has actions in addition to anticoagulant effects mediated via AT. At high blood levels (>4 IU/mL) heparin is capable of binding heparin cofactor II, potentiating its inactivation of bound activated thrombin.[9] This action does not require the specific AT binding site but does require heparins of greater than 7200 Da or 24 saccharide units in length. The clinical importance of this action is unclear, but it might account for the need for higher doses of heparin to inhibit clot-bound thrombin. Much higher levels of heparin are needed to prevent the extension of venous thrombosis compared with those required to inhibit initiation of thrombosis.[5,7] Heparin also stimulates release of tissue factor plasma inhibitor, which binds and neutralizes the tissue factor–FVIIa complex, reducing prothrombinase production via the extrinsic pathway. Plasma concentrations of tissue factor plasma inhibitor (TFPI) rise twofold to sixfold after injection of UFH and LMWH.

Heparin also impairs platelet aggregation mediated by vWF and collagen, and inhibits platelet function by direct binding to platelets. The higher-molecular-weight heparins interfere most with platelet function.[10] These actions might contribute to heparin-induced hemorrhage by a mechanism separate from its anticoagulant actions.

Metabolism and Elimination

Elimination of heparin is nonlinear and occurs by two separate processes. The rapid saturable phase of heparin clearance is thought

to be due to cellular degradation. Macrophages internalize heparin, then depolymerize and desulfate it; saturation occurs when all receptors have been used and further clearance depends on new receptor synthesis. This process accounts for the poor bioavailability after low-dose subcutaneous injection, in that the slow rate of absorption barely exceeds the capacity of cellular degradation. Significant plasma levels can only be achieved once these cellular receptors have been saturated after a loading dose. The slower phase of heparin elimination is due to renal excretion. As the dose of heparin is increased, elimination half-life increases and the anticoagulant response is exaggerated. At a dose of 25 U/kg the half-life is about 30 minutes, increasing to about 150 minutes with a bolus dose of 400 U/kg. There are no consistent reports of the effects of renal or hepatic dysfunction on the pharmacokinetics of heparin.[5,7]

Clinical Pharmacology

Pharmacokinetics and Pharmacodynamics

Heparins are usually administered by subcutaneous or intravenous injection as they are poorly absorbed from the gastrointestinal tract and cause hematomas after intramuscular injection. Safety of the two routes is comparable. Intravenous injection is the preferred route for a rapid anticoagulant effect; however, similar levels of anticoagulation can be achieved by the subcutaneous route with a delayed time to maximum effect.[7]

There is great variability in plasma concentration of heparin in relation to dose. After intravenous injection, more than 50% of heparin circulates bound to plasma proteins, including platelet factor 4, histidine-rich glycoprotein, vitronectin, fibronectin, and vWF. The first three of these neutralize heparin activity and its bioavailability. Increased levels of these proteins might account for heparin resistance sometimes seen in malignancy and inflammatory disorders.[5] Plasma levels also decline rapidly owing to redistribution and uptake by endothelial cells and macrophages.

Therapeutic Effects

Heparin is given to reduce thrombin generation and activity and therefore "anticoagulate" the patient. The therapeutic target dose depends on the indication and is tailored to patient need. For example, the degree of anticoagulation required to prevent thrombosis in a hemodialysis system is not as great as that required in cardiopulmonary bypass. Typically effectiveness of the dose is assessed at regular intervals using a coagulation test initiated by contact activation. The plasma version of this is the aPTT, which measures the effect of heparin on thrombin and factors IXa and Xa. The therapeutic range most commonly quoted is aPTT between 1.5 and 2.5 times the control value. However, commercially available kits for measurement of aPTT differ in their sensitivity to heparins. The whole blood version of the aPTT usually used when higher doses are administered is the automated or activated coagulation time (ACT), a standard of care in cardiac surgical practice; typically the ACT is maintained above 400 to 480 seconds. As there is a marked variation in response between individuals to the anticoagulant effect of a fixed dose of unfractionated heparin, regular monitoring of anticoagulation is routine.

Clinical Use

For thromboembolic prophylaxis, UFH is administered either as "low dose" (5000 U subcutaneously 8 or 12 hourly) or "adjusted dose" (3500 U 8 or 12 hourly adjusted to maintain the aPTT about 3 to 5 seconds above control). For treatment of established thromboembolic disease, full therapeutic doses of heparin are used either by intravenous infusion or subcutaneous injection after an intravenous loading dose. Long-term heparin therapy is only used during pregnancy (unlike warfarin, neither UFH nor LMWH are able to cross the placenta) and for recurrent thromboembolic complications while the patient is taking adequate doses of warfarin.

Low-dose UFH is safe and effective prophylactic treatment for surgical patients at risk for VTE. Low-dose subcutaneous UFH produces a greater than 50% reduction in the incidence of venous thrombosis and fatal or nonfatal PE.[11] Although this is associated with an increased incidence of wound hematoma, there is no increase in major or fatal hemorrhage.

Although relatively low doses of heparin are sufficient to provide thromboprophylaxis, much higher concentrations are needed to prevent thrombus propagation. Recommended regimens for the treatment of DVT with UFH include an intravenous loading dose of 5000 to 10,000 U followed by a continuous infusion of 1300 U/hr, adjusted to maintain the aPTT 1.5 to 2.5 times control. This should be continued until warfarin therapy has prolonged the PT to a therapeutic range for at least 24 hours.[12] This regimen reduces recurrence of venous thrombosis and mortality from PE. The most common reason for failure of treatment is inadequate anticoagulation, particularly within the first 24 hours, which is overcome by the large intravenous loading dose. These treatment protocols have been compared with twice-daily subcutaneous LMWHs without laboratory assessment, which is safer and more effective, with significant and important reductions in recurrence of thrombosis and major hemorrhage.[13]

Adverse Effects

Until 2008, the standard of heparin potency was different between heparins marketed in North America, which used the United States Pharmacopeia (USP) standard, and heparins that used the World Health Organization (WHO)'s international standard or international unit. In 2008, the USP adopted new manufacturing controls for heparin, which included a modification to the reference standard for heparin unit dose. These changes were precipitated by a number of cases of severe hypotension, sometimes leading to death, reported in association with administration of heparin. In March 2008, the U.S. Food and Drug Administration (FDA) identified "oversulfated chondroitin sulfate" as a contaminant in heparin originating from China. This contaminant mimics heparin activity and behaves like UFH in standard USP tests. In vitro and in vivo studies showed that oversulfated chondroitin sulfate directly activates the kinin-kallikrein pathway in human plasma, which can lead to generation of bradykinin, a potent vasodilator.[14] In addition, oversulfated chondroitin sulfate induced generation of C3a and C5a, potent anaphylatoxins derived from complement proteins. Screening of plasma samples from various species indicated that swine and humans are sensitive to the effects of oversulfated chondroitin sulfate in a similar manner. Oversulfated chondroitin sulfate–containing heparin and synthetically derived oversulfated chondroitin sulfate induce hypotension associated with kallikrein activation when administered by intravenous infusion in swine. Adopting the WHO international standard standards and introducing other safeguards allow early detection of this contaminant.

The new standardized heparin now has a different strength that results in about a 10% reduction in "anticoagulant" potency compared with the previous USP standard. The current WHO standard has a potency of 122 IU/mg heparin. The reduced potency should have no clinical effect in that dosing regimens are tailored to individual patient needs.

TABLE 45.1 Scoring System for Diagnosing Type II Heparin-Induced Thrombocytopenia (HIT)[a]

4 T's	2 Points	1 Point	0 Point
Thrombocytopenia	Platelet count fall >50% and platelet nadir >20 × 10^9/L	Platelet count fall 30%–50% or platelet nadir 10–19 × 10^9/L	Platelet count fall <30% or platelet nadir <10 × 10^9/L
Timing of platelet count fall	Clear onset between days 5 and 10 or platelet fall 1 day or less (prior heparin exposure within 30 days)	Consistent with days 5–10 fall, but not clear (e.g., missing platelet counts); onset after day 10 or fall 1 day or less (prior heparin exposure 30–100 days ago)	Platelet count fall <4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis; acute systemic reaction postintravenous unfractionated heparin bolus	Progressive or recurrent thrombosis; nonnecrotizing (erythematous) skin lesions; suspected thrombosis (not proven)	None
Other causes for thrombocytopenia	None apparent	Possible	Definite

[a]With a total score of 6 to 8, the probability is high (>80%), intermediate with a score of 4 or 5, and low (<5%) with a score of 0 to 3.[17]

Hemorrhage

Although hemorrhage is rare in patients using prophylactic doses of either UFH or LMWH, it is a frequent complication of therapeutic heparin therapy. With comparable doses, risks are similar using either continuous intravenous or subcutaneous route of administration.[5,7] Many patient factors increase the risk of hemorrhage, including length of treatment, presence of cardiac, hepatic or renal dysfunction, aspirin or other antiplatelet drug therapy, and recent surgery, trauma, or invasive procedures. Approximately 30% of patients who sustain anticoagulant-related hemorrhage have previously undiagnosed predisposing lesions, particularly of the gastrointestinal and genitourinary tracts. The incidence of major bleeding in anticoagulated patients is approximately 5%. The estimated daily frequency of fatal, major, and all types of hemorrhage in patients receiving therapeutic anticoagulation is 0.05%, 0.8%, and 2%, respectively, which is approximately twice that expected in the absence of anticoagulation.[15]

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a relatively common complication with an incidence of 1.1% and 2.3% of patients receiving therapeutic doses of intravenous porcine and bovine heparin, respectively. This usually involves high doses of UFH, but rare cases have been attributed to low-dose subcutaneous heparin prophylaxis or to flushing lines with heparin. The risk of HIT is less with LMWH than with UFH, perhaps because of less interaction with platelets.

Two distinct clinical syndromes have been described.[16] Type I involves mild thrombocytopenia with a platelet count rarely less than 100 × 10^9/L that occurs during the first few days of treatment and usually recovers rapidly even if heparin is continued. Patients are normally asymptomatic and no specific treatment is required. The underlying mechanism probably involves the action of heparin as a mild platelet aggregator. Type II HIT is characterized by delayed onset of severe, progressive thrombocytopenia with platelet counts less than 100 × 10^9/L and often less than 50 × 10^9/L. The platelet count does not recover unless heparin therapy is stopped and recurs promptly if heparin is restarted. Recovery of the platelet count usually occurs within a week but can occasionally be prolonged.

An immune mechanism has been suggested for type II HIT in which heparin binds to platelet factor 4 to stimulate production of an immunoglobulin G antibody. This antibody binds the heparin-platelet factor 4 complex, which is capable of binding to platelets to produce two separate effects. First, the immune complexes coat platelets and increase their removal from the circulation by the reticuloendothelial system. Second, the immune complexes activate platelets and the coagulation cascade, leading to a hypercoagulable state.[16] Hemorrhage is uncommon and resistance to anticoagulation can occur as the result of heparin-induced release of platelet factor 4. A high index of suspicion is necessary because only immediate withdrawal of heparin reduces mortality and morbidity. A clinical score system (4 T's—Thrombocytopenia, Timing, Thrombosis, oTher causes) as an aid has been validated in clinical practice (Table 45.1).[17] The most serious complication associated with type II HIT is new thromboembolic events owing to platelet-rich thrombi that continue to form until heparin is withdrawn. Arterial and venous thrombosis can occur either alone or together, and multiple sites are often involved. In patients receiving therapeutic doses of porcine heparin, 0.4% exhibit manifestations of thrombosis, most commonly lower limb thrombosis, thrombotic cerebrovascular events, or acute MI.

Miscellaneous

Heparin administration can cause anaphylactic reactions, osteoporosis after long-term high-dose therapy, suppression of aldosterone synthesis, delayed transient alopecia, priapism, and rebound hyperlipidemia on withdrawal.

Low-Molecular-Weight Heparin

Basic Pharmacology

Structure Activity

LMWHs are produced from UFH by depolymerization. The resulting marked changes in the properties of LMWHs lead to clinical advantages over UFH.[6,8] LMWHs have mean molecular weights of 4,000 to 6,500 Da, with a range of 2,000 to 10,000 Da. The production methods used and source of UFH lead to significant variations between different commercial preparations (Table 45.2). LMWHs differ in distribution of their fragment molecular weights, potency (anti-Xa, antithrombin, and anticoagulant activities), and consequently in their biodynamic patterns, recommended doses, and efficacy/safety ratio (Table 45.3).[4]

TABLE 45.2 Preparations of Low-Molecular-Weight Heparin

Preparation	Method of Production	Average Molecular Mass (Da)	2000–6000 Da (%)
Nadroparin	Nitrous acid depolymerization and fractionation	4200	85
Enoxaparin	Benzoylation followed by alkaline depolymerization	3900	75
Dalteparin	Nitrous acid depolymerization and gel filtration	5700	80
Tinzaparin	Depolymerization with heparinase	6000	64
Certoparin	Depolymerization with isoamylnitrate	5100	63
Ardeparin	Peroxidative cleavage	6000	
Reviparin	Nitrous acid depolymerization and chromatographic separation	4000	

TABLE 45.3 Properties of Various Low-Molecular-Weight Heparins Compared to Unfractionated Heparin

	POTENCY			
Preparation	Anti-Xa Activity (U/mg)	Anti-Xa to IIa Ratio	Half-Life (min)	Bioavailability (%)
Unfractionated heparin		1	30–150	10–20
Nadroparin	95	3.6:1	132–162	89
Enoxaparin	105	3.8:1	129–180	91
Dalteparin	130	2.7:1	119–139	87
Tinzaparin	83	1.9:1	111	90
Certoparin	88	2.0:1	240	90
Ardeparin	100	1.9:1	200	90
Reviparin	130	3.6:1	180	90

Mechanism of Action

The molecular weight profiles of LMWHs vary significantly, so their anticoagulant properties are not identical.[18] The exact mechanisms underlying the anticoagulant effects of LMWH remain uncertain. The proportion of LMWHs containing the critical pentasaccharide responsible for binding AT is less than in UFH,[6,8] which results in less inhibition of thrombin via AT in vitro. However, the heparin-AT complex inhibits Xa and this action remains intact in LMWH. Although LMWHs have a weak anti-IIa action, their high bioavailability and long half-life mean that the anti-Xa action is four times greater than for UFH. The potency of LMWHs is further increased by their resistance to inactivation by platelet factor 4 and by lack of protein binding. Like UFH, the main action of LMWHs is to prevent formation of prothrombinase and amplification of the coagulation cascade.

Metabolism and Elimination

LMWHs do not bind to endothelial cells or macrophages, and so are not subject to the rapid uptake that UFH incurs. Similar to UFH, they are partially metabolized by desulfation and depolymerization. The affinity of plasma proteins for LMWHs is much less than for UFH so that only 10% is protein bound. This increased bioavailability ensures a more predictable anticoagulant action. LMWHs have nearly complete bioavailability at all doses when given by subcutaneous injection, compared with 40% for low-dose subcutaneous UFH. Urinary excretion of anti-Xa activity for enoxaparin, dalteparin, and nadroparin, all given at doses for prevention of venous thrombosis, is between 3% and 10% of the injected dose. However, these LMWHs differ in the extent of their nonrenal clearance, resulting in different apparent elimination half-life values and relative apparent bioavailability. When given at thromboprophylactic doses, LMWHs do not significantly cross the placenta. Although clearance of LMWH depends on renal excretion, producing a half-life two to four times as long as for UFH, effects of renal dysfunction are not clinically apparent for creatinine clearance greater than 15 mL/min.

Clinical Pharmacology

LMWHs are as safe and effective as UFH in placebo-controlled and comparative trials. Meta-analysis of these trials suggests low-dose LMWHs are slightly superior to low-dose UFH, particularly in reducing the incidence of PE.[19] LMWHs given as prophylaxis cause an increase in wound hematoma formation but no change in the incidence of hemorrhage. In contrast, a significant reduction in major hemorrhage is seen when LMWHs are used to treat established thrombosis.[8,12]

Pharmacokinetics

Because LMWHs are mainly administered subcutaneously, compared to UFH they are almost completely absorbed and, in contrast to

UFH, exhibit linear pharmacokinetics with proportionality between anti-Xa (and anti-IIa in some cases) plasma activity and dose, and stationary distribution volume and clearance processes when the dosage is increased. Unlike UFH, their distribution volume is close to the blood volume.

Pharmacodynamics

Because of differences between LMWHs, the clinical profile of a given LMWH cannot be extrapolated to another or generalized to all LMWHs. These differences also lead to major problems in providing a reference standard to assess potency. This has a huge impact on licensing generic versions of currently marketed drugs.

Adverse Effects

The principal adverse effect of LMWH is hemorrhage. Unlike UFH there is no antidote such as protamine. Protamine reduces some anticoagulant effects of LMWH but is itself a drug with significant side effects. LMWHs have a high incidence of cross-reaction with the heparin-dependent antibody found in HIT. This can be monitored using a platelet aggregation test. If no cross-reaction occurs, successful anticoagulation can be safely undertaken with LMWH.

Pentasaccharide

Basic Pharmacology

Structure Activity and Mechanism of Action

Fondaparinux is a synthetic preparation of the pentasaccharide sequence found in heparin manufactured to a high degree of purity and uniformity. The antithrombotic activity of fondaparinux is the result of AT-mediated selective inhibition of factor Xa. By selectively binding to AT, fondaparinux potentiates (about 300 times) the innate neutralization of factor Xa by AT. Fondaparinux does not interact with AT to inactivate thrombin and has no known effect on platelet function. At the recommended dose, fondaparinux does not affect fibrinolytic activity or bleeding time.

Metabolism and Elimination

In healthy individuals with normal kidney function up to 75 years of age, about 80% of a single subcutaneous dose is eliminated in urine as unchanged fondaparinux in 72 hours with an elimination half-life of 17 to 21 hours. Since the majority of the administered dose is eliminated unchanged, metabolism of fondaparinux has not been investigated.

Clinical Pharmacology

Pharmacokinetics

Fondaparinux administered by subcutaneous injection is rapidly and completely absorbed (absolute bioavailability is 100%). In healthy adults, fondaparinux is highly (about 94%) and specifically bound to AT, and is thus mainly confined to the blood volume. This is reflected in the apparent volume of distribution of 7 to 11 L. It does not bind significantly to other plasma proteins (including platelet factor 4) or red blood cells.

Pharmacodynamics

Anti-Xa activity is used to define the pharmacology of this agent. As with LMWHs there is a need for a standard against which to calibrate this activity and this standard is unique to fondaparinux. Anti-Xa activity increases with increasing drug concentration, reaching maximum values in 2 to 3 hours.

Therapeutic Effects

Fondaparinux is licensed for VTE prevention in high-risk orthopedic surgery patients and in some countries for general surgical or medical patients. It also is licensed for treatment of acute DVT when administered in conjunction with a vitamin K antagonist. Fondaparinux appears more effective than LMWH for VTE prophylaxis in high-risk orthopedic patients.[20,21] It is as effective and safe as LMWH for prophylaxis in general surgical patients, and as heparin or LMWH for initial VTE treatment.[22,23]

Special Populations

Renal Impairment

Fondaparinux elimination is prolonged in patients with renal impairment in that the major route of elimination is urinary excretion of unchanged drug. In patients undergoing prophylaxis after elective hip surgery or hip fracture surgery, the clearance of fondaparinux is 25% lower in patients with mild renal impairment (creatinine clearance [CrCl] 50–80 mL/min), 40% lower in patients with moderate renal impairment (CrCl 30–50 mL/min), and 55% lower in patients with severe renal impairment (CrCl < 30 mL/min) compared with patients with normal renal function.

Hepatic Impairment

In patients with moderate hepatic impairment (Child-Pugh category B), small changes in pharmacokinetics but not pharmacodynamic parameters such as aPTT, PT/international normalized ratio (INR), and AT have been observed. Based on these data, no dosage adjustment is recommended for hepatic impairment. However, a higher incidence of hemorrhage has been noted in subjects with moderate hepatic impairment than in normal subjects.

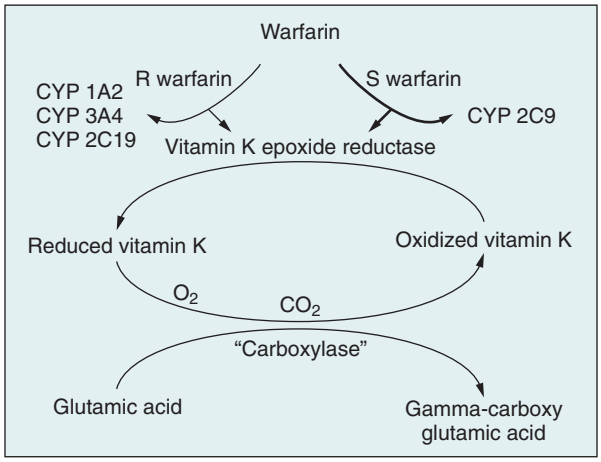
Age and Frailty

Fondaparinux elimination is prolonged in patients older than 75 years with total clearance 25% lower compared with patients younger than 65 years. Total clearance is also decreased by 30% in patients weighing less than 50 kg. The second-generation pentasaccharides, idraparinux and idrabiotaparinux, which have a longer half-life, have had their development suspended mainly because of an increased risk of bleeding.

Vitamin K Antagonists

Historical Considerations

Following an outbreak of a previously unrecognized hemorrhagic cattle disease in the northern United States and Canada in the 1920s, a Canadian veterinary pathologist determined that the cattle were ingesting moldy sweet clover that functioned as a potent anticoagulant. In 1933, Link, working at the University of Wisconsin, isolated and characterized the hemorrhagic agent as 3,3′-methylene-bis(4-hydroxycoumarin), later named *dicoumarol*. Over the next few years, numerous similar chemicals were found to have the same anticoagulant properties. The first drug in the class to be widely commercialized was dicoumarol itself, patented in 1941 and later used as a pharmaceutical. Link continued working on developing more potent coumarin-based anticoagulants for use as rodent poisons, resulting in warfarin in 1948. The name warfarin stems from the acronym WARF, for Wisconsin Alumni Research Foundation plus the ending -arin indicating its link with coumarin. Studies on the use of warfarin as a therapeutic anticoagulant found it to be generally superior to dicoumarol, and in 1954 it was approved for medical use in humans. The exact mechanism of action remained unknown until it was demonstrated in 1978 that



• **Fig. 45.3** Mechanism of action of the vitamin K antagonist warfarin. The glutamate residues of certain coagulation factors require carboxylation by gamma-glutamyl carboxylase (carboxylase) to achieve full activity. The carboxylation reaction proceeds only if the reduced form of vitamin K is available as a cosubstrate for conversion to vitamin K epoxide (oxidized vitamin K). The vitamin K epoxide is in turn recycled back to reduced vitamin K by vitamin K epoxide reductase. Warfarin inhibits the epoxide reductase, thereby blocking the carboxylase reaction. Also shown are the principal cytochrome P450 enzymes in the metabolic pathways of the two enantiomers of warfarin. The S enantiomer is clinically and functionally most important and is metabolized by CYP 2C9. *CO_2*, Carbon dioxide; *O_2*, oxygen.

warfarin inhibits epoxide reductase and hence interferes with vitamin K metabolism.

Basic Pharmacology

Mechanism of Action

Warfarin inhibits vitamin K–dependent synthesis of biologically active forms of clotting factors II, VII, IX, and X, as well as the regulatory factors protein C and protein S. The precursors of these factors require carboxylation of specific glutamic acid residues to allow the coagulation factors to bind to phospholipid surfaces such as that of activated platelets. The enzyme that carries out carboxylation of glutamic acid is gamma-glutamyl carboxylase. The carboxylation reaction proceeds only if this enzyme is able to convert reduced vitamin K (vitamin K hydroquinone) to vitamin K epoxide. Vitamin K epoxide is in turn recycled back to vitamin K and vitamin K hydroquinone by vitamin K epoxide reductase (VKOR; Fig. 45.3). Warfarin inhibits epoxide reductase (specifically the VKORC1 subunit), thereby diminishing available vitamin K and vitamin K hydroquinone, which inhibits the carboxylation activity of glutamyl carboxylase. Coagulation factors not carboxylated are incapable of binding to surface phospholipids and are thus biologically inactive.

Metabolism

Warfarin consists of a racemic mixture of two active enantiomers: R and S forms. S-warfarin has five times the potency of the R-isomer with respect to vitamin K antagonism. The enantiomers of warfarin are differentially metabolized by human cytochrome P450 (CYP). R-warfarin is metabolized primarily by CYP 1A2 to 6- and 8-hydroxywarfarin, by CYP 3A4 to 10-hydroxywarfarin, and by carbonyl reductase to diastereoisomeric alcohols. S-warfarin is metabolized primarily by CYP 2C9 to 7-hydroxywarfarin (see Fig. 45.3). The efficacy of warfarin is affected primarily when metabolism of S-warfarin is altered. Potential warfarin-drug interactions occur with a very wide range of drugs that are metabolized by these CYP isoforms; a large number of such interactions have been reported (Table 45.4).

Clinical Pharmacology

Pharmacokinetics

Warfarin has a long half-life (~35 hours) and therefore needs to be given only once daily. It takes several days for warfarin to produce a therapeutic effect because it affects only newly synthesized but not circulating coagulation factors. This also means that it remains effective for several days after administration is stopped. Loading doses of warfarin of more than 5 mg produce a rapid decline in carboxyglutamyl factor VII (half-life 5–7 hours), resulting in an initial prolongation of the INR, but full antithrombotic effect does not occur until a significant reduction in prothrombin activity occurs (half-life about 60 hours) days later. Initiation of warfarin therapy can promote clot formation temporarily because anticoagulant protein C and protein S are also dependent on vitamin K activity. Warfarin causes reduced protein C levels (half-life 14 hours). In addition, reduced levels of protein S (half-life 42 hours) lead to a reduction in activity of protein C (for which it is the cofactor) and therefore reduced inactivation of factor Va and factor VIIIa. The hemostasis system then becomes temporarily biased toward clot formation. Thus it is beneficial to coadminister heparin with initiation of warfarin therapy for 4 to 5 days until the full effect of warfarin has been achieved.

Pharmacodynamics

The effect of warfarin on blood coagulation is measured using an in vitro coagulation test, the PT, or the better standardized INR. Mathematically, $INR = (PR)^{ISI}$, where PR is the prothrombin ratio (PT divided by the laboratory control PT) and ISI is the international sensitivity index of the thromboplastin reagent. Use of the INR eliminates variation in PT results between laboratories caused by differences in thromboplastin reagents.

There is little correlation between warfarin dose, serum concentration, and therapeutic effect between patients, necessitating individualized dosing guided by therapeutic monitoring of PT or INR. The pharmacokinetic and pharmacodynamic properties of warfarin as well as its narrow therapeutic index make it particularly susceptible to interactions with other drugs (Table 45.4). This necessitates PT monitoring and warfarin dosing adjustments to maintain safe and effective anticoagulation.

Therapeutic Effects

Warfarin is used in a number of chronic thrombotic and thromboembolic conditions. Some of these, together with the recommended INR range for effective therapy or prophylaxis, are listed in Table 45.5.

Adverse Effects

Hemorrhage

The only common side effect of warfarin is hemorrhage. The risk of severe bleeding is small but definite (a median annual rate of 0.9%–2.7% has been reported). Any benefit needs to outweigh this significant risk when warfarin is considered as a therapeutic measure. Risk of bleeding is augmented if the INR is out of range (due to accidental or deliberate overdose, or to drug interactions). This can cause hemoptysis, excessive bruising, bleeding from the nose or gums, or blood in the urine or stool. The risk of bleeding is increased when warfarin is combined with antiplatelet drugs such as clopidogrel, aspirin, or other nonsteroidal antiinflammatory

TABLE 45.4 Warfarin Drug Interactions

Drugs That Change Plasma Concentration of Warfarin	Additive Anticoagulant Effect With No Change in Plasma Concentration	Unknown Mechanisms
Prolong Prothrombin Time/Increase Bleeding Risk		
Inhibit S isomer clearance	Inhibit vitamin K cycle	Ketoconazole/fluconazole
Metronidazole	Acetaminophen	Tamoxifen
Sulphinpyrazone	Antibiotics inhibiting gut vitamin K	Phenytoin
Trimethoprim	Altered diet	Erythromycin
Disulfiram		
Inhibit R isomer clearance	Inhibit coagulation and/or platelet function	
Cimetidine	Heparin	
Omeprazole	Aspirin/clopidogrel	
Ciprofloxacin		
Metronidazole		
Inhibit both S and R isomer clearance		
Amiodarone		
Reduce Prothrombin Time/Decrease Bleeding Risk		
Reduced absorption		Penicillins
Cholestyramine		
Increased metabolism		
Barbiturates		
Rifampicin		
Griseofulvin		
Carbamazepine		
St. John's wort		

TABLE 45.5 Recommended International Normalized Ratio Targets, Warfarin Therapy, and Prophylaxis

Indication	INR
Treatment of venous thrombosis. 6 weeks for calf vein and 3–6 months for proximal deep vein thrombosis	2.0–3.0
Treatment of pulmonary embolism for at least 6 months	2.0–3.0
Prevention of systemic embolism	2.0–3.0
Tissue heart valves	2.0–3.0
To prevent systemic embolism after acute myocardial infarction	2.0–3.0
To prevent recurrent myocardial infarction	2.5–3.5
Valvular heart disease	2.0–3.0
Atrial fibrillation. Older than age 75 years, consider lower range (1.5–2.5) owing to increased risk of intracranial bleed	2.0–3.0
Bileaflet mechanical valve in aortic position	2.0–3.0
Mechanical prosthetic valves with cage	2.5–3.5
Systemic recurrent emboli	2.5–3.5

drugs. The risk is also increased in older patients, those prone to falls, and those with trauma or undergoing invasive procedures.

Warfarin Necrosis

A rare but serious complication is warfarin necrosis, which occurs more frequently shortly after commencing treatment in patients with a deficiency of protein C. Protein C requires vitamin K–dependent carboxylation for its activity. Because warfarin initially decreases protein C levels faster than the coagulation factors, it can paradoxically increase coagulation when treatment is initiated, leading to thrombosis typically manifesting as skin necrosis and peripheral gangrene.

Osteoporosis

Several studies have demonstrated a link between warfarin use and osteoporosis-related fracture. A retrospective study of Medicare recipients showed that warfarin use for more than 1 year was linked with a 60% increased risk of osteoporosis-related fracture in men; there was no association in women.[24] The mechanism was thought to be a combination of reduced intake of vitamin K, which is necessary for bone health, and inhibition by warfarin of vitamin K–mediated carboxylation of certain bone proteins, rendering them nonfunctional.

Drug Interactions

Warfarin is the archetypical drug associated with drug interactions and pharmacogenetic effects (see Chapters 4, 6, and 7). Hundreds of drugs can increase the risk of hemorrhage in patients taking warfarin, including some nonprescription drugs widely perceived as innocuous. Patients receiving warfarin are typically older and take other medications concomitantly, increasing the chances for drug interactions.

Major interactions that modify bleeding risk with warfarin include the following:

- *Interference with platelet function:* Platelet aggregation is a crucial first step in primary hemostasis (see Chapter 43). Drugs that impair platelet function, especially acetylsalicylic acid (aspirin) and clopidogrel, increase the risk of major hemorrhage in patients

taking warfarin without elevating the INR. Selective serotonin reuptake inhibitors can inhibit platelet aggregation by depleting platelet serotonin. They also inhibit CYP 2C9, and coadministration with warfarin increases the risk of major bleeding.

- *Injury to gastrointestinal mucosa:* Nonsteroidal antiinflammatory drugs cause dose- and duration-dependent gastrointestinal erosions in a substantial proportion of patients. Most of these erosions are asymptomatic, but the risk of hemorrhage increases with concomitant use of warfarin, even with therapeutic INR.
- *Altered gut vitamin K availability:* Many fruits and vegetables are rich in vitamin K and increase available vitamin K. Most important in this regard are leafy greens such as broccoli, Brussels sprouts, kale, and spinach. The response to warfarin also depends on synthesis of vitamin K_2 (menaquinone) by intestinal microflora. Many antibiotics variably alter the balance of gut flora, thereby enhancing the effect of warfarin.
- *Interference with warfarin metabolism:* Many drugs modify warfarin activity through inhibition or enhancement of CYP metabolic pathways (see Table 45.4). Some antibiotics inhibit metabolism of warfarin by CYP enzymes, including cotrimoxazole, metronidazole and, to a lesser extent, the macrolides and fluoroquinolones (see Table 45.4).
- *Interruption of the vitamin K cycle:* Some patients experience a rapid and dramatic rise in the INR after standard doses of acetaminophen. Recent evidence suggests that this interaction is caused by *N*-acetyl (p)-benzoquinoneimine, the highly reactive acetaminophen metabolite that is responsible for hepatic injury after overdose, that also inhibits vitamin K–dependent carboxylase activity.

Pharmacogenetics

Warfarin effect is determined partially by genetic factors. Three single-nucleotide polymorphisms (SNPs), two in the *CYP2C9* gene and one in the *VKORC1* gene, play key roles in determining the effect of warfarin therapy. The normal variant of the *CYP2C9* gene is *1 and the two SNPs *2 and *3. The prevalence of each variant varies by race; 10% and 6% of Caucasians carry the *2 and *3 variants, respectively, but both variants are rare (<2%) in those of African or Asian descent. CYP 2C9*1 metabolizes warfarin normally, CYP2 C9*2 reduces warfarin metabolism by 30%, and CYP 2C9*3 reduces warfarin metabolism by 90%.

In the *VKORC1* SNP, the common G allele is replaced by the A allele. Because people with an A allele (or the "A haplotype") produce less VKORC1 than do those with the G allele (or the "non–A haplotype"), lower warfarin doses are needed to inhibit VKORC1 and to produce an anticoagulant effect. The prevalence of these variants also varies by race, with 37% of Caucasians and 14% of Africans carrying the A allele.

Carriers of *CYP 2C9*2* and *CYP 2C9*3* require, on average, a 19% and 33% reduction, respectively, per allele in warfarin dose compared with those who carry the *1 allele. Carriers of the *VKORC1* A allele require, on average, a 28% reduction in warfarin dose compared with those who carry the G allele. Compared to *VKORC1,* the *CYP 2C9* polymorphisms do not influence time to effective INR but do shorten the time taken to achieve INR greater than 4.

Major drug interactions come from the use of other drugs that use the same CYP pathways for their metabolism or that induce increased enzyme expression, leading to numerous potentially adverse drug interactions. More than 600 drugs reportedly interact with warfarin. The most common and most significant are listed in Table 45.4.

Special Populations

Pregnancy

Warfarin is contraindicated in pregnancy because it crosses the placenta and can cause bleeding in the fetus. Coumarin (e.g., warfarin) is also teratogenic.

Direct Thrombin Inhibitors

Intravenous Direct Thrombin Inhibitors

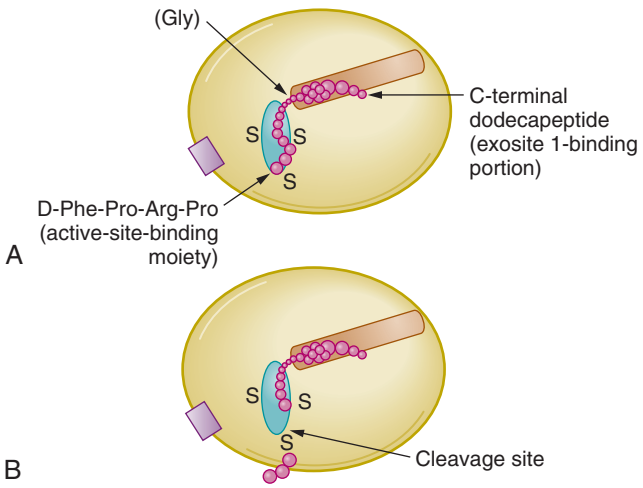
Historical Perspective

In the 1980s and early 1990s there was considerable interest in developing protease inhibitors to control both inflammatory and hemostatic processes. Many of these products were based on biomolecules found in the mouthparts of the medicinal leech. For the antiinflammatory pathway a powerful antielastase called *eglin-c* was investigated. Control of hemostasis focused on modifications to the direct thrombin inhibitor hirudin to produce a series of hirudin analogs or hirulogs. There was also interest in developing modifications to an agent called PPACK (D-Phe-Pro-Arg-chlormethylketone) to inhibit thrombin and other proteases.

Basic Pharmacology

Structure Activity and Mechanism of Action

The hirudin-like molecules are made by recombinant technology in cultured yeast. Bayer Healthcare stopped production of lepirudin for business reasons in 2012 so this is no longer available. Desirudin is identical to hirudin but omits the sulfate on the tyrosine residue. It has the benefit of subcutaneous as well as intravenous administration. Bivalirudin has a unique structure with a dodecapeptide attached to the active binding site moiety by four glycine residues (Fig. 45.4). This structure together with recombinant desirudin binds to both the active site and an exosite-binding site. For this reason they are termed *bivalent direct thrombin inhibitors*.



• **Fig. 45.4** Mechanism of bivalirudin. A shows the binding of bivalirudin to thrombin. The *pink circles* represent amino acid residues of the inhibitor. Binding of the C-terminal dodecapeptide is at the anion-binding site used by fibrinogen *(brown area),* and the 4 amino acid residue D-Phe-Pro-Arg-Pro binds in the active site *(turquoise oval).* B shows the effect of thrombin to cleave the Pro-Arg bond of the active site binding moiety to inactivate the direct thrombin inhibition.

TABLE 45.6 Basic Pharmacokinetics, Monitoring Method, and Excretion for Intravenous Direct Thrombin Inhibitors[a]

Drug	Administration	Half-Life	Dosing Schedule	Monitoring	Renal Excretion	Dose Reductions
Desirudin	Intravenous and subcutaneous	2–3 hours after intravenous injection	15 mg twice daily	aPTT of 1.5 times control. Stop drug if >2 times control	40%–50%	3-fold reduction with creatinine clearance 30–49 mL/min 9-fold reduction with creatinine clearance <30 mL/min
Bivalirudin	Intravenous	25 minutes Coagulation tests within normal limits after 2 hr	0.75 mg/kg bolus then 1.75 mg/kg per hr		25%–50%	Creatinine clearance <30 mL/min infusion rate to 1 mg/kg per minute
Argatroban	Intravenous	Coagulation tests are within normal limits 4 hours after discontinuing infusion	2 μg/kg per minute increasing to 10 μg/kg per minute based on raising aPTT 2- to 3-fold	aPTT, ACT	None	Hepatic failure/ impairment

aPTT, Activated partial thromboplastin time; *ACT,* activated clotting time; *NR,* None reported.
[a]Also shown are the conditions for reductions in dose in patients with renal or hepatic failure.

Argatroban is also a synthetic compound derived from arginine but binds only to the active enzymatic site of thrombin and is termed a monovalent inhibitor. All of these compounds inhibit both free and bound thrombin, and none are affected by platelet factor 4.

Clinical Pharmacology

Direct thrombin inhibitors are indicated for the treatment and prevention of thrombosis in patients with HIT.[25] Desirudin is approved in Europe for prevention of DVT/PE after hip replacement. Bivalirudin is also licensed for use during percutaneous coronary intervention/angioplasty procedures.

Pharmacokinetics

Table 45.6 outlines the basic pharmacokinetic profile of each drug. Excretion of the recombinant hirudins is affected by renal function, whereas argatroban is entirely metabolized by the liver. Although impaired liver function is not a contraindication to the use of argatroban, the dose should be lowered and full reversal of anticoagulant effects might require more than 4 hours. Bivalirudin has renal excretion but also a unique metabolic elimination process. Thrombin can cleave the Pro-Arg bond of the active site binding moiety to metabolize bivalirudin (see Fig. 45.4). This improves the safety of use of bivalirudin in patients with impaired renal function such as the elderly.

Pharmacodynamics

The anticoagulant effect of thrombin inhibitors is monitored by the aPTT or ACT (see Table 45.6); coagulation time increases in a dose-dependent manner. Argatroban also prolongs the PT in a dose-dependent manner. This has implications for assessing anticoagulation when transferring patients to long-term anticoagulation with vitamin K antagonists. Manufacturers recommend no loading dose of warfarin, but starting with a dose near the anticipated maintenance dose. The individual effects of argatroban and a vitamin K antagonist on the INR can be calculated using a nomogram.

Adverse Effects

The major adverse effect of direct thrombin inhibitors is hemorrhage. Hemorrhagic complications, particularly when combined with thrombolytic or antiplatelet agents, can be life threatening. There is no antidote to any of these agents, so the antithrombin effect cannot be reversed pharmacologically.

In addition, the recombinant hirudins are associated with allergic/anaphylactic reactions that limit their use. Allergy to bivalirudin and argatroban is rare.

Oral Direct Thrombin Inhibitors

The first oral direct thrombin inhibitor licensed for human use was ximelagatran, a prodrug administered twice daily. It was licensed in certain European and South American countries for prophylaxis against DVT after knee and hip replacement; it has also shown efficacy in atrial fibrillation and acute coronary syndromes. Subsequent postmarketing surveillance showed that about 56% of patients given the drug had elevation of hepatic enzymes, even after withdrawal. This led to its withdrawal from the market. The only oral direct thrombin inhibitor currently available is dabigatran.

Basic Pharmacology

Structure Activity and Mechanism of Action

Dabigatran is a competitive direct thrombin inhibitor. It is orally administered as the prodrug dabigatran etexilate. The active drug inhibits both free and clot-bound thrombin and thrombin-induced platelet activation.

Clinical Pharmacology

Pharmacokinetics and Pharmacodynamics

Dabigatran has a predictable pharmacokinetic and pharmacodynamic profile, allowing for a fixed-dose regimen. Peak plasma concentrations are reached 2 hours after oral administration in healthy volunteers, with no unexpected accumulation upon multiple dosing. This is followed by a rapid distribution and elimination phase and a terminal phase, with associated estimated half-lives of 8 to 10

hours and 14 to 17 hours with single- and multiple-dose administrations, respectively. Dabigatran exhibits linear pharmacokinetic characteristics with dose-proportional increases observed in maximum plasma concentration and area under the curve.

Excretion is predominantly renal as unchanged drug. The dose should be reduced from 150 mg twice daily to 75 mg twice daily if the estimated creatinine clearance is 30 to 50 mL/min. Dabigatran is not metabolized by CYP isoenzymes. Concomitant use with P-glycoprotein inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided. Administration with the P-glycoprotein inhibitors ketoconazole, verapamil, amiodarone, quinidine, or clarithromycin does not require dose adjustments.

The dabigatran formulation is highly acidic and was associated with an increased incidence of gastritis in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study.[26] Of more importance, bioavailability after oral administration is only 6% to 7%. This is increased to about 75% if the capsule is chewed before swallowing, so patients should be warned to swallow the capsule whole.

Time curves for aPTT, INR, thrombin time (TT), and ecarin clotting time (ECT) parallel plasma concentration–time curves with values increasing rapidly in a dose-dependent manner. At the highest dose of 400 mg administered three times daily, maximum prolongations over baseline of 3.1-fold (aPTT), 3.5-fold (INR), 29- (TT), or 9.5-fold (ECT) were observed.[27] Dabigatran undergoes conjugation with glucuronic acid to form pharmacologically active conjugates that account for approximately 20% of total dabigatran in plasma.

Therapeutic Effects

Dabigatran has been investigated for prevention of VTE after knee and hip replacement and prevention of stroke in patients with chronic atrial fibrillation. When data from various studies (RE-NOVATE, RE-MODEL, RE-MOBILIZE) were combined, dabigatran was found to be noninferior to enoxaparin using the efficacy endpoint of VTE, which had a 3% to 4% incidence in each treatment arm.[28] The safety endpoint of major bleeding also did not show a difference between the two treatments, at about 1% to 1.5% of patients. Because there was no efficacy benefit, the drug was not initially licensed for prevention of VTE by the FDA in the United States, but it did get a license for this indication in Europe.

The RE-LY study compared two blinded doses of dabigatran (110 mg or 150 mg twice daily) with open-label warfarin (dosed to target INR of 2 to 3) in patients with nonvalvular, persistent, paroxysmal, or permanent atrial fibrillation.[26] The primary objective of this study was to determine whether dabigatran was noninferior to warfarin in reducing the occurrence of the composite endpoint, stroke (ischemic and hemorrhagic) and systemic embolism. Dabigatran at a dose of 110 mg was associated with rates of stroke and systemic embolism similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage at 3.1%. These data led to dabigatran being licensed in the United States, Europe, and other countries for use as an alternate to vitamin K antagonists for prevention of stroke with atrial fibrillation. Regulatory authorities are reviewing postmarketing surveillance data after reports of 260 deaths caused by hemorrhage.

Special Situations and Adverse Events

As with other anticoagulants, the major risk is for bleeding, which can be life threatening, particularly with major trauma. It is recommended to discontinue dabigatran 1 to 2 days (CrCl ≥ 50 mL/min) or 3 to 5 days (CrCl < 50 mL/min) before invasive or surgical procedures because of increased risk for bleeding. If surgery cannot be delayed, a monoclonal antibody to dabagatran has been developed[29] and licensed and is discussed in later text. Bleeding risk can be assessed by the ECT, a laboratory test used to monitor anticoagulation during treatment with hirudin, which is a better marker of the anticoagulant activity of dabigatran than aPTT, PT/INR, or TT. If ECT is not available, the aPTT provides the next best approximation of dabigatran anticoagulant activity.

Inhibitors of Activated Factor X

Historical Perspective

Factor Xa is at the convergence of the extrinsic and intrinsic pathways leading to thrombin activation. The crystal structure of human factor Xa reveals an active site divided into four subpockets (S1-4). The S1 subpocket is the major determinant of selectivity and binding of inhibitors. The first generation of oral factor Xa inhibitors was based on dibasic inhibitors binding to both the primary specificity pocket and a putative cation-binding site. The high basicity of these compounds limited oral bioavailability. Recent efforts have focused on development of nonpeptide inhibitors of low basicity by screening and rational design.

Basic Pharmacology

Structure-Activity and Mechanism of Action

Because of shortcomings of vitamin K antagonists as the only form of oral anticoagulant (Table 45.7) and the critical role of factor Xa in the coagulation cascade, factor Xa has become an important target for anticoagulant development. These novel agents bind to and inhibit factor Xa directly without a requirement for AT. The major advantage of direct factor Xa inhibitors is their small size and resultant ability to inactivate circulating, as well as bound, forms of factor Xa. Inhibition is produced by stoichiometric binding to factor Xa. In theory, the capacity to inhibit factor Xa within the prothrombinase complex, as well as clot-bound factor Xa, suggests more powerful control over thrombus formation and progression, and therefore potentially greater clinical efficacy. It also seems rational to inhibit the system at this point, because inhibition of one factor Xa moiety can lead to a 50-fold reduction in thrombin production.

Inhibitors of activated factor Xa generally bind in an L-shaped conformation involving the anionic S1 pocket and the aromatic S4 pocket. Typically, a fairly rigid linker group bridges these two inhibitor moieties. This rational design follows analysis of the binding site by x-ray crystallography.[30] The L-shaped structure of the currently available and licensed agents is shown in (Fig. 45.5).

TABLE 45.7 Limitations and Clinical Consequences of Vitamin K Antagonists

Limitation	Consequence
Slow onset	Overlap with parenteral anticoagulation
Genetic variation in metabolism	Variable dose requirements
Multiple food and drug interactions	Frequent coagulation monitoring
Narrow therapeutic index	Frequent coagulation monitoring

Apixaban, betrixaban, edoxaban, and rivaroxaban are the most advanced factor Xa inhibitors in clinical development. Apixaban, edoxaban, and rivaroxaban have licensed indications in most countries for preventing stroke with nonvalvular atrial fibrillation and prevention of VTE after hip or knee replacement surgery.

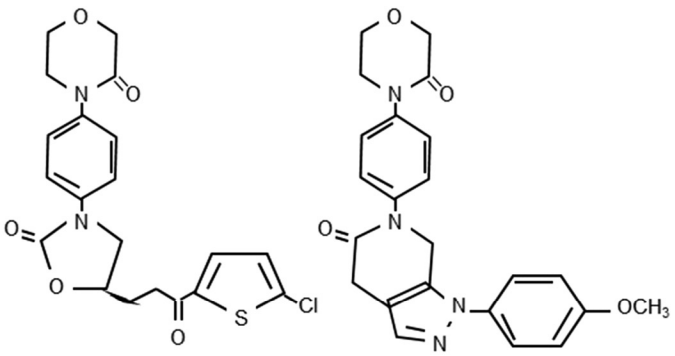
Rivaroxaban (BAY-59-7939) is an oral, direct, reversible, competitive, rapid, and dose-dependent inhibitor of factor Xa. Rivaroxaban inhibits factor Xa with more than 10,000-fold greater selectivity than other biologically relevant serine proteases, such as thrombin, trypsin, plasmin, factor VIIa, factor IXa, urokinase, and activated protein C.

Apixaban is a follow-up compound of the oral direct factor Xa inhibitor razaxaban. Apixaban is a highly selective and potent (inhibitory constant [K_i] = 0.8 nM) inhibitor of both free and prothrombinase bound factor Xa.

Clinical Pharmacology

Pharmacokinetics and Pharmacodynamics

The relative pharmacokinetic profiles for the four most clinically advanced factor Xa antagonists are shown in Table 45.8. The most striking difference between the agents is the very low renal clearance of betrixaban. This should lead to a more consistent effect without dose adjustments in older patients and those with impaired renal function, compared, for example, with rivaroxaban. Betrixaban is also unique in that the pharmaceutical company developing the drug was also developing a specific antidote, which is discussed later. All of the agents have protein binding of about 90%, meaning they will be difficult to remove by dialysis. These agents induce a prolongation of coagulation time by 2 to 3 hours after ingestion, with increases in PT and aPTT of approximately 20%.



• **Fig. 45.5** Chemical structures for the activated Factor Xa inhibitors rivaroxaban and apixaban. The configuration allows the upper part of the molecule to bind to the anionic S1 pocket of the Xa proteolytic site and the lower part to bind to the aromatic S4 pocket.

Therapeutic Effects

Several phase II/III studies of oral factor Xa inhibitors are underway. The targets for these studies are typically short-term thromboprophylaxis to prevent DVT/VTE when the comparator is LMWH. The second short-term indication is treatment of acute coronary syndrome. Longer-term thromboprophylaxis studies center around stroke prevention in patients with atrial fibrillation and prevention of thrombosis in prosthetic heart valves. For the latter studies the comparator is a vitamin K antagonist or aspirin. Results of the studies published thus far have not been universally positive for this class of compound, in part because of the design of the studies and also because of increased bleeding. It may be that this class of compound will replace vitamin K antagonists, but there could be safety issues when the drug is combined with antiplatelet therapy.[31]

Adverse Effects and Special Situations

The obvious adverse event with any anticoagulant is hemorrhage. Spontaneous hemorrhage while taking these compounds appears not to be a problem in the absence of antiplatelet therapy. Both apixaban and rivaroxaban prescribing information warn of the use of neuraxial block when these drugs are being administered. Novel agents are in late stages of development to produce acute reversal of anticoagulation.[32]

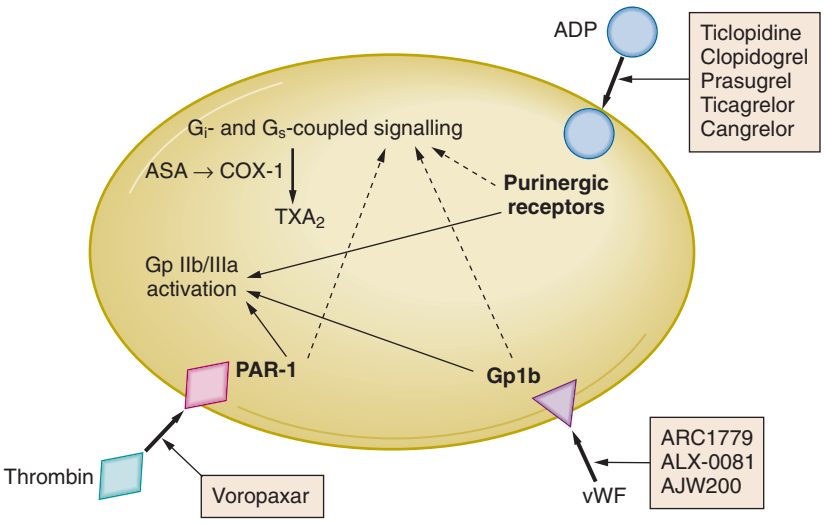
Antiplatelet Agents

Examination of histologic sections from postmortem material shows that the major component of the occlusive thrombus in arterial disease is the platelet. Because acute arterial occlusion leading to MI or stroke is a leading cause of death worldwide, it is not surprising that considerable effort has been made to develop drugs to modify platelet function and reduce these cardiovascular events. In the past, aspirin was the mainstay of therapy. With increasing knowledge of the mechanisms of action of platelet activation, more recent therapies have concentrated on specific receptor inhibition.

TABLE 45.8 Basic Pharmacology of Orally Active Factor Xa Inhibitors

Drug	Bioavailability	Half-Life	Metabolism	Renal Excretion	Dose Reduction Criteria
Rivaroxaban	90%	9–12 hr 16 hr if age >75 yr	CYP 3A4	35%	Age >75 yr Caution if creatinine clearance <49 mL/min
Apixaban	50%–80%	12 hr	CYP 3A4	25%	Age >80 yr Weight <60 kg Creatinine >1.5 mg/dL (132 μmol/L)
Edoxaban	45%	9–11 hr	NR	35%	Creatinine clearance 15–50 mL/min
Betrixaban	45%–50%	20 hr	NR	5%	NR

All these agents inhibit coagulation factor Xa, none is a prodrug and all are given orally on a once per day regimen.
CYP, Cytochrome P450; *NR,* none recorded.



• **Fig. 45.6** Sites of action of various agents that inhibit platelet function or activation. *ADP,* Adenosine diphosphate; *ASA,* acetylsalicylic acid; *COX,* cyclooxygenase; *Gp1b,* glycoprotein 1b; *PAR-1,* protease-activated receptor 1; *TXA_2,* thromboxane A_2, *vWF,* von Willebrand factor. See text for further details.

Platelets can be activated in a number of ways. The major targets for pharmacologic intervention have been inhibition of cyclooxygenase with aspirin and phosphodiesterase with dipyridamole. More recent pharmacologic interventions have been to inhibit receptors at the platelet surface. In particular there is considerable interest in inhibition of purinergic receptors and those binding fibrinogen (the GpIIb/IIIa receptor). Agents that inhibit vWF binding to the glycoprotein Ib receptor are in early clinical development. Inhibitors of the protease-activated receptor 1 (PAR-1 or thrombin receptor) on the platelet surface are more advanced. The targets and agents in clinical use or development are shown in Fig. 45.6.

Oral Agents

Aspirin

Historical Considerations

Acetylsalicylic acid (ASA) is a derivative of salicylic acid that works by inhibiting the enzyme prostaglandin H-synthase also known as *cyclooxygenase* (COX). The history of ASA as an analgesic can be traced back to the time of Hippocrates (who lived between 460 BC and 377 BC), who recorded pain relief treatments, including the use of powder made from the bark and leaves of the willow tree to treat headache, pain, and fever. By 1829, the salicin in willow plants was identified as analgesic and this was later converted to salicylic acid.

In 1853, Gerhardt neutralized salicylic acid by buffering it with sodium (sodium salicylate) and acetyl chloride, creating ASA, but he did not market it. In 1899, Hoffmann working for the German company Bayer, rediscovered Gerhardt's formula and convinced Bayer to market the drug. Aspirin was patented in1900; the name *Aspirin* comes from "A" in acetyl chloride, "spir" in *Spiraea ulmaria* (the plant the salicylic acid came from), and "in," a familiar name ending for medicines.

Basic Pharmacology

Mechanism of Action. Prostaglandin H-synthase 1 and 2 (also known as COX 1 and 2) catalyze the conversion of arachidonic acid to prostaglandin H_2 (PGH_2). Human platelets and vascular endothelial cells convert PGH_2 primarily to thromboxane A_2 (TXA_2) and prostaglandin I_2 (PGI_2).[33] TXA_2 induces platelet aggregation and vasoconstriction, whereas PGI_2 inhibits platelet aggregation and induces vasodilatation. Platelet TXA_2 synthesis is reduced by about 98% after ASA administration. Whereas TXA_2 is largely a COX-1–derived product (mostly from platelets) and thus highly sensitive to aspirin inhibition, vascular PGI_2 can derive both from COX-1 and, to a greater extent even under physiologic conditions, from COX-2. COX-2–mediated PGI_2 production occurs mainly in response to shear stress and is insensitive to aspirin inhibition at conventional antiplatelet doses.

The molecular mechanism of permanent inactivation of COX activity by aspirin is a consequence of acetylation of a serine residue (Ser529 in human COX-1, Ser516 in human COX-2) that results in a lack of access of the substrate to the catalytic site.[33] Acetylation of the COX-2 site is inhibited in cells with a raised oxidative state, including nucleated cells such as the endothelium. Additionally, nucleated cells rapidly resynthesize COX-2.

Inhibition of COX-1–dependent platelet function can be achieved with low doses of ASA given once daily. Inhibition of COX-2–dependent inflammatory processes requires larger doses of aspirin and a much shorter dosing interval. Thus there is an approximately 100-fold variation in daily doses of aspirin when used as an antiinflammatory rather than as an antiplatelet agent.

Clinical Pharmacology

Pharmacokinetics. ASA is rapidly absorbed in the stomach and upper intestine. Peak plasma levels occur 30 to 40 minutes after ingestion, and inhibition of platelet function is evident by 1 hour. In contrast, it can take 3 to 4 hours to reach peak plasma levels after administration of enteric-coated aspirin. The oral bioavailability of regular aspirin tablets is approximately 40% to 50% over a wide range of doses and is less for enteric-coated tablets.[34] Lower bioavailability of some enteric-coated preparations and poor absorption from the higher pH environment of the small intestine can result in inadequate platelet inhibition.

Pharmacodynamics. The plasma concentration of ASA decays with a half-life of 15 to 20 minutes. Despite rapid clearance from the circulation, its platelet-inhibitory effect lasts for the life span of the platelet because it irreversibly inactivates platelet COX-1.[35,36] Aspirin also acetylates the enzyme in megakaryocytes before new platelets are released into the circulation.[37] The mean life span of human platelets is 5 to 10 days, so 10% to 20% of circulating platelets are replaced daily.[38] Bleeding times, implying normal primary hemostasis, require about 20% to 30% of normal platelet

numbers/function. This suggests that cessation of ASA ingestion for 48 hours will result in a return to normal hemostatic activity.

Numerous studies have shown a risk reduction of about 15% to 20% for myocardial ischemia and stroke, with doses starting at about 60 mg ASA daily.[39–41] Some patients are resistant to usual doses, as manifested by incomplete inhibition of platelet aggregation and/or ongoing TXA_2 production. Such patients might be more prone to recurrent cardiovascular events.[42] One approach to this phenomenon would be to increase the dose of ASA, but this has potential problems. There is no substantive evidence for greater efficacy with greater dosage, but there is evidence for increasing morbidity as dose increases. In particular, bleeding is dose dependent in patients treated for stroke and with acute coronary syndrome.[43] A retrospective subgroup analysis of the relationship between aspirin dose and risk of major bleeding found a dose of 100 mg/day to have the lowest rate of major or life-threatening bleeding complications.[44] Bleeding risks increased with increasing ASA dose with or without clopidogrel. Approximately 300 mg/day produce fewer gastrointestinal side effects than 1200 mg/day, and 30 mg/day produces fewer side effects than 300 mg/day.

In summary, the antiplatelet effect of ASA at low doses, the lack of dose-response relationship in clinical studies evaluating its antithrombotic effects, and the dose dependence of its side effects all support the use of as low a dose as has been found to be effective in the treatment of various thromboembolic disorders (Table 45.9). Use of the lowest effective dose (50–100 mg/day for long-term treatment) is currently the most appropriate strategy to maximize efficacy and minimize toxicity.[40] ASA has been studied in a wide range of diseases ranging from preeclampsia to bowel cancer, usually at doses of 50 to 100 mg/day. The mechanisms of action for the observed benefits in these conditions remain to be elucidated.

Dipyridamole

Basic Pharmacology

Mechanism of Action. Dipyridamole is a pyrimido-pyrimidine derivative with vasodilator and antiplatelet properties. The mechanism of action of dipyridamole as an antiplatelet agent involves increased intracellular cyclic adenosine monophosphate (cAMP), which inhibits the platelet shape change. Increased cAMP concentration is due to one or both of two mechanisms: inhibition of phosphodiesterase and blockade of uptake of adenosine (which acts at adenosine A_2 receptors to stimulate platelet adenylyl cyclase and thus increase cAMP).

TABLE 45.9 Lowest Effective Daily Dose of Aspirin to Reduce the Risk of Thrombotic Events by Condition

Disorder	Lowest Effective Daily Dose (mg)
Transient ischemic attack or ischemic stroke[a]	50
Men at high cardiovascular risk	50
Hypertension	75
Stable angina	75
Unstable angina[a]	75
Severe carotid artery stenosis[a]	75
Polycythemia vera	100
Acute myocardial infarction	160
Acute ischemic stroke[a]	160

[a]Higher doses have been studied but did not show added benefit.

Clinical Pharmacology

Pharmacokinetics. Following an oral dose of dipyridamole tablets, the average time to peak concentration is about 75 minutes. The decline in plasma concentration fits a two-compartment model with an α half-life (initial decline following peak concentration) of 40 minutes and a β half-life of 10 hours. This is consistent with the twice-daily regimen used in recent clinical studies.

Absorption of dipyridamole from conventional formulations is quite variable and can result in low systemic bioavailability. A modified-release formulation of dipyridamole with improved bioavailability has been developed. Dipyridamole is highly bound to plasma proteins, and is metabolized in the liver where it is conjugated to a glucuronide and excreted in the bile. It is subject to enterohepatic recirculation.

Pharmacodynamics and Therapeutic Effects. Early clinical trials questioned the efficacy of dipyridamole, alone or in combination with ASA, probably because of variability in bioavailability. Recent studies have suggested significant benefit with the new formulation. Addition of modified-release dipyridamole 200 mg twice daily to ASA 25 mg twice daily was associated with a 22% relative risk reduction of major vascular events compared with ASA alone.[45] In a study of ASA (30–325 mg/day) with or without dipyridamole (200 mg twice daily) in patients within 6 months of a transient ischemic attack (TIA) or minor stroke showed 20% reduction of a composite of major vascular events by the combined treatment.[46] The fixed combination of modified-release dipyridamole and low-dose ASA has been approved for stroke prevention.

Platelet Receptor Inhibitors

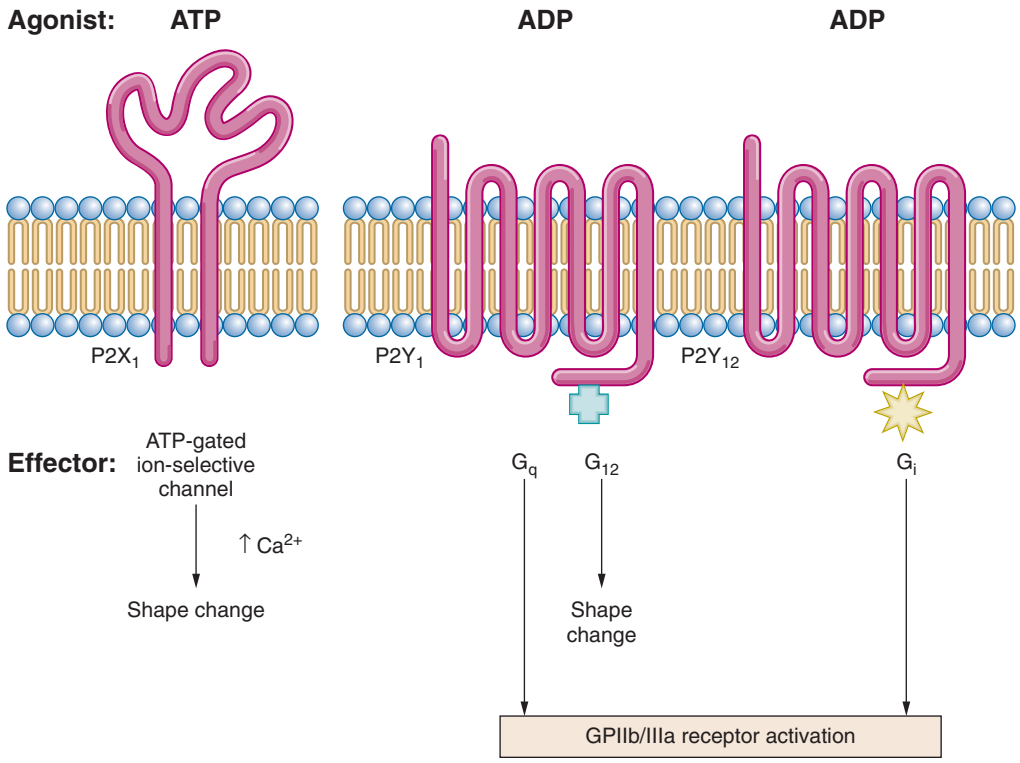
Purinergic Receptors

There are three known subtypes of adenosine diphosphate (ADP) receptors on platelets: $P2X_1$, $P2Y_1$, and $P2Y_{12}$ (Fig. 45.7). The $P2Y_{12}$ receptor (previously known as $P2T_{AC}$, P_{2T}, and $P2Y_{cyc}$) is abundantly expressed on human platelets and smooth muscle. ADP is released from damaged vessels, red blood cells, and platelets stimulated by other agonists. ADP binds to the $P2Y_1$ receptor to initiate platelet aggregation and to the $P2Y_{12}$ receptor, which amplifies platelet aggregation. Sustained ADP-induced platelet aggregation requires coactivation of $P2Y_1$ and $P2Y_{12}$ receptors. The $P2Y_{12}$ receptor acts by inhibiting adenylyl cyclase via a G_i protein and potentiates dense granule secretion, procoagulant activity, and platelet aggregation. Without continued $P2Y_{12}$ activation, aggregated platelets disaggregate. Inhibition of the $P2Y_{12}$ receptor became a recent focus of clinical drug development and licensing.

Thienopyridines

Basic Pharmacology

Thienopyridines selectively inhibit ADP-induced platelet aggregation with no direct effects on arachidonic acid metabolism. Although thienopyridines can also inhibit platelet aggregation induced by collagen and thrombin, these inhibitory effects are abolished by increasing the agonist concentration and therefore are likely to reflect blockade of ADP-mediated amplification of the platelet response to other agonists.



• **Fig. 45.7** Three types of purinergic receptors expressed on platelets and their mechanisms of platelet activation. The two seven-transmembrane receptors act through G-protein mechanisms. The $P2Y_1$ receptor initiates platelet aggregation and the $P2Y_{12}$ receptor amplifies and completes the aggregation process. Continued stimulation of $P2Y_{12}$ receptors is needed to prevent platelet disaggregation. *ADP,* Adenosine diphosphate; *ATP,* adenosine triphosphate; *Ca^{2+},* calcium ion.

The thienopyridines do not act directly, but are administered as prodrugs requiring hepatic transformation. Clopidogrel is metabolized into 2-oxo-clopidogrel through a CYP-dependent pathway (Fig. 45.8). The most important of these clinically is CYP 2C19. Prasugrel is not detected in plasma after oral administration. It is rapidly hydrolyzed by esterase in the intestine to a thiolactone, which is then converted to the active metabolite by a single step, primarily by CYP 3A4 and CYP 2B6, and to a lesser extent by CYP 2C9 and CYP 2C19. The active metabolite of prasugrel is metabolized to two inactive compounds by S-methylation or conjugation with cysteine. The major inactive metabolites are highly bound to plasma proteins. Clopidogrel is also metabolized by esterases to produce an inactive carboxylic acid derivative designated as SR 26334, which is thought to represent more than 80% of circulating metabolites.

The active metabolites of both clopidogrel and prasugrel couple through a covalent disulfide bond to $P2Y_{12}$ receptors, rendering the receptor unresponsive to ADP. Because the bond is covalent it is essentially irreversible; thus platelets exposed to the active thiol are affected for the remainder of their life span (about 7–10 days). Return of global platelet function requires the generation of a new platelet pool. The relevance of the CYP system in producing the active metabolite is discussed in later text in the sections on drug interactions and pharmacogenetics.

Clinical Pharmacology

Pharmacokinetics. After oral administration, about 80% of prasugrel and about 50% of clopidogrel is absorbed; this is not affected by food ingestion.[47] Metabolism of both drugs is rapid, with peak plasma concentrations of the active metabolite occurring approximately 30 minutes after dosing. For prasugrel and clopidogrel, repeat daily doses do not lead to accumulation of the active metabolite, which has an elimination half-life of about 7 hours in both cases. Both drugs are highly protein bound (>95%).

Approximately 70% of the prasugrel dose is excreted in urine and 30% in feces as inactive metabolites. The corresponding figures for clopidogrel are about 50% by each route.

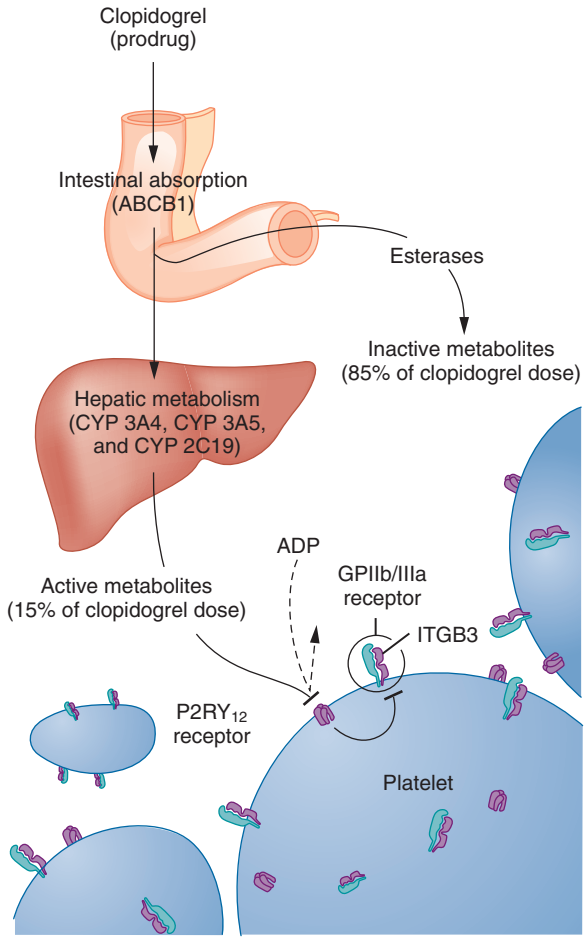
With both drugs the recommendation is to give a loading dose followed by a once-daily maintenance dose: a 300-mg load and 75 mg/day for clopidogrel and for prasugrel 60 mg and 10 mg/day, respectively.

Pharmacodynamics. Dose-dependent inhibition of platelet aggregation occurs about 2 hours after ingestion. With prasugrel, platelet inhibition reaches about 50% 1 hour after a loading dose of 60 mg. Steady-state inhibition of about 70% occurs after 3 to 5 days with a maintenance dose of 10 mg/day. Platelet aggregation returns to baseline over 5 to 9 days, reflecting production of new platelets. With clopidogrel at a dose of 75 mg once daily, platelet inhibition reaches a steady-state of 40% to 60% after 3 to 7 days. Platelet aggregation and bleeding time return to baseline about 5 days after stopping therapy.

Because both thienopyridines are prodrugs, their pharmacodynamic effects could be affected by alterations in metabolism. This apparently is the case only with clopidogrel, in that prasugrel has not been shown to have significant metabolic drug interactions.

Therapeutic Effects

Both clopidogrel and prasugrel are indicated in patients with acute coronary syndromes. This includes patients with unstable angina or non-ST-elevation myocardial infarction and patients with



• **Fig. 45.8** Role of metabolism in activation of the prodrug clopidogrel. Intestinal absorption of the prodrug clopidogrel is limited by an intestinal efflux pump P-glycoprotein *(ABCB1)*. The majority of the prodrug is metabolized into inactive metabolites by ubiquitous esterases. The minority is bioactivated by various cytochrome P450 *(CYP)* isoforms into active metabolites. These metabolites irreversibly antagonize the adenosine diphosphate *(ADP)* receptor, which in turn inactivates the fibrinogen receptor (the glycoprotein *[GP]* IIb/IIIa receptor) involved in platelet aggregation. Many of these genes are subject to genetic polymorphisms that can affect drug response and result in nonresponders. (Modified from Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med.* 2009;360:363–375.)

ST-elevation myocardial infarction when managed with primary or delayed percutaneous coronary intervention (PCI).

Clopidogrel reduces the rate of a combined endpoint of cardiovascular death, MI, or stroke, as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia. Compared with clopidogrel, prasugrel reduces the rate of a combined endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke.[48] The difference between treatments was driven predominantly by the incidence of MI, with no difference in stroke and little difference in cardiovascular death. Prasugrel is also indicated to reduce the rate of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with PCI. The U.S. FDA allowed a license for use of prasugrel only after a considerable debate and inclusion of black box warnings.

TABLE 45.10 Effect of Aspirin Dose and Age on Bleeding Event Rates

Treatment Group	ASPIRIN DOSE		
	<100 mg/day	100–200 mg/day	>200 mg/day
Clopidogrel	2.6%	3.5%	4.9%
Placebo	2.0%	2.3%	4.0%
Age	<65 yr	65–75 yr	>75 yr
Clopidogrel	2.5%	4.1%	5.9%
Placebo	2.1%	3.1%	3.6%

Data from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study.[44]

Adverse Outcomes

The principal adverse effect of thienopyridines is bleeding.[49] The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study showed similar rates for nonfatal and major hemorrhage but highlighted dose-dependent effects of ASA on rates for bleeding and factor Xa inhibitors an effect of age in both clopidogrel-treated and placebo groups (Table 45.10). In the TRITON TIMI38 (TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38) study, bleeding rates with prasugrel were markedly higher than with clopidogrel. Major bleeding was reported in 11.3% of prasugrel-treated patients compared with 3.6% in clopidogrel-treated patients, with differences in rate of fatal bleeding (0.9% to 0%), need for reoperation (3.8% to 0.5%), and requirement for red blood cell transfusion of at least 5 units (6.6% to 2.2%). As expected, there was also an effect of time on the rate of bleeding after stopping the drugs. Patients who had surgery within 3 days of stopping the thienopyridine had rates of major/minor bleeding of 26.7% for prasugrel and 5% for clopidogrel. These rates fell to 11.3% and 3.4%, respectively, for patients who had surgery 4 to 7 days after stopping the drug. These issues resulted in the FDA adding a black box warning for prasugrel.

Drug Interactions

Major interactions with clopidogrel involve drugs that modify CYP 2C19 and CYP 3A4. An example of the former is the proton pump inhibitor omeprazole, which reduces platelet ADP response. The CYP 3A4 and 3A5 isozymes metabolize clopidogrel more rapidly than other CYP enzymes and are most abundant in liver. Atorvastatin and other CYP 3A4 inhibitors reduce platelet inhibition, and a CYP 3A4 activator enhances platelet inhibition when coadministered with clopidogrel.[50] Despite these known interactions, there is no evidence that this is clinically relevant, as shown by a lack of a statistically discernible effect on cardiovascular outcomes.[51]

Pharmacogenetics

In contrast to the lack of clinically evident adverse outcomes from drug interactions, there is considerable interest in polymorphisms of CYP 2C19. Among clopidogrel-treated subjects in the TRITON-TIMI 38 study, carriers of the *2 variant had a relative increase of 53% in the risk of death from cardiovascular causes, MI, or stroke compared with noncarriers (12.1% vs. 8.0%); and an increase by a factor of 3 in the risk of stent thrombosis (8% vs. 2.6%).[52]

These observations resulted in the FDA requiring a black box warning for clopidogrel. A parallel study of prasugrel found no effect of this polymorphism on pharmacodynamic or clinical outcomes.[53]

Specific Populations

Transient Ischemic Attack or Stroke Prasugrel is contraindicated in patients with a history of prior TIA or stroke.[54] Patients with a history of TIA or ischemic stroke (>3 months before enrollment) had a higher rate of stroke when taking prasugrel (6.5%; of which 4.2% of cases were thrombotic stroke and 2.3% were intracranial hemorrhage) than when taking clopidogrel (1.2%; all thrombotic). Prasugrel is not recommended for patients 75 years of age or older owing to an increased incidence of fatal and intracranial bleeding, except in higher-risk situations such as diabetes mellitus or history of previous MI. The mean exposure to the prasugrel active metabolite is approximately 30% to 40% higher in subjects with a body weight of less than 60 kg than in those weighing 60 kg or more. Although prasugrel is not contraindicated in this group, a higher rate of bleeding can be anticipated. There are no published age or weight limitations with clopidogrel.

Renal Impairment Patients with renal dysfunction are more prone to bleeding when receiving antithrombotic drugs. In a post hoc analysis of data from the CURE trial, cardiovascular death, MI, and stroke combined and bleeding occurred more frequently in the lowest glomerular filtration rate tercile.[55] This observation is not reflected in the effects of renal function on drug activity. For patients with end-stage or severe chronic renal failure (estimated creatinine clearance <15 mL/min), exposure to the active prasugrel metabolite was *reduced* to about half that in healthy controls. Similarly, for clopidogrel in these patients platelet inhibition was about half that anticipated following administration of 75 mg daily at only 25%. The reason for opposed effects on pharmacodynamic endpoints and patient outcomes is unclear.

Adenosine Diphosphate Analogs

Ticagrelor

Basic Pharmacology Ticagrelor is the first of a new class of antiplatelet agents, the cyclopentyl-triazolo-pyrimidines. Similar to the thienopyridines, ticagrelor is an oral $P2Y_{12}$ receptor antagonist that exerts antiplatelet effects by blocking ADP. In contrast to the other antiplatelet drugs, ticagrelor has a binding site different from ADP, making it an allosteric antagonist, and the block is reversible. Unlike the thienopyridines, ticagrelor is not a prodrug and therefore does not require metabolic activation to inhibit platelets. These properties give ticagrelor several theoretical advantages over clopidogrel. Since ticagrelor does not require metabolic activation, it avoids the variability seen with CYP polymorphisms and therefore produces a more consistent antiplatelet effect. However, the parent drug is metabolized, principally by CYP 3A, to about 10 metabolites. The major metabolite, AR-C124910XX, formed by O-deethylation, is as active as ticagrelor in inhibiting ADP-induced platelet aggregation.

Clinical Pharmacology

Pharmacokinetics Ticagrelor is about 36% bioavailable after oral administration and is rapidly absorbed with a maximum plasma concentration at 1.5 hours. Both ticagrelor and AR-C124910XX are highly (>95%) protein bound. Total clearance is about 25 L/hr with an apparent half-life of 8 to 12 hours.

Pharmacodynamics and Therapeutic Effects

Inhibition of platelet activity (IPA) using ADP-stimulated platelet aggregation showed 88% platelet inhibition with ticagrelor in the ONSET/OFFSET study.[56] Ticagrelor inhibited platelets to a greater extent than did clopidogrel at 30 minutes mean IPA, 40% compared with approximately 5%, respectively, and at 2 hours mean IPA, approximately 90% compared with approximately 40%, respectively. Other measures of platelet function showed more rapid and robust IPA (typically threefold to fivefold greater effectiveness) for ticagrelor compared with clopidogrel, and that the rate of recovery after withdrawal of therapy was more rapid with ticagrelor than clopidogrel.

Ticagrelor and clopidogrel were compared head to head in the PLATO (Platelet Inhibition and Patient Outcomes) study. The primary endpoint—death from vascular causes, MI, or stroke—occurred significantly less often in the ticagrelor group than in the clopidogrel group (9.8% compared with 11.7% at 12 months). This difference was apparent as early as 30 days after the start of treatment. In patients who progressed to have coronary artery bypass graft surgery, there was an early (at 1 month) difference in cardiovascular death, which continued to 1-year follow-up (7.9% with clopidogrel compared with 4.1%). This striking benefit was unrelated to excess bleeding in either group.[57] These data have led to licensing of ticagrelor for use in ACS in Europe and the United States. The FDA has also stipulated a black box warning that the effectiveness of ticagrelor is reduced when used with aspirin at doses higher than 100 mg per day.

Adverse Effects

Bleeding In the PLATO study, the two treatment groups did not differ significantly in rates of major bleeding (11.6% and 11.2%), even though ticagrelor was only withheld for 24 to 72 hours before coronary artery bypass surgery while clopidogrel was withheld for 5 days. However, there was a higher rate of nonsurgical major bleeding. The prescribing information has been amended to suggest this drug be withheld for 5 days before surgery or invasive procedure.

Adenosine-Related Adverse Effects Ticagrelor is metabolized to adenosine, and administration is associated with related effects. Patients receiving ticagrelor had significantly more episodes of dyspnea (10%–20%) and ventricular pauses lasting longer than 3 seconds (6%). However, with ticagrelor most of the episodes of dyspnea were minor, and only 1% of patients in the ticagrelor group stopped therapy because of this adverse event. Even so, these events suggest that close monitoring of patients taking ticagrelor is necessary during early exposure.

Drug Interactions

Inhibitors of CYP 3A4 such as ketoconazole and drugs that are metabolized by CYP 3A4 such as simvastatin are associated with increased plasma levels. Conversely, CYP 3A4 inducers—for example, rifampicin and possibly St. John's wort—are associated with reduced ticagrelor plasma concentrations. Ticagrelor inhibits P-glycoprotein, leading to increased plasma levels of digoxin, cyclosporin, and other substrates. P-glycoprotein inhibitors do not significantly influence ticagrelor and AR-C124910XX levels.

Special Populations

Plasma concentrations of ticagrelor are slightly increased (12%–23%) in older patients, women, patients of Asian ethnicity, and patients with mild hepatic impairment. The pharmacodynamics of ticagrelor are not materially affected in patients with severe renal impairment.

TABLE 45.11 Basic Pharmacology and Safety Aspects of Available Purinergic Receptor Antagonists[a]

	Clopidogrel	Prasugrel	Cangrelor	Ticagrelor
Chemical structure	Thienopyridine	Thienopyridine	ADP analog	Cyclopentyltriazolopyridine (ADP analog)
Prodrug	Yes	Yes	No	No
Administration	Oral	Oral	Intravenous	Oral
Time to peak effect	Dose-dependent	2 hr	30 min	2 hr
Platelet inhibition with ADP stimulus 2 hr after loading dose	40%–50%	70%–90%	90%–100%	80%–90%
Half-life	6 hr	8 hr	1.5–3 min	6–12 hr
Time to steady-state platelet inhibition	4–5 days	2–4 days	30 min	2–3 days
Reversible	No	No	Yes	Yes
Time to recovery of platelet aggregation	5 days	7 days	60–90 min	24–48 hr
Safety with prior CVA	Yes	No	NA	Yes
Non-CABG bleeding		Increased risk		Increased risk
CABG bleeding		Increased risk		Reduced risk

ADP, Adenosine diphosphate; *CABG,* coronary artery bypass graft; *CVA,* cerebrovascular accident; *NA,* not available.
[a]The risk of CABG and non-CABG related bleeding is in comparison to standard dose clopidogrel therapy.

The drug has not been tested in patients with severe hepatic impairment.

Unique Features

Consistent with its reversible mode of action, ticagrelor acts more quickly and is effective for a shorter time than clopidogrel. This means it has to be taken twice instead of once daily, which is a disadvantage with respect to compliance, but its effects are more quickly reversible, which can be useful before surgery or if side effects occur. The compliance issue has relevance to patients with stents in situ, because the effects of missing doses of ticagrelor will increase the risk for in-stent thrombosis.

Cangrelor

Basic Pharmacology

Cangrelor is an intravenous $P2Y_{12}$ purinoreceptor antagonist. Manipulation of the chemical structure of ATP resulted in a novel class of compounds known as purinoreceptor modulators. Cangrelor inhibits platelet aggregation by inhibition of the $P2Y_{12}$ receptor, leading to an increase in cAMP. This compound increases intraplatelet cAMP by an additional mechanism that is thought to act via a G_s signaling pathway.

Clinical Pharmacology

Pharmacokinetics Cangrelor has a short half-life (2.6 minutes) and rapid plasma clearance (50 L/hr). Steady-state inhibition of ADP-induced platelet aggregation is achieved within 30 minutes of infusion of cangrelor titrated up to 4 μg/kg per minute in healthy volunteers. Return of baseline platelet aggregation occurs in 70% of volunteers within 1 hour of infusion termination.

Pharmacodynamics Cangrelor produces concentration-dependent inhibition of thrombin receptor–activating, peptide-induced aggregation in human platelets, indicating competitive antagonism. Furthermore, cangrelor acts directly at the $P2Y_{12}$ receptor without need for hepatic conversion to an active metabolite. Plasma concentrations of cangrelor are unaffected by severe renal or hepatic impairment.

Cangrelor was studied in two large-scale phase III studies that were both ended early after a decision by the interim analysis review committee that the study would not demonstrate the "persuasive" clinical efficacy needed for regulatory approval. Cangralor is currently approved for use during percutaneous coronary interventions when an oral ADP receptor blocker of glycoprotein IIb/IIIa receptor blocker has not been administered. Table 45.11 compares and contrasts the basic pharmacology and safety data for available purinergic receptor antagonists.

Glycoprotein IIb/IIIa Antagonists

Basic Pharmacology

GpIIb/IIIa is a member of a family of adhesive receptors (integrins) composed of α and β transmembrane proteins. GpIIb/IIIa itself is composed of αIIα and β3 units and is specifically expressed in platelets. There are an estimated 50,000 to 80,000 GpIIb/IIIa receptors on the surface of each platelet. Internal stores of GpIIb/IIIa can be mobilized to join the existing surface receptors and further increase overall surface expression. Platelet activation results in a change in the conformation of the receptor, which greatly increases its low affinity for fibrinogen and vWF.

Two types of GpIIb/IIIa receptor antagonists are available: noncompetitive (monoclonal antibodies) and competitive (a peptide and a peptidomimetic).[59] Abciximab is a chimeric mouse-human antibody modified from an original murine monoclonal antibody to reduce its immunogenicity. The ability of abciximab to bind to the vitronectin receptor and the leukocyte receptor (Mac-1) might also contribute to the antiinflammatory properties of this drug. It is taken up by the reticular endothelial system where it is degraded by proteolysis.

Eptifibatide is a cyclic heptapeptide containing six amino acids and one mercaptopropionyl (des-amino cysteinyl) residue. Tirofiban

TABLE 45.12 Basic Pharmacology of Noncompetitive (Monoclonal Antibody) and Two Competitive Inhibitors of the Glycoprotein IIb/IIIa Receptor

Compound	Chemistry	Plasma Half-Life	Biologic Half-Life	Clearance Mechanism
Abciximab	Monoclonal antibody	10 min	12–24 hr	Reticuloendothelial system
Tirofiban	Peptidomimetic	2 hr	4–8 hr	Renal
Eptifibatide	Polypeptide	2.5 hr	4–6 hr	Renal

is a nonpeptide peptidomimetic. Both agents mimic the arginine-glycine-aspartate sequences on fibrinogen. They contain either the arginine-glycine-aspartate sequence itself or a similar sequence. The therapeutic efficacy of these drugs depends on maintaining plasma levels high enough to compete with fibrinogen for GpIIb/IIIa. Neither agent is significantly metabolized and both are renally excreted. Neither tirofiban nor eptifibatide react with the vitronectin or Mac-1 receptor.

Clinical Pharmacology

Pharmacokinetics

Comparator data for the three available GpIIb/IIIa receptor antagonists are listed in Table 45.12. All three drugs are administered as a bolus followed by a continuous intravenous infusion. After bolus administration of abciximab, free plasma concentrations decrease very rapidly, with an initial half-life of less than 10 minutes and a second-phase half-life of about 30 minutes, probably related to rapid binding to platelet GpIIb/IIIa receptors and uptake by the reticuloendothelial system. High receptor affinity results in a long biologic half-life of 12 to 24 hours. Platelet function generally recovers over the course of 48 hours, although abciximab remains in the circulation for 15 days or more in a platelet-bound state. Abciximab can redistribute from the originally bound platelet to newly produced platelets, thus prolonging the antiplatelet effect. GpIIb/IIIa receptor occupancy by abciximab exceeds 30% at 8 days and 10% at 15 days, with residual binding documented as late as 21 days after therapy. Intravenous administration of a 0.25-mg/kg bolus followed by continuous infusion of 10 μg/min produces relatively constant free plasma concentrations throughout the infusion. At the termination of the infusion period, free plasma concentrations fall rapidly for approximately 6 hours then decline at a slower rate.

Tirofiban has a half-life of approximately 2 hours. It is cleared from the plasma largely by renal excretion, with about 65% appearing in urine and about 25% in feces, both largely as unchanged tirofiban. Tirofiban is not highly bound to plasma proteins; the unbound fraction in human plasma is 35%.

The pharmacokinetics of eptifibatide are linear and dose related. Plasma elimination half-life is approximately 2.5 hours. Administration of a single 180-μg/kg bolus combined with an infusion produces an early peak level, followed by a small decline before attaining steady-state (4–6 hours). The extent of eptifibatide binding to human plasma protein is about 25%. In healthy subjects, renal clearance accounts for approximately 50% of total body clearance, with the majority of the drug excreted in the urine as eptifibatide, deaminated eptifibatide, and other more polar metabolites. No major metabolites have been detected in human plasma.

Pharmacodynamics

The most commonly used method for assessing the pharmacodynamic effects of the various GpIIb/IIIa antagonists is platelet aggregometry. Administration of these agents alone does not prolong PT or aPTT. Intravenous administration in humans of a single bolus dose of abciximab of 0.25 mg/kg followed by a continuous infusion of 10 μg/min produced a relatively constant plasma concentration and sustained high-grade GpIIb/IIIa receptor blockade (>80%) and inhibition of platelet function.[60] Skin bleeding time recovers within 12 hours of stopping the infusion. Although low levels of GpIIb/IIIa receptor blockade are present for more than 10 days after cessation of the infusion, platelet function typically returns to normal over a period of 24 to 48 hours.

Tirofiban inhibits ADP-induced platelet aggregation ex vivo and prolongs bleeding time. After a loading dose of 0.4 μg/kg over 30 minutes, platelet aggregation was inhibited by more than 90% and bleeding time was prolonged about threefold. After discontinuation of an infusion of tirofiban, ex vivo platelet aggregation returns to near baseline in approximately 90% of patients in 4 to 8 hours.[61]

In clinical trials, eptifibatide inhibits platelet aggregation ex vivo induced by ADP and other agonists in a dose- and concentration-dependent manner.[62] The effect of eptifibatide was observed immediately after administration. Platelet aggregation is inhibited by about 85% after bolus injection and more than 90% during the steady-state infusion. Platelet aggregation returns to less than 50% inhibition 4 hours after discontinuing the infusion, and bleeding time returns to baseline within 6 hours of discontinuing the drug.

Therapeutic Effects

The benefit of GpIIb/IIIa inhibitors is mainly limited to high-risk patients with unstable angina or non–ST-elevation MI.[63] The most notable conditions where benefit is shown are in troponin-positive patients, regardless of whether they undergo revascularization, and those with diabetes mellitus. The TARGET (Treatments Against RA and Effect on FDG-PET/CT) trial provides the only direct comparison of a small molecule (tirofiban) agent with abciximab, and this trial demonstrated superiority for abciximab in reducing ischemic endpoints. For diabetic patients, abciximab is the only GpIIb/IIIa inhibitor observed to provide a significant survival advantage in patients undergoing PCI with angioplasty or stent placement, and thus is singled out as the agent of choice for use in diabetic patients undergoing stent implantation. Abciximab also has the most data supporting safety in patients with severe renal insufficiency, likely because of its nonrenal mode of metabolism and elimination.

Current American College of Cardiology/American Heart Association guidelines recommend a platelet GpIIb/IIIa antagonist in patients with moderate- to high-risk ACS in whom catheterization and PCI are planned (class I, level A). Patients receiving a bolus plus infusion of abciximab have a significant (35%–50%) reduction in the composite endpoint of death, nonfatal MI, refractory ischemia, or urgent revascularization within 30 days. Treatment

benefits are observed within hours after intervention and are sustained through 6 to 12 months. Eptifibatide or tirofiban should be administered in patients with high-risk ACS in whom invasive management is not planned (class IIa, level A). In contrast to the data for abciximab, treatment with eptifibatide in the IMPACT II (Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II) study showed a treatment effect over 30 days that was lost at 6-month follow-up. Similarly in the RESTORE (Randomized Evaluation of Sedation Titration fOr Respiratory failure) study, the early treatment effect to prevent restenosis after angioplasty with tirofiban was lost at 6-month follow-up. An evidence-based approach would thus favor abciximab as the standard GpIIb/IIIa inhibitor for administration during PCI, especially in patients with ACS accompanied by high-risk features, including diabetes mellitus.

Adverse Effects

Bleeding. As with all anticoagulant and antiplatelet agents, bleeding is a risk. The main concern is when these agents are given with anticoagulants, especially heparin. With abciximab, the incidence of bleeding decreases to only about 2% when used with low-dose heparin (70 U/kg) and further studies have reported major bleeding rates that are at least as low, if not lower, than that owing to heparin alone. With tirofiban, the addition of heparin does not significantly alter inhibition of platelet aggregation, but it does increase the average bleeding time, as well as the number of patients with bleeding times prolonged to more than 30 minutes. The principal site for bleeding is the femoral artery puncture site used for vascular access. To reduce the risk of bleeding, manufacturers recommend stopping heparin 3 to 4 hours before cannula withdrawal.

Thrombocytopenia. Thrombocytopenia can occur with all the GpIIb/IIIa receptor antagonists, with some variability related to the agent administered, dosage, duration of treatment, and the various drugs coadministered. Incidence of thrombocytopenia ranges from 1.1% to 5.6%. An immune mechanism is believed to be responsible. Binding of the antagonist to GpIIb/IIIa receptors might lead to exposure of ligand-induced binding sites to preexisting or induced antibodies. Another possible mechanism for thrombocytopenia is drug-induced activation of platelets. Thrombocytopenia induced by these mechanisms occurs within the first 24 hours of administration. All patients receiving parenteral GpIIb/IIIa antagonists should be monitored within 24 hours of initiation of therapy for development of thrombocytopenia and the drug discontinued if this occurs.

Special Populations and Contraindications

Treatment with GpIIb/IIIa receptor antagonists is contraindicated in patients with severe hypertension (systolic blood pressure >200 mm Hg or diastolic blood pressure >110 mm Hg) not adequately controlled by antihypertensive therapy, major surgery or history of major trauma within the preceding 4 to 6 weeks, history of stroke within 30 days or any history of hemorrhagic stroke (for tirofiban and eptifibatide), increased to 2 years before the use of abciximab, or a history of intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation, or aneurysm.

For abciximab, additional contraindications are administration of oral anticoagulants within 7 days unless the PT is less than or equal to 1.2 times control, use of intravenous dextran before percutaneous coronary intervention, or intent to use it during intervention, or presumed or documented history of vasculitis.

Tirofiban is also contraindicated with a history, symptoms, or findings suggestive of aortic dissection or pericarditis. As both tirofiban and eptifibatide are principally cleared by the kidney, both should have the dose of the maintenance infusion reduced to half with an estimated creatinine clearance less than 50 mL/min. Both are also contraindicated in patients receiving long-term renal dialysis, as is abciximab, but in this case because of a lack of safety data in this population.

Special Populations and Unique Features

Except for patients with renal disease, there are no groups of patients in whom these drugs are associated with a relative increase in adverse effects. Administration of abciximab can result in the formation of human antichimeric antibodies that could potentially cause allergic or hypersensitivity reactions (including anaphylaxis), thrombocytopenia, or diminished benefit upon readministration.

Protease Activated Receptor-1 (Thrombin Receptor)

Platelets have a specific surface G protein–coupled receptor known as *protease-activated receptor-1* (PAR-1) receptor for thrombin. The extracellular portion is a long polypeptide, which has an arginine residue at position 41 and a serine at position 42. Thrombin cleaves this peptide at this position, resulting in a hexapeptide SFLLRN at the N-terminal end. This is the tethered ligand for the stimulation of the receptor. Compounds have been developed that inhibit the ligand-binding site on PAR-1. Because the proteolytic activity of thrombin to cleave fibrinogen is not inhibited, coagulation should be unaffected.

Vorapaxar is the only currently licensed protease activated receptor 1 or thrombin receptor inhibitor for human use. It is a derivative of himbacine, which is found in the bark of the Australian magnolia tree. Himbacine's marked activity as a muscarinic M_2 receptor agonist made it a potential medication for Alzheimer disease but this action was engineered out of the current medication.

Vorapaxar is available as a tablet containing 2.08 mg of vorapaxar sulfate. It is licensed as an adjunct to aspirin or clopidogrel therapy for reduction of thrombotic cardiovascular events in patients with a history of MI or peripheral arterial disease. Vorapaxar was administered to more than 13000 patients in the TRA 2P (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events) (TIMI [Thrombolysis in Myocardial Infarction] 50) study to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization. This study also showed an increased rate of intracranial bleeding, and the prescribing information has a black box warning that intracranial bleeding is more common with varapaxar and that it is contraindicated in patients with a history of stroke, TIA, intracranial hemorrhage, or active pathologic bleeding. At the recommended dose varapaxar achieves 80% or higher inhibition of thrombin receptor activation peptide–induced platelet aggregation by one week.

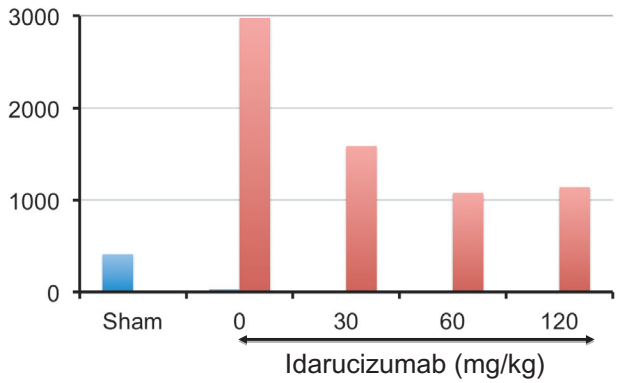
Vorapaxar is 99% protein bound and is metabolized by cytochromes CYP 3A4 and CYP 2J2 to an active metabolite. The apparent terminal elimination half-life is about 8 days (range 5–13), and this is also the case for the metabolite. The manufacturers suggest that there will still be 50% inhibition of thrombin receptor activation peptide–induced platelet aggregation 4 weeks after discontinuation of the drug based on elimination kinetics. There is no known antidote, so this raises serious concerns about urgent surgical interventions.

Emerging Developments

Reversal of Novel Anticoagulants

The introduction of orally administered direct thrombin and factor Xa inhibitors has produced a search for specific antidotes to these agents. Three lines of development are being pursued.

The first is drug specific. Idarucizumab is a monoclonal antibody developed by the manufacturers of dabigatran etexilate and raised against fragments of the dabigatran molecule and its metabolites. It is given intravenously at a dose of 5 g. This dose will reverse the coagulation tests associated with dabigatran use (dilute thrombin time and ECT) within minutes of administration. However, there are some concerns if this is a biologically relevant endpoint in preventing bleeding. In animal studies of traumatic hepatic injury, idarucizumab did reverse the effect of dabigatran on blood loss but not to the values measured with no pharmaceutical intervention[64] (Fig. 45.9). Early results of the ongoing RE-VERSE AD (Reversal Effects of Idarucizumab on Active Dabigatran) study[29] reported that, as determined by local investigators, hemostasis was restored in 35 patients presenting with serious bleeding by a median of 11.4 hours after administration of idarucizumab. This time is about the same as the half-life of dabigatran, leading to speculation as to the effectiveness of the antibody to provide very rapid reversal.

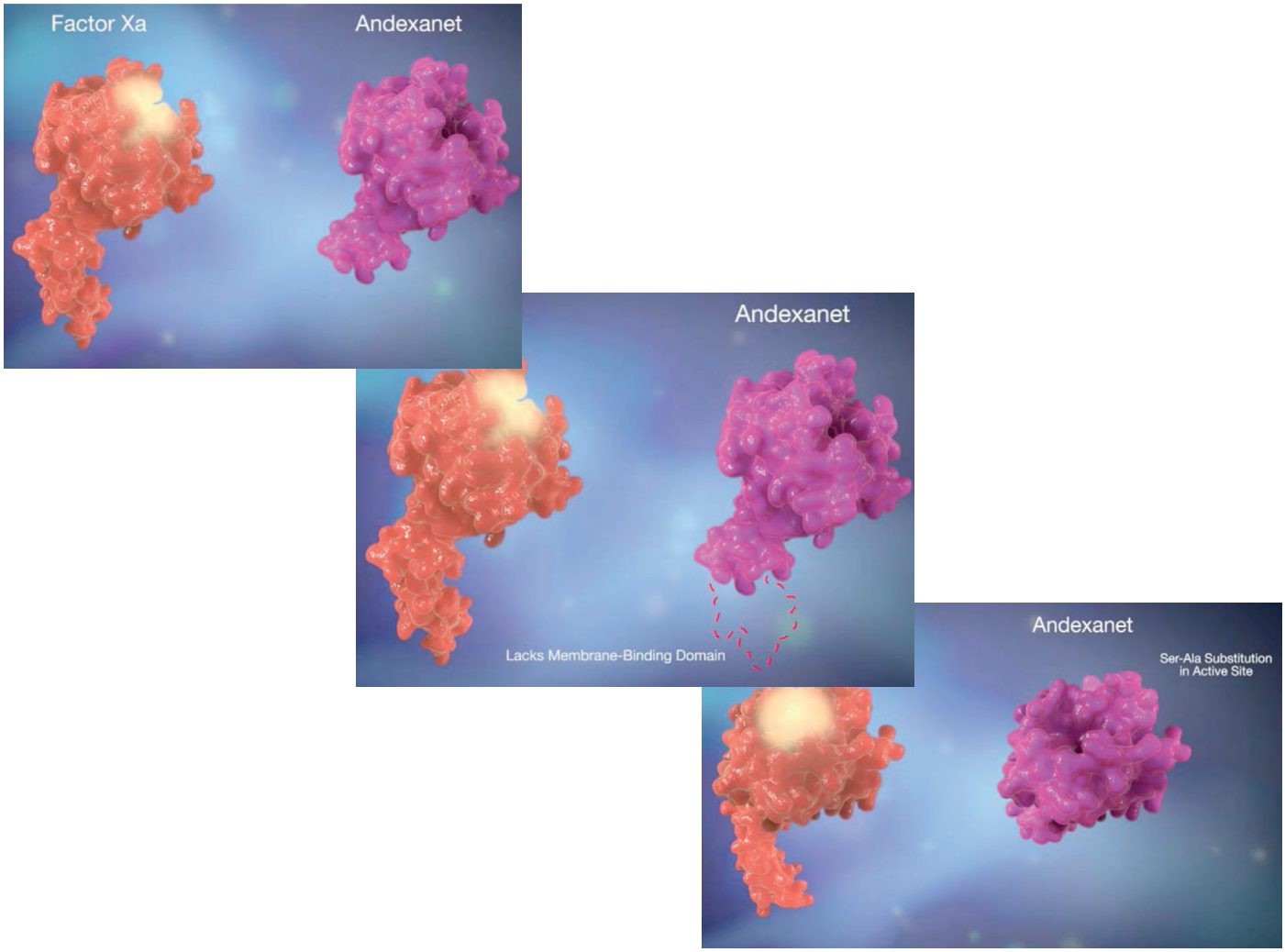


• **Fig. 45.9** Effects of increasing dose of idarucizumab on mean blood loss 120 minutes after hepatic trauma in male pigs given dabigatran exilate 30 mg/kg twice daily for 3 days. Data show idarucizumab effectively reduces acute bleeding. However, mean total loss with the highest dose is greater than that in *Sham* (no dabigatran, no idarucizumab) animals.[64]

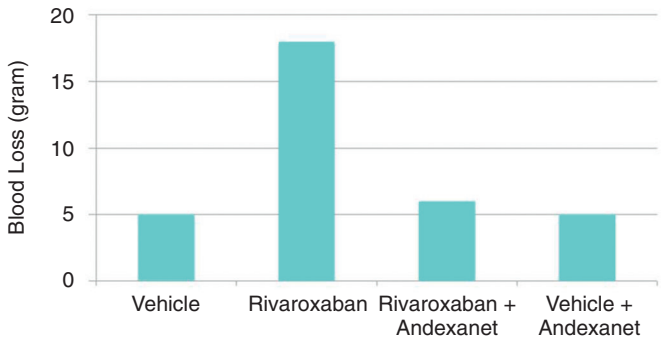
Sorbitol at a high concentration is used as an excipient for the commercially available preparation, and thus this agent should be used with extreme caution in patients with inherited fructose intolerance. The drug is expensive with a wholesale cost of a single treatment of 5 g in the United States of $3500 (about £2600 or €3200).

The second drug is a class-specific reversal agent for both direct and indirect factor Xa antagonists. Andexanet alfa is a recombinant factor Xa "decoy molecule" that has been designed so that it lacks the glutamic acid–rich membrane-binding domain, is enzymatically inactive as it has a serine to alanine substitution at the active cleavage site of factor Xa, and finally has deletion of the heavy-chain activation peptide (Fig. 45.10). The molecule inhibits all oral factor Xa inhibitors and is unique in being able to inhibit indirect inhibitors such as LMWH and fondaparinux. This agent has been extensively studied in animal models of traumatic hemorrhage and has been shown to fully reverse the effects of both the oral Xa inhibitors and enoxaparin.[65] Data from studies to reverse rivaroxaban inhibition in a hepatic trauma model (Fig. 45.11) show complete reversal of the effect of rivaroxaban on blood loss. Initial studies have been reported in humans with bleeding and who were recently taking an Xa inhibitor.[32] Of the 67 patients (mean age 77 years), 32 were receiving rivaroxaban, 31 apixaban, and 4 enoxaparin. The site of bleeding was gastrointestinal in 33 (49%) and intracranial in 28 (42%). Based on data from prior studies andexanet alfa was given as a bolus over 15 minutes followed by an infusion over 2 hours. Two doses were administered. In patients who had received rivaroxaban or apixaban more than 7 hours before hospital admission, a bolus of 400 mg and the total for infusion of 480 mg. For patients taking edoxiban, enoxaparin, or rivaroxaban within 7 hours of admission the dose was doubled to a bolus of 800 mg and an infusion of 960 mg. The rates for good or excellent hemostasis were more than 80% for both gastrointestinal and intracranial hemorrhage.

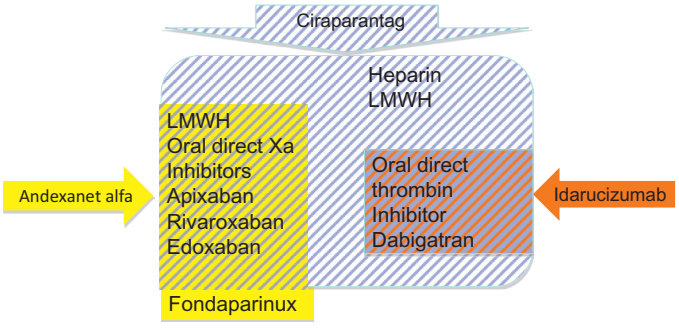
The final agent being developed potentially has universal applicability. Ciraparantag has been developed to bind to specific portions of all of the novel anticoagulants and also LMWHs. Ciraparantag consists of two L-arginine units connected with a piperazine-containing linker chain. Binding to substrate is by electrostatic or hydrogen bonding. Phase II studies in humans showed that ciraparantag administration reversed the anticoagulant activity of enoxaparin. Phase III studies are currently underway. The spectrum of inhibitor activity (drug, class, or overall) is shown schematically in Fig. 45.12.



• **Fig. 45.10** The structure of the 'decoy' factor Xa molecule andexanet. The molecule is factor Xa without the membrane binding domain. Andexanet is also enzymatically inactive owing to a serine to alanine substitution at the active pocket site.



• **Fig. 45.11** Effects of andexanet administration on mean blood loss in a rabbit hepatic laceration model of bleeding. Animals that were treated with rivaroxaban orally for 3 days showed a 3- to 4- fold increase in blood loss, which was totally prevented by administration of andexanet before trauma.[65]



• **Fig. 45.12** Schematic representation of antidotes to anticoagulating agents. Idarucizumab is an antibody specific for dabigatran. Andexanet alfa is a "decoy" factor X analog that is class specific for direct- and indirect-acting factor Xa inhibitors. Ciraparantag is being developed to have a universal inhibitory action on all anticoagulants except the pentasaccharide fondaparinux.

Key Points

- Arterial and venous occlusion with thrombus is a major contributor to mortality and morbidity.
- Improvements in physical chemistry have allowed targeting many receptors associated with the coagulation network and platelet function to inhibit coagulation and platelet aggregation.
- Until recently the mainstay of anticoagulant therapy was heparin and vitamin K antagonists, and the mainstay for platelet inhibition was acetylsalicylic acid.
- Understanding the receptor structure and function of platelets and the active proteolytic sites of coagulation proteins has allowed rational development of novel drugs to modify or inhibit thrombogenesis and coagulation.
- However, the new direct oral anticoagulant drugs and new platelet-inhibiting agents increase bleeding risk associated with surgery and invasive procedures.
- In the case of the new oral anticoagulants, there is no ability to monitor their effect using simple standard laboratory assays, and antiplatelet activity can be measured only by specialized methods.
- Pharmacokinetics and pharmacodynamics of anticoagulant and antiplatelet drugs can differ significantly between patients depending on factors such as renal function, age, and frailty.

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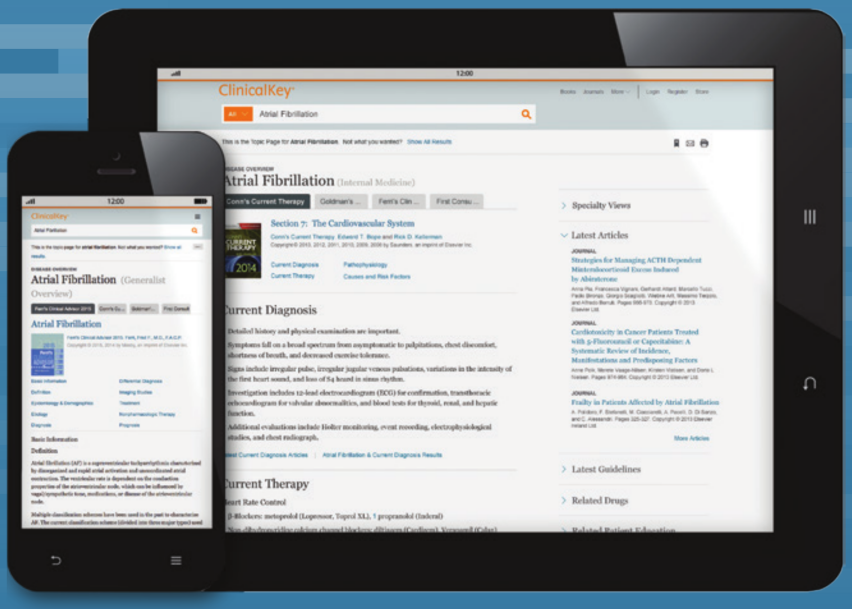

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