Second Edition

# PHARMACOLOGY FOR AND PHYSIOLOGY FOR ANESTHESIA

## FOUNDATIONS AND CLINICAL APPLICATION


Hugh C. Hemmings, Jr.
Talmage D. Egan

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*whose support and understanding were essential to the*
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*from whom I continue to learn.*

**H.C. Hemmings, Jr.**

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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.

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# Contents

# 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



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.



## 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]

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

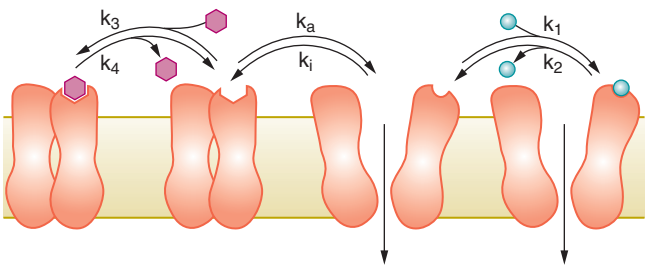
To initiate its pharmacologic action, a drug (D) first needs to bind its receptor"

[3]

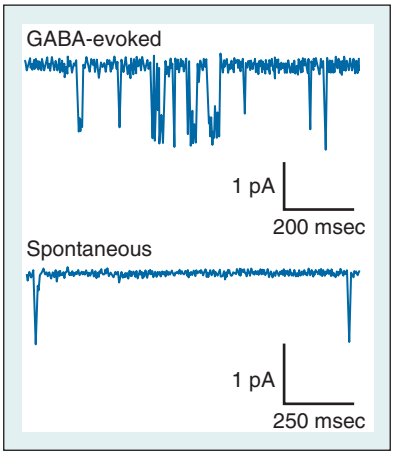
$$R^I \underset{k_i}{\overset{k_a}{\rightleftharpoons}} R^A + D \underset{k_2}{\overset{k_1}{\rightleftharpoons}} R^A * D$$

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.

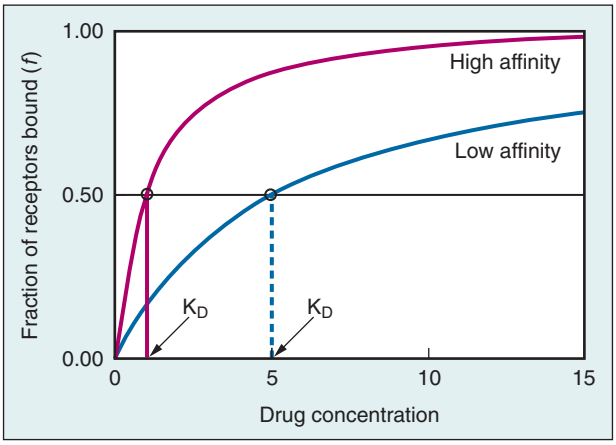
Although it might seem at first counterintuitive that even in the absence of agonist a receptor can be found in its active form, modern experimental methods such as single-channel patch clamp recordings can show this directly.[12] An example of such a recording is shown in Fig. 1.2.[13]




• **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]

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

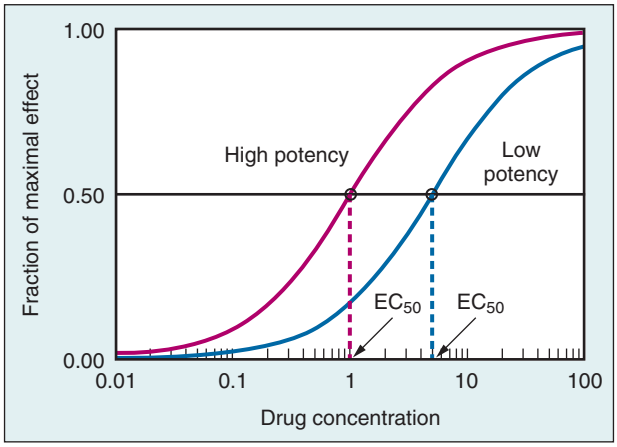
$K_D$ is a fundamental property of the drug-receptor interaction (given constant conditions such as temperature, pH, and so on) but can be different for different drug-receptor pairs. To illustrate the effect of differences in $K_D$ on the formation of drug-receptor complexes, Eq. 7 is plotted for two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

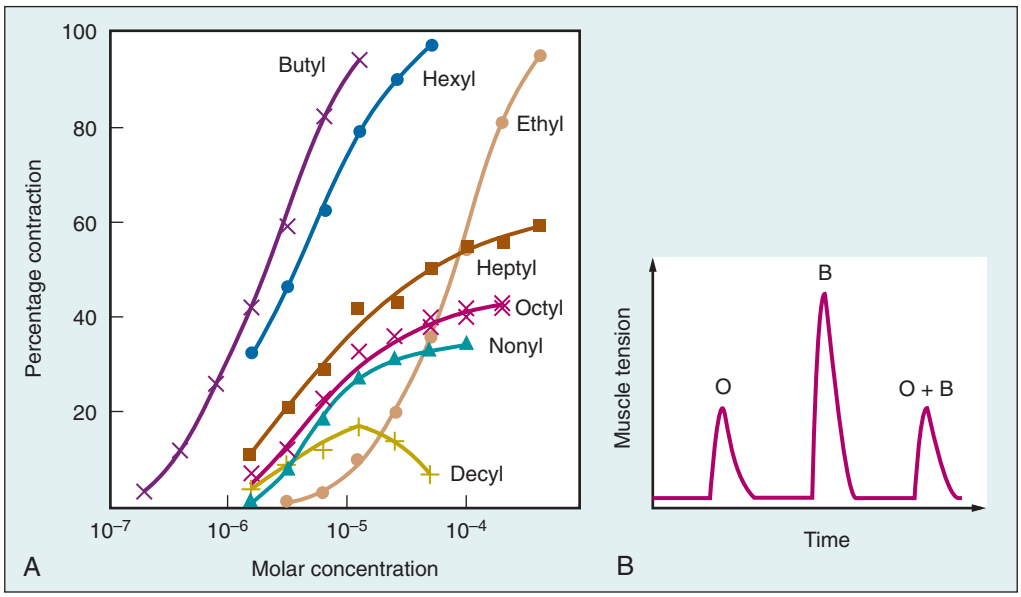
The curve in Fig. 1.4 is derived from an abstract notion of equilibrium between bound and free receptors. It is totally independent of the chemical identity of the drug or the receptor—it reflects the general property of drug-receptor interactions and is fundamental to the understanding of the action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

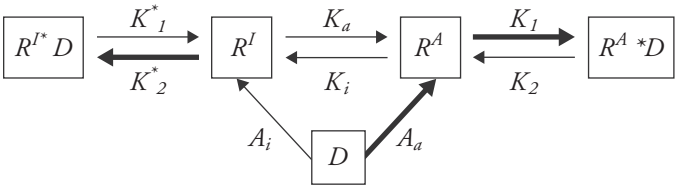
$$S = eAD$$

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]

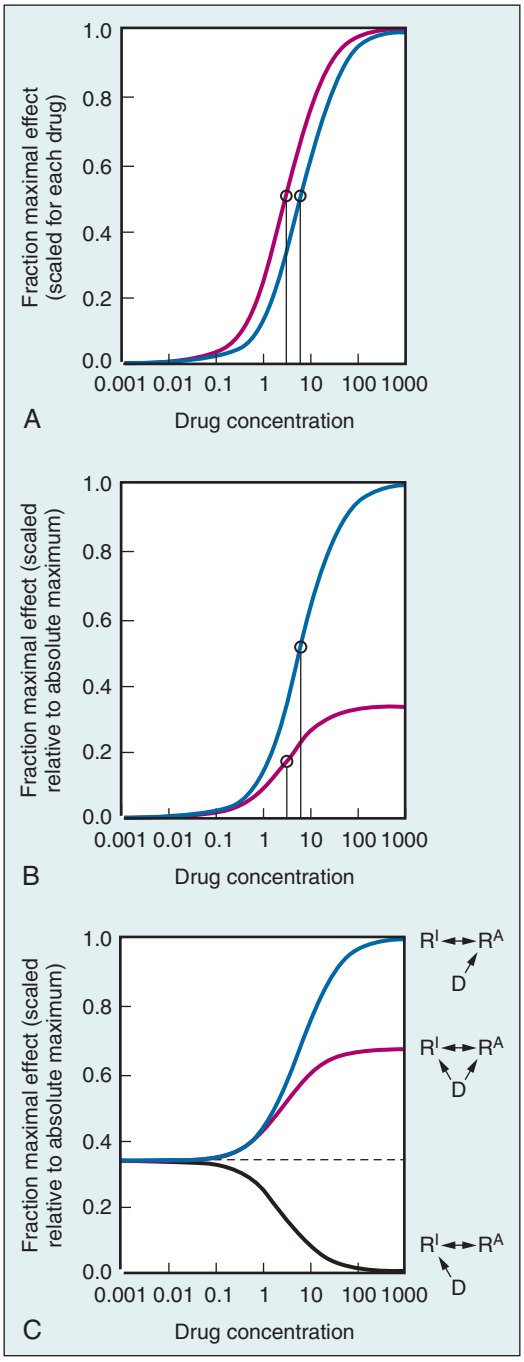
There is, however, a way to discover differences between agonists by characterizing their concentration-effect curves on a macroscopic level. Recall that the overall effect of a drug depends on two factors: affinity and efficacy. According to Eq. 10, efficacy determines the maximal effect attainable 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]

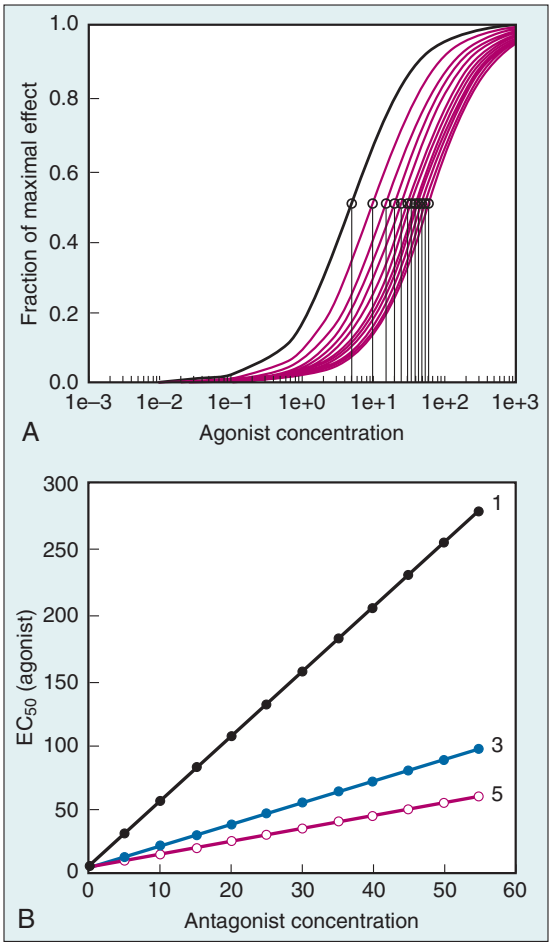
## Antagonism

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.

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.




• **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.

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]

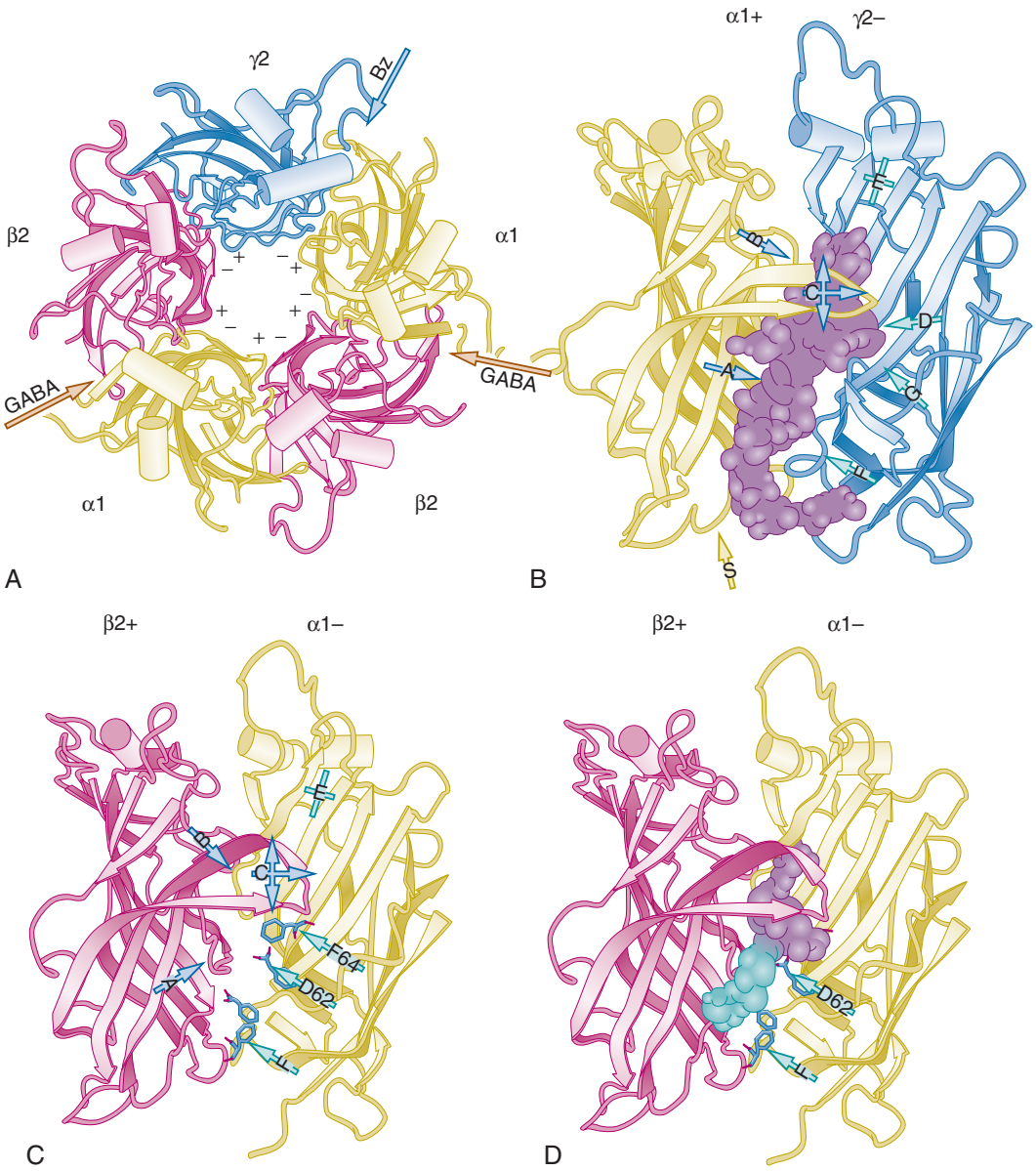
The binding site itself typically consists of a very small fraction of the total amino acid sequence of the protein. Yet binding of drug to the binding site induces a set of complex conformational changes in the overall receptor protein. For instance, binding of GABA to its binding site leads to opening 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.

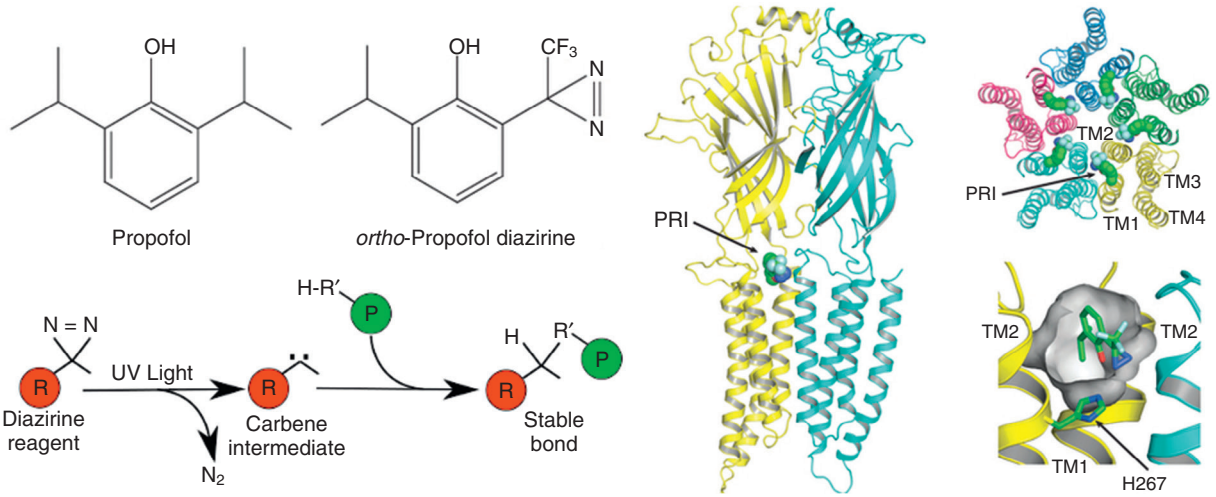



• **Fig. 1.8** Model of the extracellular domains of a pentameric $GABA_A$ receptor. The subtype illustrated consists of two α subunits, two β subunits, and one γ2 subunit. A, View from the extracellular space. GABA binds to the interface between the α and β subunits, benzodiazepines bind to the interface 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.)

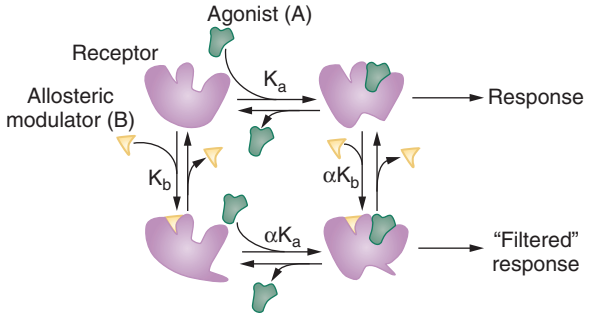
## Pharmacogenetics

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 $\rho$ 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

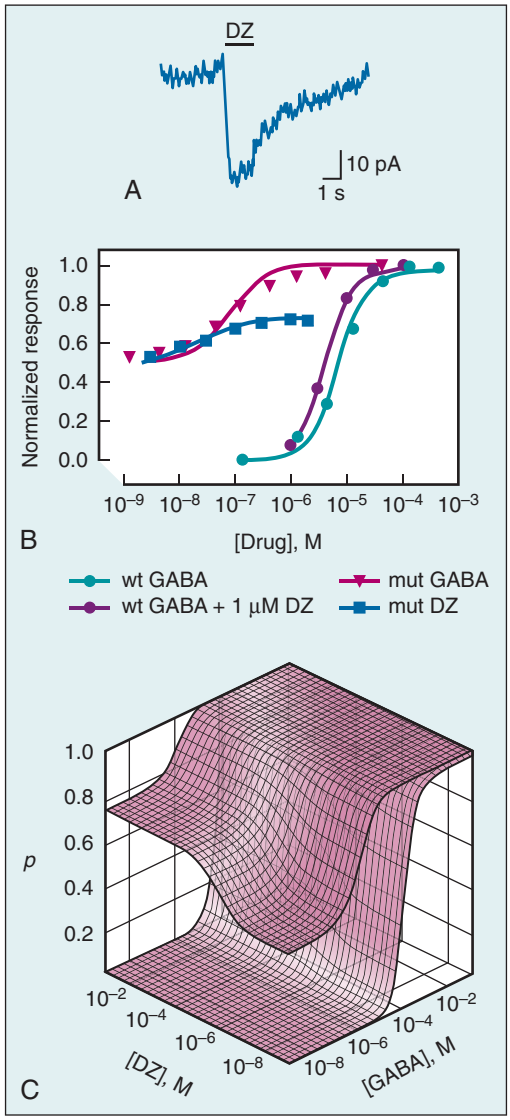
In the early to mid-20th century, many new drugs were synthesized as modifications of physiologically active plant and animal-derived compounds, yielding new drugs with desirable characteristics. The similarity between the structure of tyramine and epinephrine, for instance (Fig. 1.12), suggested the 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.)

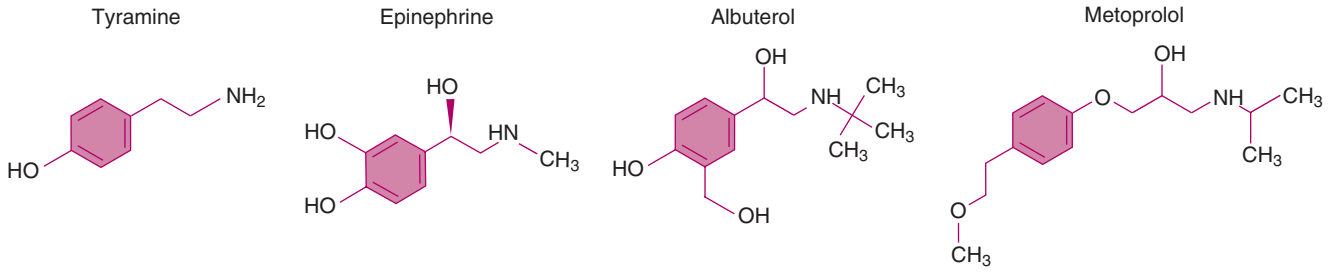
for drugs. In the 1980s, receptors were identified using high-affinity ligands, usually specific antagonists, that were used as bait in affinity chromatography to isolate the low-abundance receptor protein from detergent-solubilized tissue extracts.[37,38] Amino acid sequences of these purified receptors 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]

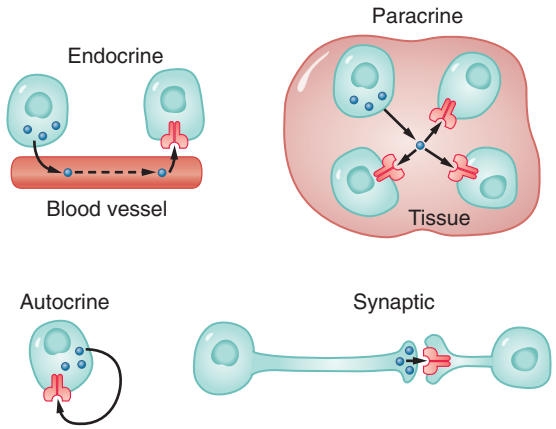
## Drug Targets

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.

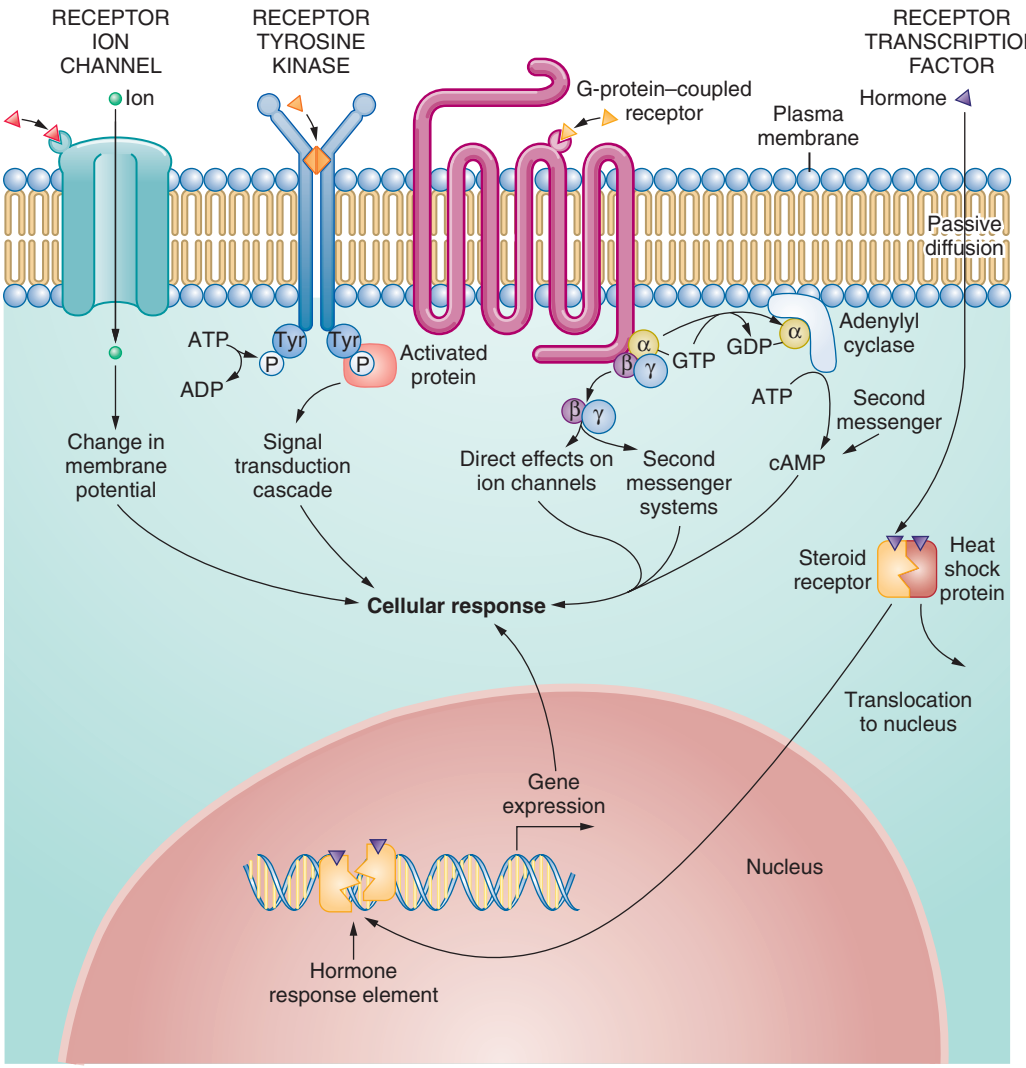
The most common types of drug target proteins involved in signal transduction are G protein-coupled receptors (GPCRs), ligand-gated ion channels (ionotropic receptors), which are major targets of general anesthetics, and voltage-gated ion channels, the major targets of local anesthetics and certain antihypertensive 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 |
|---|---|---|---|
| $G\alpha_s$ | $\beta_1$, $\beta_2$, $\beta_3$—adrenergic, $D_1$, $D_5$-dopamine | Adenylyl cyclase, $Ca^{2+}$ channels | Increased cAMP, increased $Ca^{2+}$ influx |
| $G\alpha_i$ | $\alpha_2$-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; $\alpha_1$-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

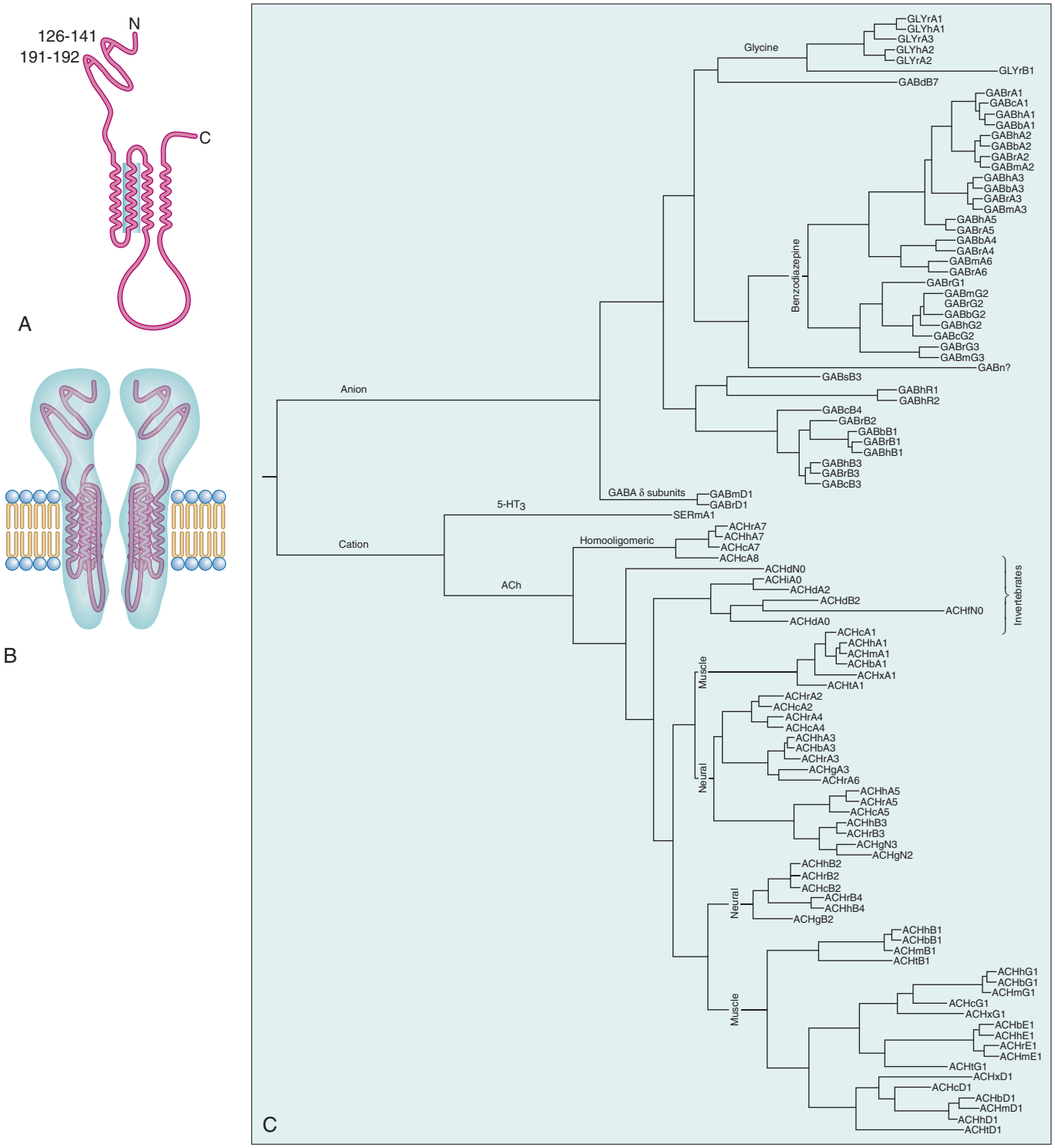
### *Pharmacophore Modeling*

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.

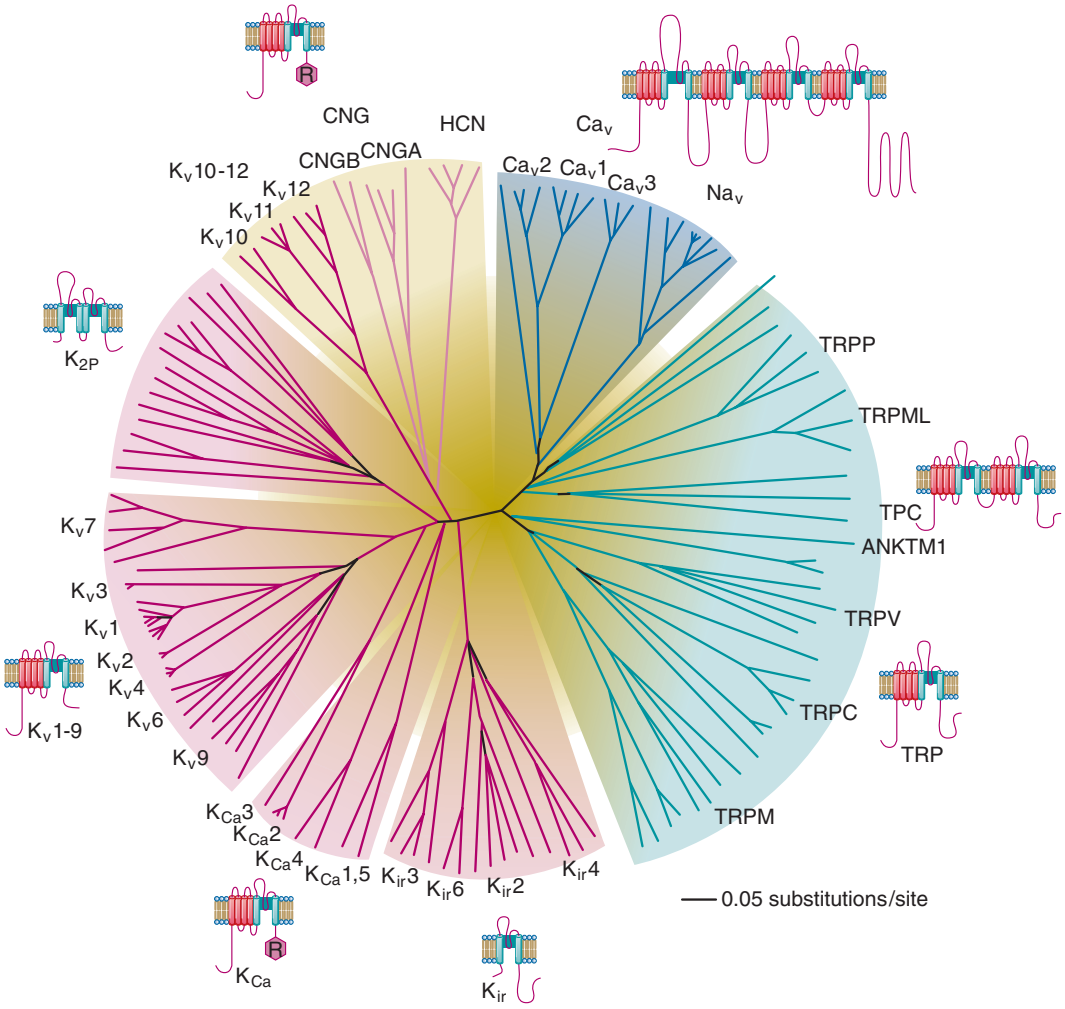
### *Phenotype-Based Drug Discovery*

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

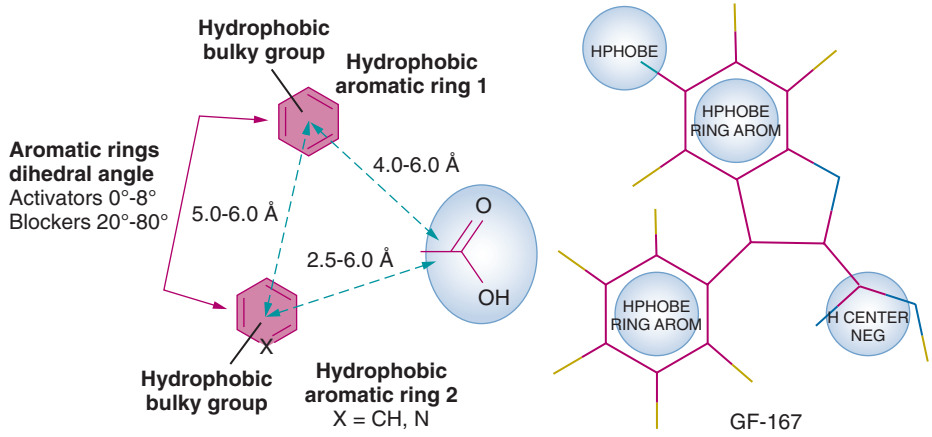



• **Fig. 1.15** Structure and evolutionary relationship of ligand-gated ion channels. A, Proposed structure of a single subunit of a pentameric ligand-gated ion channel. B, Structure of the whole pentamer viewed from the side (in plane). C, Evolutionary relationship between different members of the superfamily 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.

## Key References


Bean BP, Cohen CJ, Tsien RW. Lidocaine block of cardiac sodium channels. *J Gen Physiol*. 1983;81:613–642. Characterization of the effect of lidocaine on cardiac $Na^+$ channels, including use-dependent and use-independent blockade. Mechanisms responsible for antiarrhythmic properties of lidocaine are proposed. (Ref. 16).

Beneski DA, Catteral WA. Covalent labeling of protein components of the sodium channel with a photoactivable derivative of scorpion toxin. *Proc Natl Acad Sci USA*. 1980;77:639–643. Purification of the sodium channel by covalently labeling cells with a toxin. (Ref. 38).

Black JW, Duncan WA, Shanks RG. Comparison of some properties of pronethalol and propranolol. *Br J Pharmacol Chemother*. 1965;25:577–591. Synthesis of the first receptor-specific β-adrenergic antagonist—propranolol, the prototype β-blocker. (Ref. 36).

Cherezov V, Rosenbaum DM, Hanson MA, et al. High-resolution crystal structure of an engineered human beta2-adrenergic G protein-coupled receptor. *Science*. 2007;318:1258–1265. High-resolution crystal structure of human $\beta_2$-adrenergic receptor crystallized with a diffusible ligand. This study illustrates the properties of the ligand binding site in a G-protein–coupled receptor of major clinical and scientific significance. (Ref. 51).

Gaddum JH, Hameed KA, Hathway DE, et al. Quantitative studies of antagonists for 5-hydroxytryptamine. *Q J Exp Physiol Cogn Med Sci*. 1955;40:49–74. Derivation of the relationship between antagonist concentration and concentration-effect curve for the agonist. (Ref. 21).

Logothetis DE, Kurachi Y, Galper J, et al. The beta gamma subunits of GTP-binding proteins activate the muscarinic $K^+$ channel in heart. *Nature*. 1987;325:321–326. Direct experimental demonstration that the βγ-subunits of G proteins activate $K^+$ channels in the heart as a result of activation of the muscarinic acetylcholine receptor. (Ref. 55).

Stephenson RP. Modification of receptor theory. *Br J Pharmacol Chemother*. 1956;11:379–393. Landmark study where Stephenson modified Clark's receptor theory to account for different efficacies of drugs acting at the same receptor. (Ref. 10).


## References


1. Maehle AH. A binding question: the evolution of the receptor concept. *Endeavour*. 2009;33:135–140.
2. Maehle AH. *Drugs on Trial: Experimental Pharmacology and Therapeutic Innovation in the Eighteenth Century*. Amsterdam: Rodopi; 1999:223–309.
3. Bynum WF. Chemical structure and pharmacological action: a chapter in the history of 19th century molecular pharmacology. *Bull Hist Med*. 1970;44:518–538.
4. Parascandola J. The controversy over structure-activity relationships in the early twentieth century. *Pharm Hist*. 1974;16(2):54–63.
5. Kaufman RD. Biophysical mechanisms of anesthetic action: historical perspective and review of current concepts. *Anesthesiology*. 1977;46:49–62.
6. Silverstein AM. *Paul Ehrlich's Receptor Immunology: The Magnificent Obsession*. San Diego: Academic Press; 2002.
7. Langley JN. On the reaction of cells and of nerve endings to certain poisons, chiefly as regards the reaction of striated muscle to nicotine and to curari. *J Physiol (Lond)*. 1905;33:374–413.
8. Clark AJ. *The Mode of Action of Drugs on Cells*. London: Edward Arnold; 1933.
9. Ariens EJ, De Groot WM. Affinity and intrinsic-activity in the theory of competitive inhibition. III. Homologous decamethonium-derivatives and succinyl-choline-esters. *Arch Int Pharmacodyn Ther*. 1954;99:193–205.
10. Stephenson RP. Modification of receptor theory. *Br J Pharmacol Chemother*. 1956;11:379–393.
11. Ahlquist RP. A study of the adrenotropic receptors. *Am J Physiol*. 1948;153:586–600.
12. Hamill OP, Marty A, Neher E, et al. Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches. *Pflugers Arch*. 1981;391:85–100.
13. Neelands TR, Fisher JL, Bianchi M, et al. Spontaneous and gamma-aminobutyric acid (GABA)-activated GABA(A) receptor channels formed by epsilon subunit-containing isoforms. *Mol Pharmacol*. 1999;55:168–178.
14. Catterall WA. From ionic currents to molecular mechanisms: the structure and function of voltage-gated sodium channels. *Neuron*. 2000;26:13–25.
15. Tank DW, Huganir RL, Greengard P, et al. Patch-recorded single-channel currents of the purified and reconstituted Torpedo acetylcholine receptor. *Proc Natl Acad Sci USA*. 1983;80:5129–5133.
16. Bean BP, Cohen CJ, Tsien RW. Lidocaine block of cardiac sodium channels. *J Gen Physiol*. 1983;81:613–642.
17. Mortensen M, Kristiansen U, Ebert B, et al. Activation of single heteromeric GABA(A) receptor ion channels by full and partial agonists. *J Physiol*. 2004;557:389–413.
18. Chen PE, Wyllie DJ. Pharmacological insights obtained from structure-function studies of ionotropic glutamate receptors. *Br J Pharmacol*. 2006;147:839–853.
19. Swaminath G, Deupi X, Lee TW, et al. Probing the beta2 adrenoceptor binding site with catechol reveals differences in binding and activation by agonists and partial agonists. *J Biol Chem*. 2005;280:22165–22171.
20. Chidiac P, Hebert TE, Valiquette M, et al. Inverse agonist activity of beta-adrenergic antagonists. *Mol Pharmacol*. 1994;45:490–499.
21. Gaddum JH, Hameed KA, Hathway DE, et al. Quantitative studies of antagonists for 5-hydroxytryptamine. *Q J Exp Physiol Cogn Med Sci*. 1955;40:49–74.
22. Boileau AJ, Evers AR, Davis AF, et al. Mapping the agonist binding site of the GABAA receptor: evidence for a beta-strand. *J Neurosci*. 1999;19:4847–4854.
23. Pike AC, et al. Structure of the ligand-binding domain of oestrogen receptor beta in the presence of a partial agonist and a full antagonist. *EMBO J*. 1999;18:4608–4618.
24. Armstrong N, Sun Y, Chen GQ, et al. Structure of a glutamate-receptor ligand-binding core in complex with kainate. *Nature*. 1998;395:913–917.
25. Rosenbaum DM, Rasmussen SG, Kobilka BK. The structure and function of G-protein-coupled receptors. *Nature*. 2009;459:356–363.
26. Herzig MC, Leeb-Lundberg LM. The agonist binding site on the bovine bradykinin B2 receptor is adjacent to a sulfhydryl and is differentiated from the antagonist binding site by chemical cross-linking. *J Biol Chem*. 1995;270:20591–20598.
27. de Azevedo WF Jr, Dias R. Computational methods for calculation of ligand-binding affinity. *Curr Drug Targets*. 2008;9:1031–1039.
28. Li G-D, et al. Identification of a GABAA receptor anesthetic binding site at subunit interfaces by photolabeling with an etomidate analog. *J Neurosci*. 2006;26(45):11599–11605.
29. Yip GM, Chen ZW, Edge CJ, et al. A propofol binding site on mammalian GABAA receptors identified by photolabeling. *Nat Chem Biol*. 2013;9(11):715–720.
30. Xi J, Liu R, Asbury GR, et al. Inhalational anesthetic-binding proteins in rat neuronal membranes. *J Biol Chem*. 2004;279(19):19628–19633.
31. Kash TL, Jenkins A, Kelley JC, et al. Coupling of agonist binding to channel gating in the GABA(A) receptor. *Nature*. 2003;421:272–275.
32. Korpi ER, Grunder G, Luddens H. Drug interactions at GABA(A) receptors. *Prog Neurobiol*. 2002;67:113–159.
33. Ehlert FJ. Estimation of the affinities of allosteric ligands using radioligand binding and pharmacological null methods. *Mol Pharmacol*. 1988;33:187–194.
34. Soyka M, Preuss UW, Hesselbrock W, et al. GABA-A2 receptor subunit gene (GABRA2) polymorphisms and risk for alcohol dependence. *J Psychiatr Res*. 2008;42:184–191.

35. Arranz MJ, de Leon J. Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research. *Mol Psychiatry*. 2007;12:707–747.
36. Black JW, Duncan WA, Shanks RG. Comparison of some properties of pronethalol and propranolol. *Br J Pharmacol Chemother*. 1965;25:577–591.
37. Agnew WS, Moore AC, Levinson SR, et al. Identification of a large molecular weight peptide associated with a tetrodotoxin binding protein from the electroplax of Electrophorus electricus. *Biochem Biophys Res Commun*. 1980;92:860–866.
38. Beneski DA, Catterall WA. Covalent labeling of protein components of the sodium channel with a photoactivable derivative of scorpion toxin. *Proc Natl Acad Sci USA*. 1980;77:639–643.
39. Sundberg SA. High-throughput and ultra-high-throughput screening: solution- and cell-based approaches. *Curr Opin Biotechnol*. 2000;11:47–53.
40. Garthwaite J, Charles SL, Chess-Williams R. Endothelium-derived relaxing factor release on activation of NMDA receptors suggests role as intercellular messenger in the brain. *Nature*. 1988;336: 385–388.
41. Garthwaite J, Boulton CL. Nitric oxide signaling in the central nervous system. *Annu Rev Physiol*. 1995;57:683–706.
42. Ryter SW, Otterbein LE, Morse D, et al. Heme oxygenase/carbon monoxide signaling pathways: regulation and functional significance. *Mol Cell Biochem*. 2002;234–235, 249-263.
43. Kaplan DR, Miller FD. Neurotrophin signal transduction in the nervous system. *Curr Opin Neurobiol*. 2000;10:381–391.
44. Ferrell JE Jr. Self-perpetuating states in signal transduction: positive feedback, double-negative feedback and bistability. *Curr Opin Cell Biol*. 2002;14:140–148.
45. Xiong W, Ferrell JE Jr. A positive-feedback-based bistable 'memory module' that governs a cell fate decision. *Nature*. 2003;426:460–465.
46. Kohout TA, Lefkowitz RJ. Regulation of G protein-coupled receptor kinases and arrestins during receptor desensitization. *Mol Pharmacol*. 2003;63:9–18.
47. Whitmarsh AJ, Davis RJ. Structural organization of MAP-kinase signaling modules by scaffold proteins in yeast and mammals. *Trends Biochem Sci*. 1998;23:481–485.
48. Wise A, Gearing K, Rees S. Target validation of G-protein coupled receptors. *Drug Discov Today*. 2002;7:235–246.
49. Alkire MT, Hudetz AG, Tononi G. Consciousness and anesthesia. *Science*. 2008;322:876–880.
50. Braunwald E. Mechanism of action of calcium-channel-blocking agents. *N Engl J Med*. 1982;307:1618–1627.
51. Cherezov V, Rosenbaum DM, Hanson MA, et al. High-resolution crystal structure of an engineered human beta2-adrenergic G protein-coupled receptor. *Science*. 2007;318:1258–1265.
52. Warne T, Serrano-Vega MJ, Baker JG, et al. Structure of a beta1-adrenergic G-protein-coupled receptor. *Nature*. 2008;454:486–491.
53. Palczewski K, Kumasaka T, Hori T, et al. Crystal structure of rhodopsin: A G protein-coupled receptor. *Science*. 2000;289:739–745.
54. Kobilka B, Schertler GF. New G-protein-coupled receptor crystal structures: insights and limitations. *Trends Pharmacol Sci*. 2008;29:79–83.
55. Logothetis DE, Kurachi Y, Galper J, et al. The beta gamma subunits of GTP-binding proteins activate the muscarinic K+ channel in heart. *Nature*. 1987;325:321–326.
56. Menniti FS, Faraci WS, Schmidt CJ. Phosphodiesterases in the CNS: targets for drug development. *Nat Rev Drug Discov*. 2006;5:660–670.
57. Pierce KL, Lefkowitz RJ. Classical and new roles of β-arrestins in the regulation of G-protein-coupled receptors. *Nat Rev Neurosci*. 2001;2(10):727–733.
58. Hille B. *Ionic Channels of Excitable Membranes*. 2nd ed. Sunderland, Mass: Sinauer Associates Inc.; 1992.
59. Avruch J. Insulin signal transduction through protein kinase cascades. *Mol Cell Biochem*. 1998;182:31–48.
60. Hubbard SR, Till JH. Protein tyrosine kinase structure and function. *Annu Rev Biochem*. 2000;69:373–398.
61. Tonks NK, Neel BG. From form to function: signaling by protein tyrosine phosphatases. *Cell*. 1996;87:365–368.
62. Wermuth G, Ganellin CR, Lindberg P, et al. Glossary of terms used in medicinal chemistry (IUPAC Recommendations 1998). *Pure Appl Chem*. 1998;70:1129–1143.
63. Clader JW. The discovery of ezetimibe: a view from outside the receptor. *J Med Chem*. 2004;47:1–9.
64. Haerter F, Eikermann M. Reversing neuromuscular blockade: inhibitors of the acetylcholinesterase versus the encapsulating agents sugammadex and calabadion. *Expert Opin Pharmacother*. 2016;17(6):819–833.
65. Heerdt PM, Sunaga H, Savarese JJ. Novel neuromuscular blocking drugs and antagonists. *Curr Opin Anaesthesiol*. 2015;28(4):403–410.
66. Samuelson BT, Cuker A. Measurement and reversal of the direct oral anticoagulants. *Blood Rev*. 2017;31(1):77–84.

# 2

# Pharmacokinetic and Pharmacodynamic Principles for Intravenous Anesthetics

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## CHAPTER OUTLINE



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

## 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 |

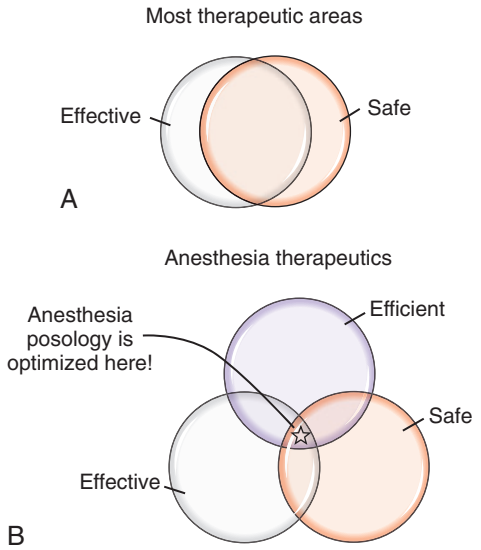
Another important difference between anesthesiology and other therapeutic areas relates to efficiency. Most settings in clinical medicine do not require immediate onset and rapid offset of pharmacologic effect. When an internist prescribes an antihypertensive, for example, the fact that a few days may 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).

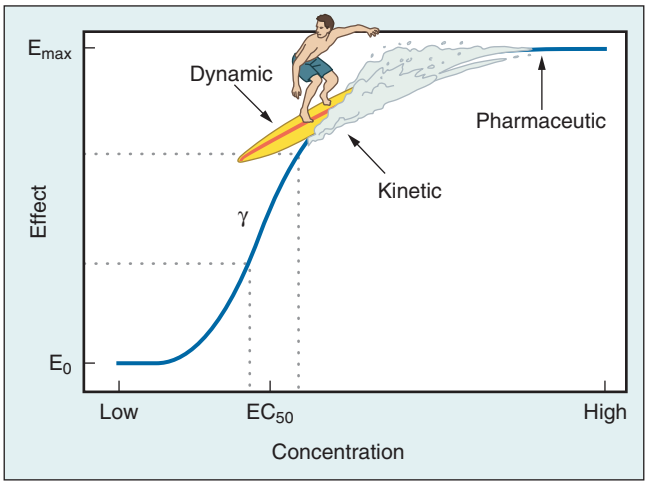
In summary, the profound physiologic alterations of the anesthetized state (and their reversal) must be produced on demand to ensure the rapid achievement and maintenance of the anesthetic state intraoperatively with return of responsiveness, spontaneous ventilation, and other vital functions at the 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; $\gamma$, 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).

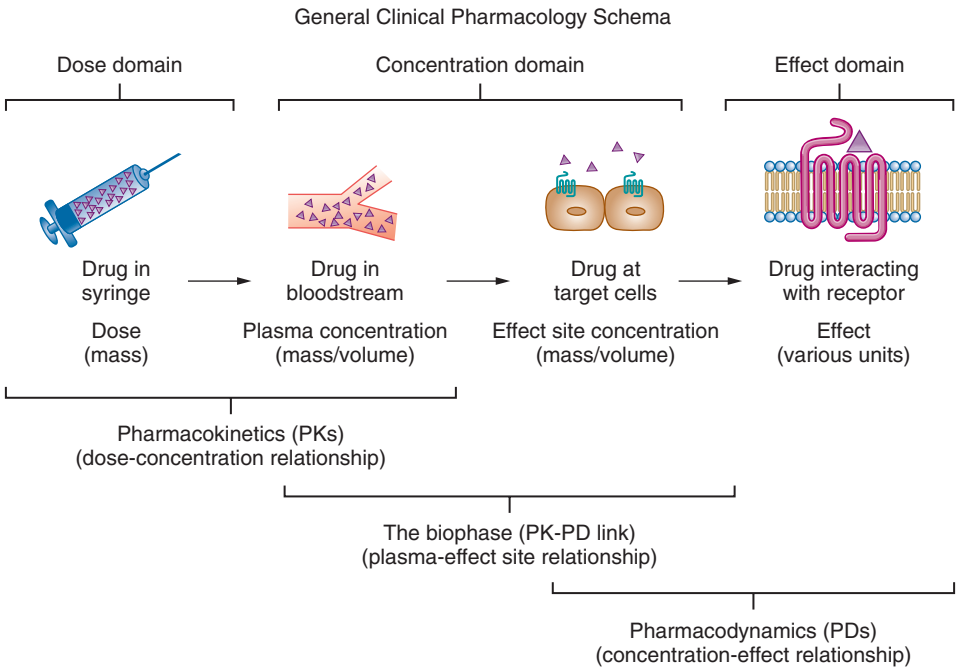
**TABLE 2.2 Selected Clinically Important Questions in the Posology of Anesthesia**

- 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.

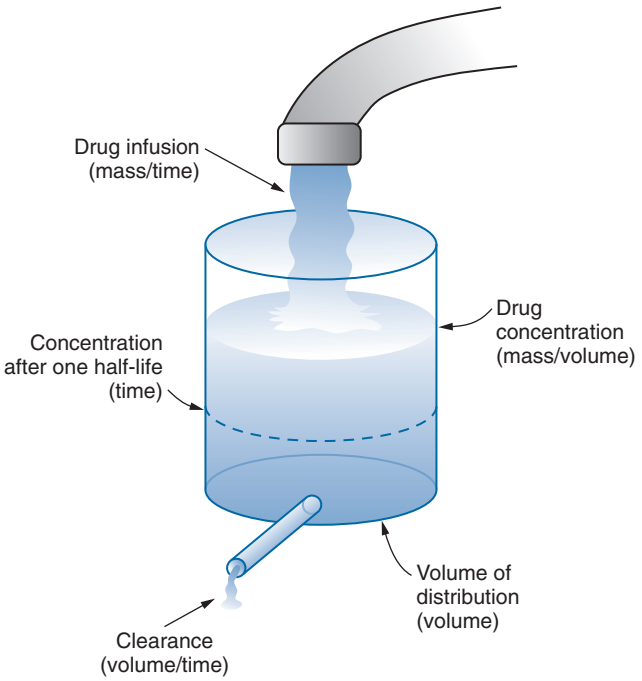
Consider the fate of drug molecules as summarized in Fig. 2.3. The anesthesiologist administers the desired dose intravenously using a handheld syringe or pump (the dose domain). The drug is then distributed via the circulation to body tissues and eventually eliminated through biotransformation and/or 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.

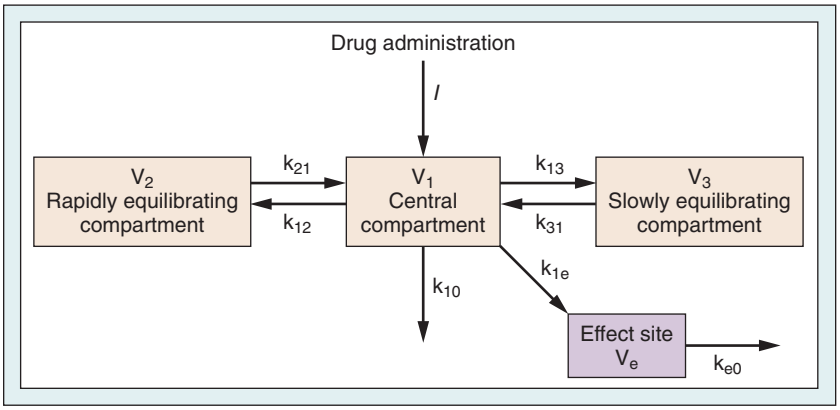



• **Fig. 2.4** A hydraulic representation of a one-compartment pharmacokinetic (PK) model simply illustrating various PK parameters. Water running from the faucet into the container represents an infusion of drug. The size of the container represents the volume into which the drug will distribute (i.e., 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

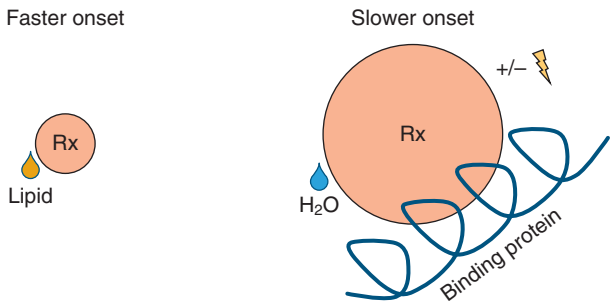
The biophase concept is a nuance of clinical pharmacology that is perhaps not as widely covered in pharmacology courses because its clinical application is most relevant to just a few acute care disciplines like anesthesiology. "Pharmacobiophasics," a neologism not in common usage (coined by author TDE), 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

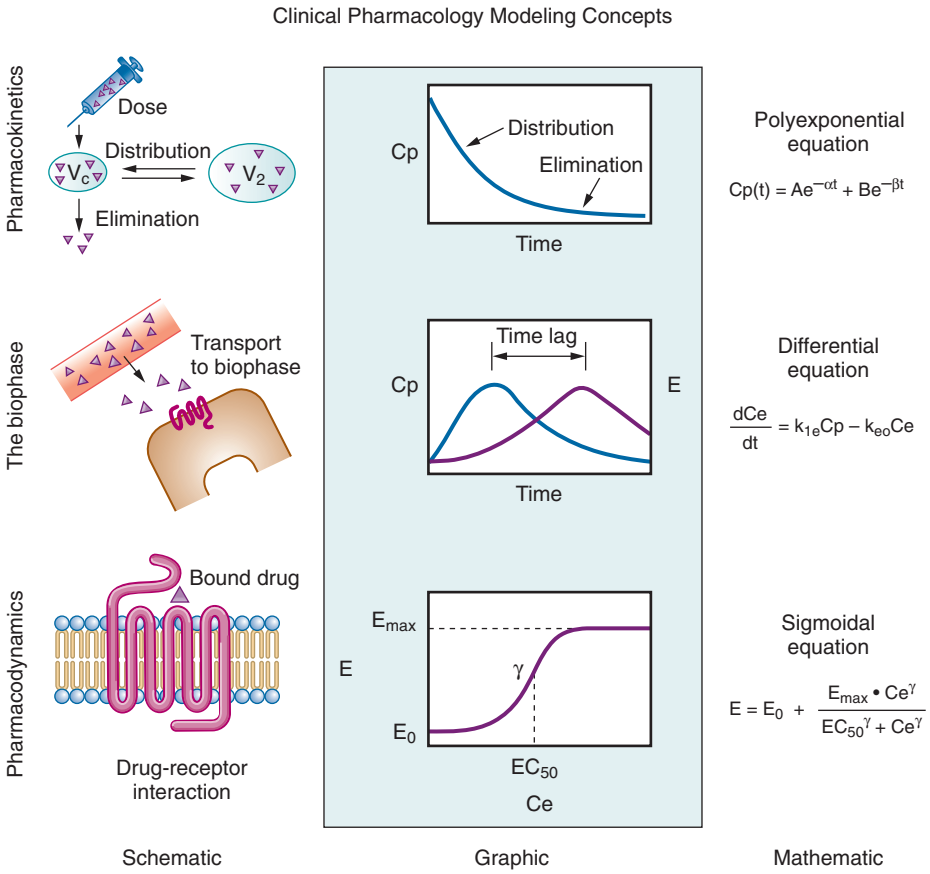
A summary of the PK-PD model building process is outlined in Fig. 2.7. The process, of course, begins with the gathering of the raw data in appropriately designed experiments.[34,35] Elements of a well-designed PK-PD modeling experiment for an intravenous anesthetic include careful attention to the administered 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.

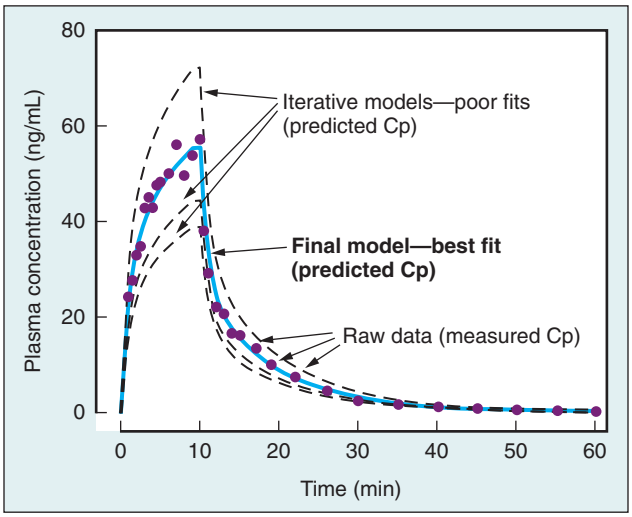
Schematically, basic PK processes are well represented by a compartmental model (see upper panel of Fig. 2.7). After injection into the central compartment, a drug is either distributed to other compartments or is eliminated from the central compartment altogether. Graphing these PK processes reveals 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



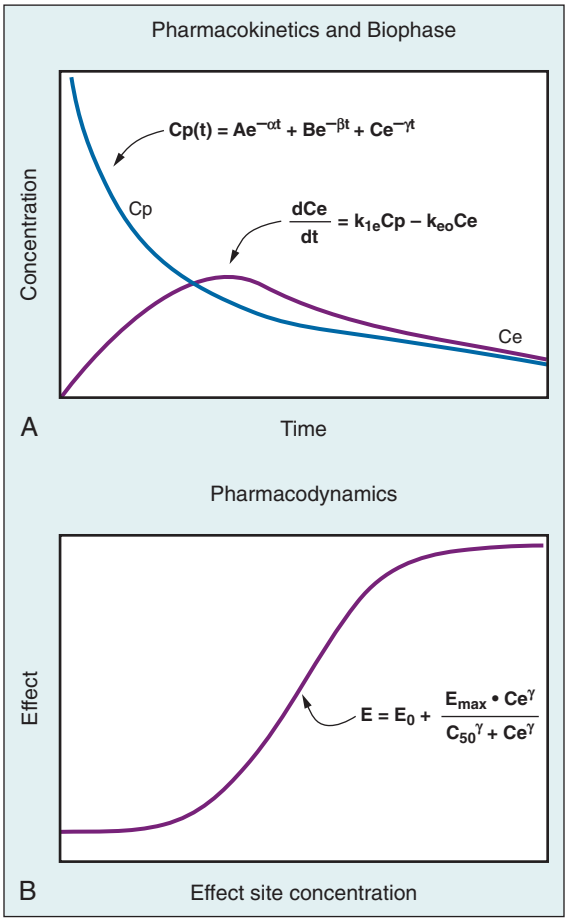

• **Fig. 2.7** A summary of clinical pharmacology modeling concepts for the disciplines of pharmacokinetics, the biophase, and pharmacodynamics. The modeling foundation for each area is presented schematically, graphically, and mathematically. The purple triangles represent a drug. See the accompanying 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; $\gamma$, 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*

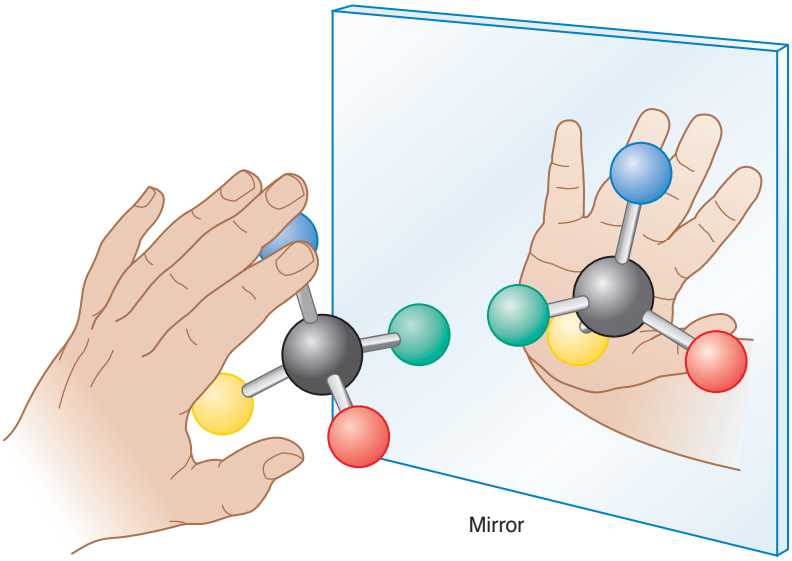
A major shortcoming of the standard compartmental PK model is a function of model misspecification during the early period after drug injection.[47] Standard compartmental models assume the central volume is well stirred and that peak plasma concentration occurs immediately after injection, an assumption 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 ($\gamma$) | **Concentration Domain Issue** |
| | Concentration necessary to achieve specified effect? |

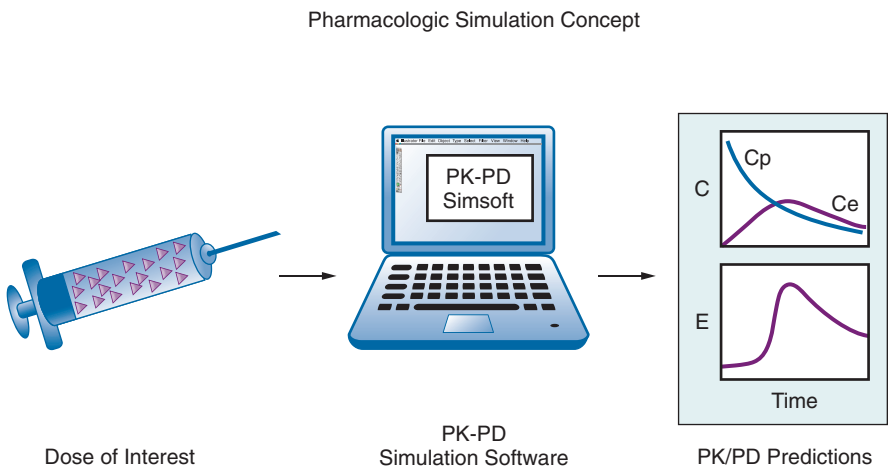
*$E_0$*, Effect at zero drug concentration; *$EC_{50}$*, concentration that produces 50% of maximal drug effect; *$E_{max}$*, maximal drug effect; *gamma ($\gamma$)*, steepness of the curve; *$k_{e0}$*, rate constant for drug elimination out of the effect compartment.
[a]Single PK-PD parameters considered in isolation are not clinically useful; predictions from model simulations are very useful (see text for complete explanation).

## Importance of PK-PD Model Simulation

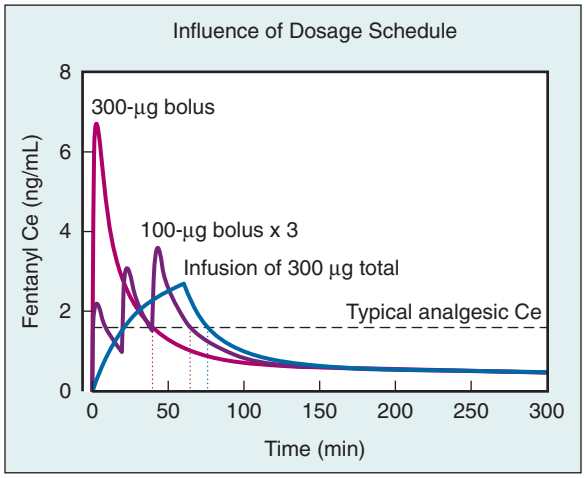
Understanding the clinical implications of a table of PK-PD parameters is best accomplished through in silico application of the associated model by computer simulation.[73] Through simulation, the practically oriented clinical questions shown on the right column of Table 2.3 (among many other questions) 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]

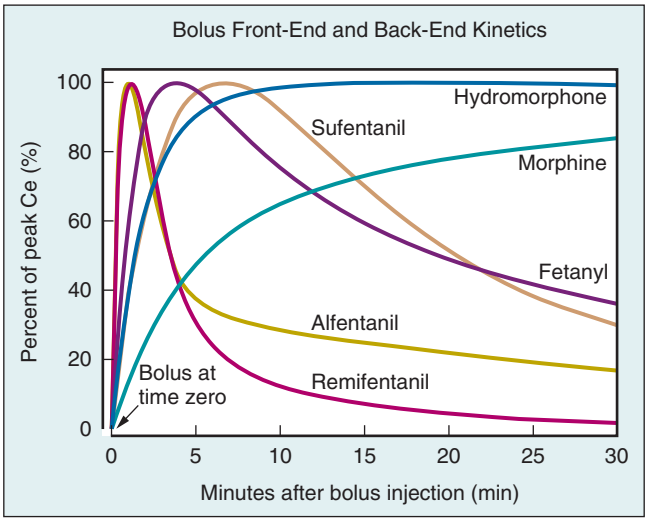
The simulation in Fig. 2.12 illustrates the power of PK-PD simulation in terms of intuitively understanding the implications of various dosing schemes. The simulation depicts the very different time courses of drug concentration in the biophase when identical total doses of fentanyl (i.e., 300 µg) are 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

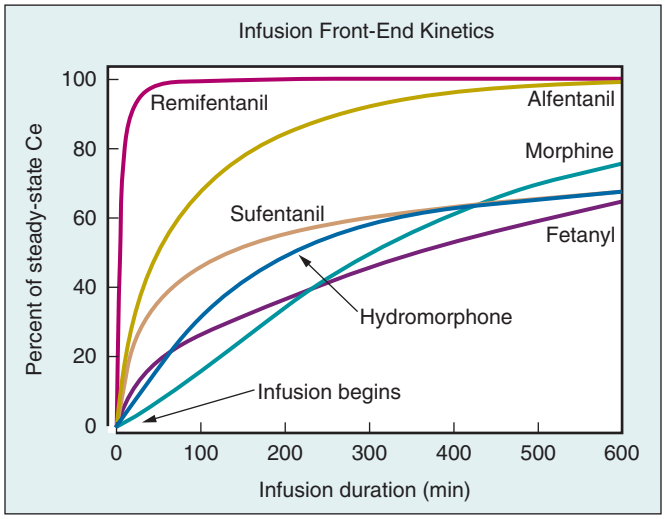
As noted in Table 2.2, important posologic questions regarding bolus injections include "How long will it take to reach peak effect and how long will it take for the effect to dissipate?" The simulations plotted in Fig. 2.13 explore these questions for a number of commonly used opioids. After bolus injection, 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.

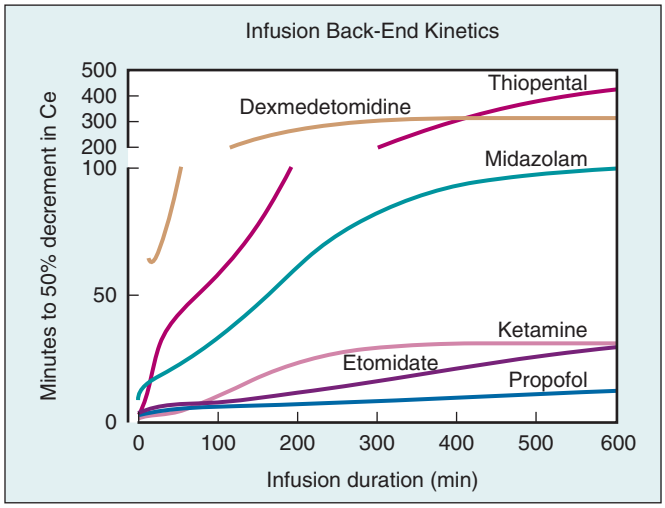
### Infusion Front-End Kinetics

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.

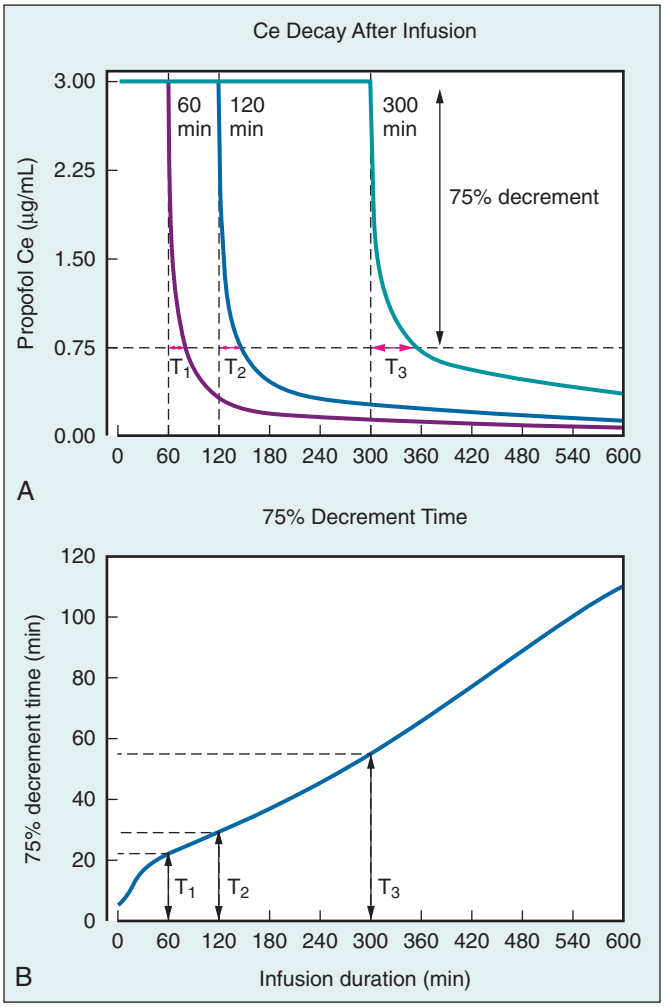
The simulations in Fig. 2.15 predict the time necessary to achieve a 50% decrease in drug concentration after termination of a variable length continuous infusion to a steady-state drug level. Using concepts originally developed for opioids,[7] these simulations are an attempt to provide *context-sensitive 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

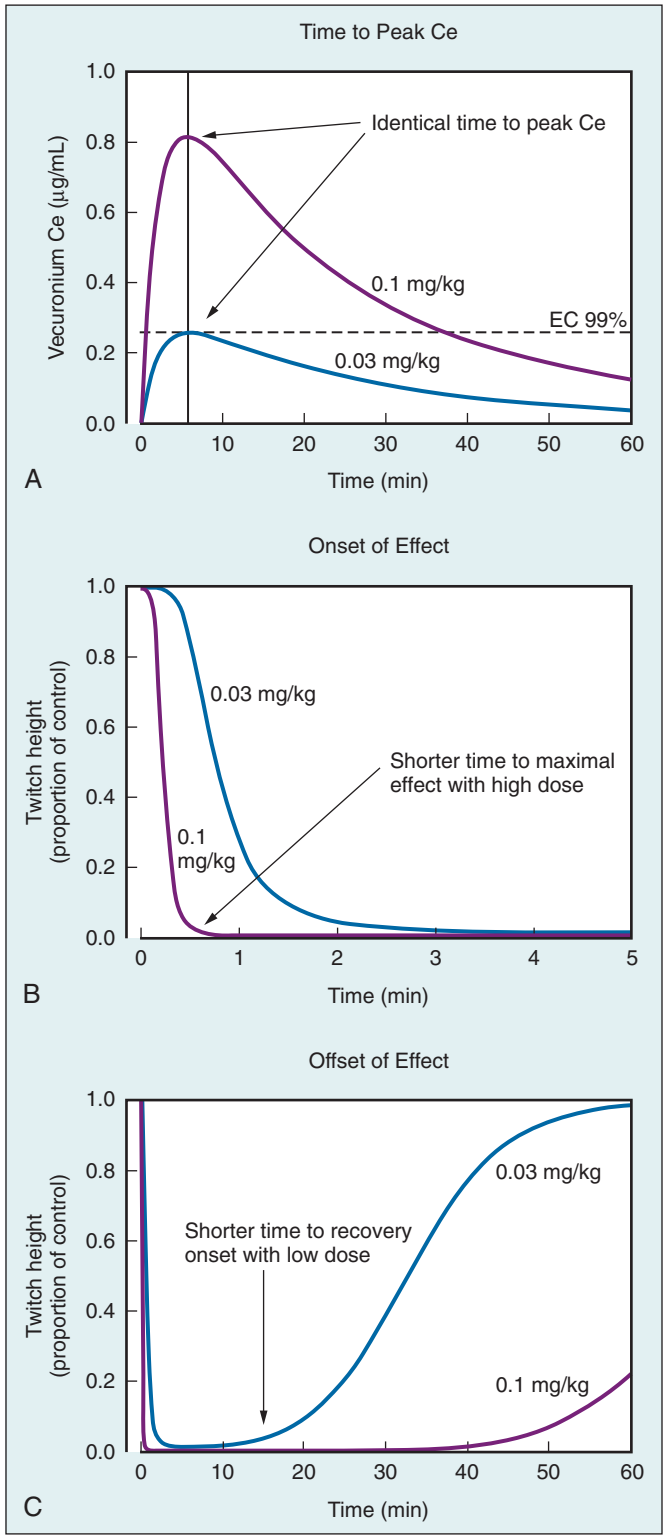
The simulations presented graphically in Fig. 2.17 summarize the influence of dose on the onset and offset of drug effect using the




• **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

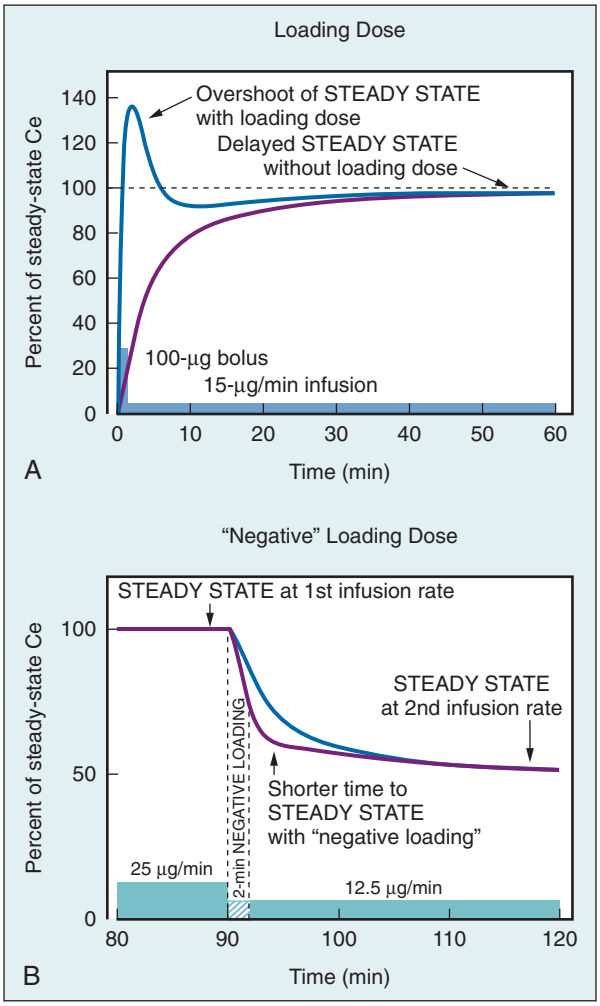
The simulations presented graphically in Fig. 2.18 illustrate the concept of "loading" doses. A bolus injection loading dose before starting an infusion shortens the time to achievement of concentrations nearer the ultimate steady state. Similarly, while the term is not firmly established, a "negative" 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,

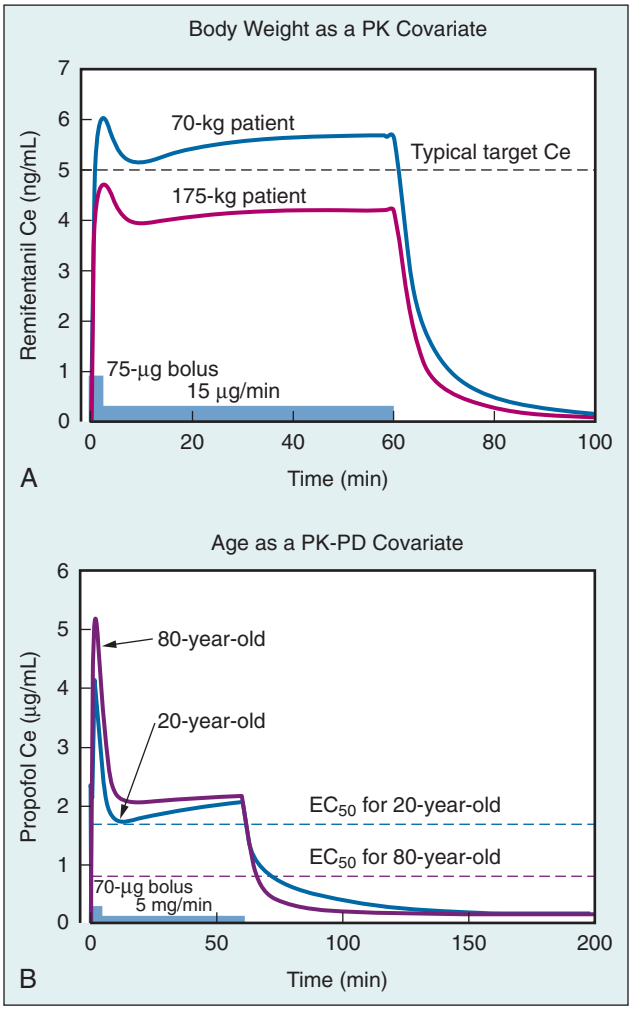



• **Fig. 2.18** A pair of simulations exploring the influence of loading doses on the time to reach steady-state effect site concentrations using remifentanil infusions as an example. The standard loading dose concept, in which a bolus injection is given before starting a continuous infusion, is illustrated 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