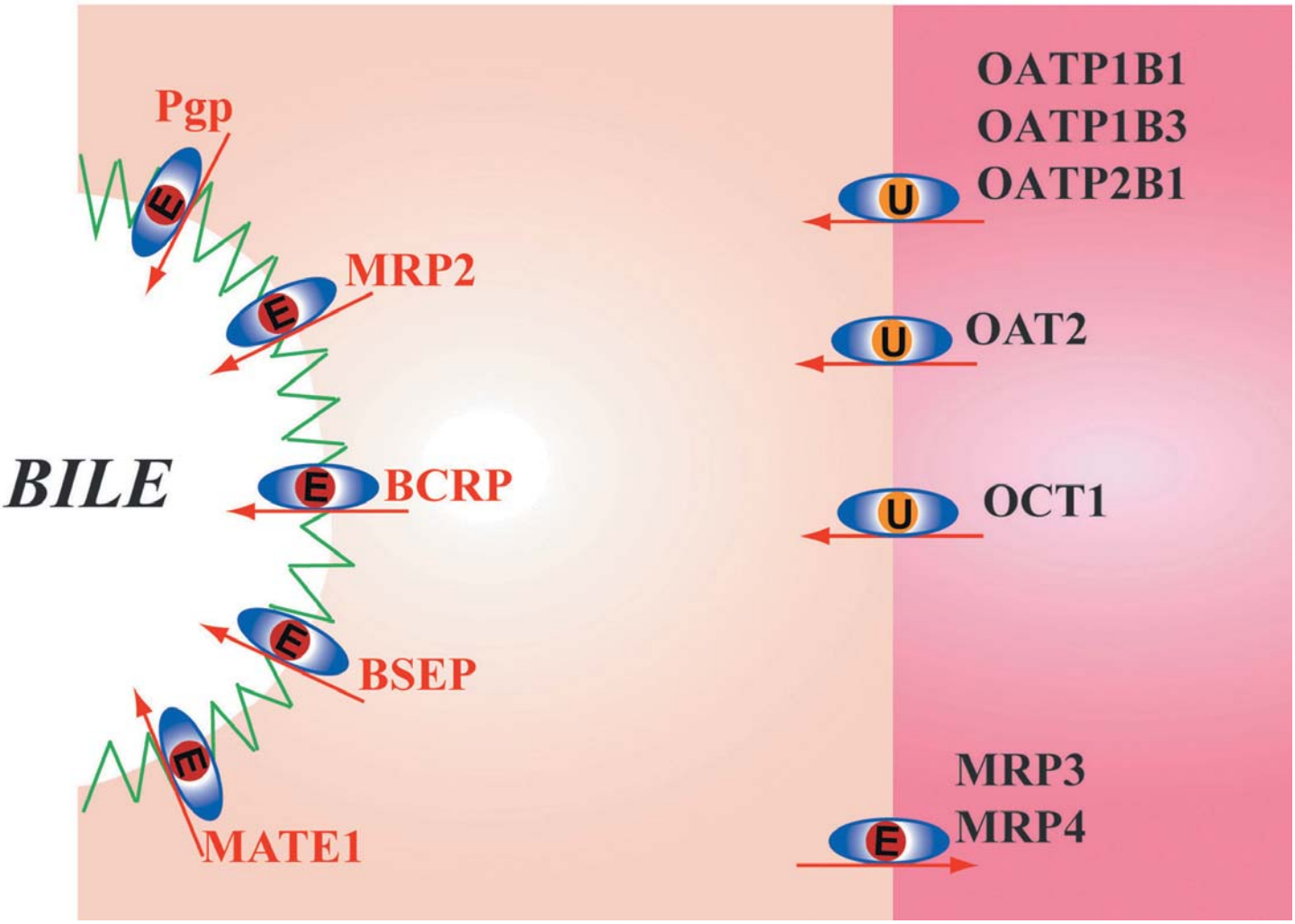
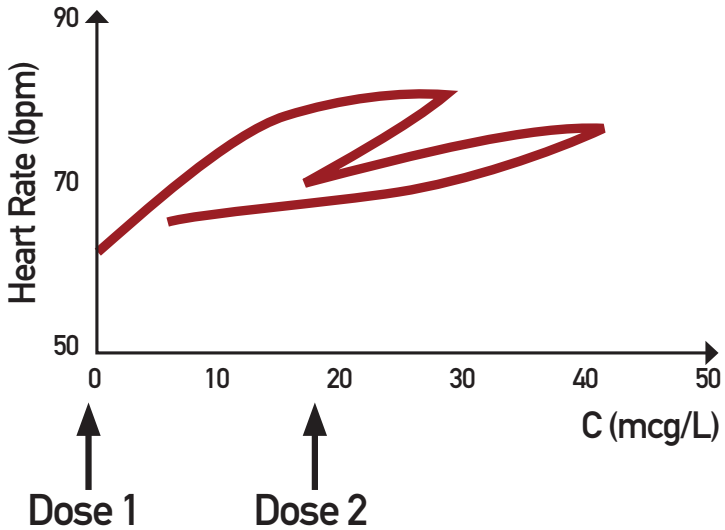
# BASIC PHARMACOKINETICS AND PHARMACODYNAMICS




## AN INTEGRATED TEXTBOOK AND COMPUTER SIMULATIONS




EDITED BY
SARA E. ROSENBAUM

SECOND EDITION

with website

WILEY

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## An Integrated Textbook and Computer Simulations

Second Edition

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**SARA E. ROSENBAUM**

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*To Steve, Molly and Lucy*

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# PREFACE

The goal of the second edition of Basic Pharmacokinetics and Pharmacodynamics is to update and strengthen existing chapters of the book and to add additional chapters in response to recent trends in the application of pharmacokinetics and pharmacodynamics in clinical practice and pharmaceutical research.

Notable areas of update and expansion include both the text and the interactive computer models associated with drug transporters and hepatic clearance. Additionally, the chapters on drug absorption/bioavailability and pharmacodynamics have been updated, expanded and strengthened to reflect the importance of these topics and the need to cover the material both comprehensively and in a manner compatible with their present application. I felt that these areas would be most effectively strengthened by experts in each of the fields. To this end, I am delighted that Dr. Steven Sutton, who has had extensive experience as a researcher in the pharmaceutical industry and as an educator at the College of Pharmacy, University of New England, agreed to take over Chapters 3 and 9 that cover drug absorption and bioavailability. I am also delighted that Drs. Diane Mould and Paul Hutson agreed to revamp and expand the chapters on pharmacodynamics (Chapters 19 and 20). Dr. Mould of Projections Research Inc is a well-known pharmacokinetic and pharmacodynamic modeler, who has extensive experience in the application of pharmacodynamic models. Dr. Hutson from University of Wisconsin, School of Pharmacy, is similarly experienced and was able to provide an academic perspective to the overhaul of this material.

Owing to the increasing prominence of personalized and precision medicine, it has become important that clinical pharmacists and researchers in pharmaceutical fields have a basic knowledge of pharmacogenomics. Dr. Daniel Brazeau, an experienced educator and researcher in this area from the College of Pharmacy, University of New England, graciously agreed to write an introductory chapter on pharmacogenetics for the second edition. In response to the increasing use and diverse application of physiologically based pharmacokinetic (PBPK) modeling that has occurred over the last 15 years, it has become essential for modern students of pharmacokinetics to have a foundation in this topic. Chapter 18 introduces PBPK models and describes how they are built and applied. The third new chapter in the second edition presents the predictive models used to evaluate drug–drug

interaction (DDI) risk using *in vitro* data. These models are used increasingly by pharmaceutical companies and drug regulators to try to reduce the large health risks and costs posed by DDIs. While not all readers of the book will need to apply these models professionally, an understanding of this topic will allow students to better understand and appreciate the mechanism, characteristics, and varied outcome of DDIs. Finally, in order to provide interested students with a foundation to this latter chapter, the second edition includes an appendix on basic enzyme kinetics and the mathematical basis of the predictive models. My colleague at the College of Pharmacy, Dr. Roberta King, an expert in drug metabolism, collaborated in the preparation of this material. Each of the new chapters is supported by new interactive computer models.

It is hoped that the second edition of this textbook provides a comprehensive and thorough presentation of all essential topics in the contemporary application of pharmacokinetics and pharmacodynamics. While not all chapters will be necessary for the immediate needs of all audiences, collectively the book should serve as a valuable reference for the future.

I would like to thank the many scientists who generously gave of their time and provided me with information and input in many areas. I would especially like to thank Dr. Karthik Venkatakrishnan for his valuable input on the chapter on predictive models for DDIs. I would also like to thank and recognize the wonderful work of Pragati Nahar who prepared the custom color figures in the book, including the figure used on the cover. I would also like to thank many undergraduate and graduate students at URI who helped in a variety of ways especially Jamie Chung who provided valuable support for the preparation of the materials, and Benjamin Barlock and Rohitash Jamwal for their input in the creation of the simulation models. Finally, I would like to thank Jonathan Rose at Wiley for his patience, understanding, and responsiveness in the preparation of this edition.

# CONTRIBUTORS

**Daniel Brazeau** Daniel Brazeau is a Research Associate Professor at the University of New England. He holds joint appointments in the Department of Pharmaceutical Sciences in the College of Pharmacy and Department of Biomedical Sciences in the College of Osteopathic Medicine. Dr. Brazeau is a Director of UNE's Genomics Core, a research training core providing the expertise, technologies and most importantly, training support for faculty and students. He received his B.S. and M.S. in Biology from the University of Toledo and earned his Ph.D. in Biological Sciences (1989) from the University at Buffalo. After completing postdoctoral training in population genetics at the University of Houston, he was a Research Assistant Professor in the Department of Zoology at the University of Florida and Director of the University of Florida's Genetic Analysis Laboratory in the Interdisciplinary Research Center for Biotechnology. For 10 years prior to joining UNE, he was a Research Associate Professor in the Department of Pharmaceutical Sciences at the University at Buffalo and Director of the University at Buffalo's Pharmaceutical Genetics Laboratory. Dr. Brazeau's research interests involve the areas of population molecular genetics and genomics. He teaches courses in molecular genetics methodologies and a required course in pharmacogenomics for graduate and pharmacy professional students. Dr. Brazeau is also a participating scientist in the National Science Foundation's Geneticist-Educator Network Alliances (GENA) working with high school science teachers to incorporate genetics into the classroom.

**Paul Hutson** Paul Hutson, whose baccalaureate and master's degrees are in biochemistry and chemistry, respectively, completed an oncology/pharmacokinetics fellowship at St. Jude Children's Research Hospital in Memphis. He was a Faculty Member at the University of Illinois for 5 years before moving to the University of Wisconsin School of Pharmacy in Madison in 1988. He now practices pharmacy with the oncology and palliative care group at the UW Hospital and Clinics and is an Associate Member of the UW Carbone Cancer Center. His three course offerings at the School of Pharmacy are Clinical Pharmacokinetics, Pediatric Pharmacotherapy, and Dietary Supplements, and he supervises an Advanced Pharmacy Practice Experience (APPE) in basic pharmacometrics. Dr. Hutson

provides pharmacometric modeling services to the pharmaceutical industry and to University of Wisconsin—Madison investigators through its CTSA-funded Institute for Clinical and Translational Research.

**Roberta S. King** Roberta S. King is an Associate Professor at the University of Rhode Island, College of Pharmacy. Her research expertise is in metabolism and enzymology focusing on individual variation in activity of the drug-metabolizing enzymes. She teaches Drug Metabolism and Structure-based Drug Design.

**Dr. Mould** Dr. Mould obtained her bachelors degree at Stevens Institute of Technology in 1984 in Chemistry and Chemical Biology. She received her Ph.D. in Pharmaceutics and Pharmaceutical Chemistry at The Ohio State University (OSU) in 1989. She spent 26 years as a pharmacokineticist in industry where she specialized in population pharmacokinetic/pharmacodynamic modeling and was an Associate Research Professor at Georgetown University. She has conducted population PK/PD analyses of hematopoietic agents, monoclonal antibodies, anticancer and antiviral agents, antipsychotic, cardiovascular, and sedative/hypnotic agents. Dr Mould is involved in clinical trial simulation and optimal study design in drug development. She was a member of the Scientific Advisory Group for PharSight, where she assisted in development of clinical trial simulation software.

Currently, Dr Mould is President of Projections Research Inc., a consulting company offering pharmacokinetic and pharmacometric services. She is also the founder of iDose LLC, a company that develops systems to individualize doses of drugs that are difficult to manage. She has published 62 peer-reviewed articles, 16 book chapters, made 97 national and international presentations, and presented six podium sessions on advanced modeling and simulation approaches. Dr Mould has authored 97 posters at both national and international meetings. She is an Adjunct Professor at the University of Rhode Island (URI), OSU, and the University of Florida, and teaches an annual class on disease progression modeling at the National Institutes of Health. Dr Mould taught nine courses (OSU, URI, and SUNY Buffalo) on specialized aspects of population pharmacokinetic and dynamic modeling. She is a member of the editorial board for Journal of Pharmacokinetics and Pharmacodynamics, Clinical Pharmacology and Therapeutics, and Clinical Pharmacology and Therapeutics Pharmacometrics and Systems Pharmacology. Dr. Mould is a member of the Board of Regents for the American College of Clinical Pharmacology and is a Chairman of the Publications committee for this organization. She is a Fellow of the American College of Clinical Pharmacology and the American Association of Pharmaceutical Sciences.

**Steven C. Sutton** Steven (Steev) C. Sutton, B.S. Pharmacy, Ph.D., University of New England, Portland, Maine Dr. Sutton is an Associate Professor and Chair of Pharmaceutics, College of Pharmacy, University of New England in Portland, Maine. He received his B.S. in Pharmacy from Massachusetts College of Pharmacy and a Ph.D. in Pharmaceutical Sciences from the State University of New York at Buffalo, New York. Dr Sutton began his career in the pharmaceutical industry working for CIBA-Geigy in Ardsley, NY (now Novartis), for INTERx in Lawrence, KS (then a part of Merck), and for Pfizer in Groton, CT, before embarking in a second career—that of academia—at the University of New England College of Pharmacy in Portland in 2009. Dr. Sutton founded the AAPS Oral Absorption Focus Group and in 2003, he became a Fellow of the AAPS. His research interests include predicting active pharmaceutical ingredient concentration–time profile in human after oral administration from chemical structure, modeling, and simulation of oral absorption of low permeability and/or low aqueous soluble compounds, *in vitro—in vivo* correlation of orally

administered controlled release dosage forms, species differences in gastrointestinal (GI) physiology, and transport of nanoparticles across the GI epithelium. Dr. Sutton has authored or coauthored over 120 book chapters, abstracts of work in progress, invited presentations, and patents.

# 1

# INTRODUCTION TO PHARMACOKINETICS AND PHARMACODYNAMICS

Sara E. Rosenbaum



**Objectives**

The material in this chapter will enable the reader to:

1. Define pharmacodynamics and pharmacokinetics
2. Understand the processes that control the dose–response relationship
3. Gain a general appreciation of how mathematical expressions in pharmacodynamics and pharmacokinetics can be used for the rational determination of optimum dosing regimens

*Basic Pharmacokinetics and Pharmacodynamics: An Integrated Textbook and Computer Simulations*, Second Edition. Edited by Sara E. Rosenbaum.

## 1.1 INTRODUCTION: DRUGS AND DOSES

*Drugs* may be defined as chemicals that alter physiological or biochemical processes in the body in a manner that makes them useful in the treatment, prevention, or cure of diseases. Based on this definition, any useful drug must affect body physiology or biochemistry. By extension, any useful drug must, if used inappropriately, possess the ability to do harm. Drug action begins with administration of the drug (input) and concludes with the biological response (output, which can be a beneficial and/or an adverse effect). The inputs (dose, frequency of administration, and route of administration) must be selected carefully to optimize the onset, intensity, and duration of therapeutic effects for a particular disease condition. At the same time, the inputs selected must minimize any harmful effects of drugs.

The design of optimum dosing regimens requires a complete understanding of the processes and steps that translate the input into the output. It also requires an understanding of how the input–output relationship may be influenced by individual patient characteristics that may exist at the very beginning of therapy, as well as conditions that may arise during the course of drug therapy. These will include the age and weight of the patient, the presence of other diseases, genetic factors, concurrent medications, and changes in the disease being treated over time.

The material presented in this book will address and explain why, as shown in Table 1.1, there is such tremendous variability in the value of drug doses and dosing frequencies among therapeutic drugs. Additionally, it will address why different routes of administration are used for different drugs and different indications (Table 1.1).

The steps between drug input and the emergence of the response can be broken down into two phases: pharmacokinetic and pharmacodynamic. The *pharmacokinetic phase* encompasses all the events between the administration of a dose and the achievement of drug concentrations throughout the body. The *pharmacodynamic phase* encompasses all the events between the arrival of the drug at its site of action and the onset, magnitude, and duration of the biological response (Figure 1.1). The rational design of optimum dosing regimens must be based on a thorough understanding of these two phases and will, ideally, include the development of one or more mathematical expressions for the relationship between dose and the time course of drug response.

Optimum drug administration is important not only for ensuring good patient outcomes in clinical practice, but also in the design of clinical trials during drug development. The

**TABLE 1.1 Examples of Common Daily Doses and Dosing Intervals**

| Drug | Daily Dose (mg) | Dose Frequency (h) | Route |
|---|---|---|---|
| Calcium carbonate | 3000 | 2 | Oral |
| Ibuprofen | 1600 | 6 | Oral |
| Vancomycin (for MRSA[a]) | 2000 | 12 | Intravenous |
| Amoxicillin | 750 | 8 | Oral |
| Vancomycin (for pseudomembranous colitis) | 1000 | 6 | Oral |
| Atenolol | 100 | 24 | Oral |
| Fluoxetine | 20 | 24 | Oral |
| Ramipril | 10 | 12 | Oral |
| Digoxin | 0.250 | 24 | Oral |
| Chloroquine | 300 | Weekly | Oral |

[a]Methicillin-resistant *Staphylococcus aureus*.

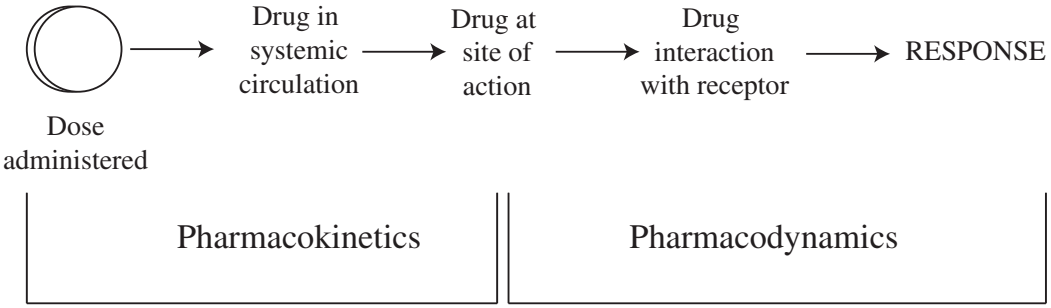


**FIGURE 1.1** The two phases of drug action. The pharmacokinetic phase is concerned with the relationship between the value of the dose administered and the value of the drug concentrations achieved in the body; the pharmacodynamic phase is concerned with the relationship between drug concentrations at the site of action and the onset, intensity, and duration of drug response.

cost of drug research and development is enormous, so it is critical that all drug candidates selected for human trials are evaluated in the most efficient, cost-effective manner possible.

The application of pharmacokinetic and pharmacodynamic principles to this process has been shown to enhance the selection of optimum doses and optimum designs of phase II clinical trials.

## 1.2 INTRODUCTION TO PHARMACODYNAMICS

*Pharmaco-* comes from the Greek word for "drug," *pharmackon*, and *dynamics* means "of or relating to variation of intensity." *Pharmacodynamics (PD) is the study of the magnitude of drug response. In particular, it is the study of the onset, intensity, and duration of drug response and how these are related to the concentration of a drug at its site of action.* An overview of some basic drug terminology and the drug response–concentration relationship is provided below.

### 1.2.1 Drug Effects at the Site of Action

Note that although some references and textbooks distinguish the terms drug *effect* and drug *response*, this distinction has not been adopted universally. In this book, *effect* and *response* are used interchangeably.

#### *1.2.1.1 Interaction of a Drug with Its Receptor*

Drug response is initiated by a chemical interaction between a drug and a special binding site on a macromolecule in a tissue. This macromolecule is known as a drug *receptor.* The drug–receptor interaction results in a conformational change in the receptor, which results in the generation of a stimulus that ultimately leads to a biochemical or physiological response (Figure 1.2). Most receptors (over 95%) are proteins; however, other types of receptors exist such as the DNA receptors of the alkylating agents used in cancer chemotherapy. The drug–receptor interaction involves chemical bonding, which is usually reversible in nature and can be expressed using the law of mass action (Figure 1.2). Thus, at the site of action, the drug binds to its receptor and equilibrium is established between the bound and the unbound drug. As the drug is eliminated from the body and removed from its site of action, it dissociates from the receptor, which is left unchanged, and the response dissipates.

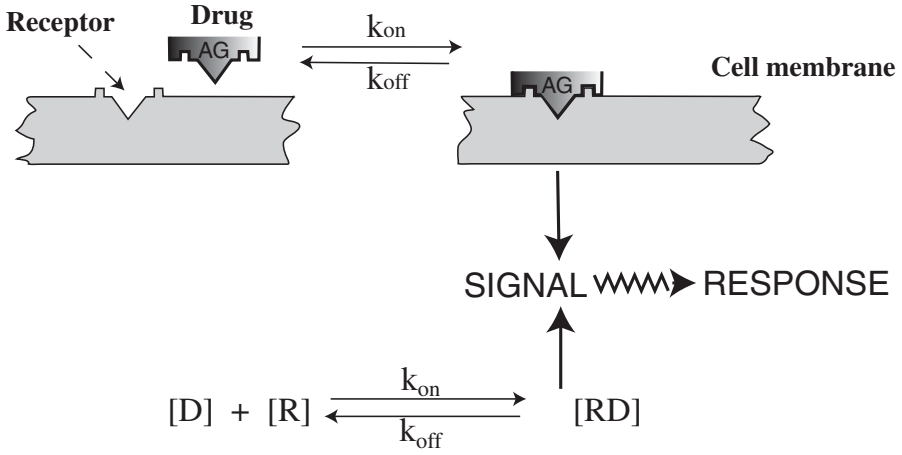


**FIGURE 1.2** Drug–receptor interaction. Here, AG signifies a drug agonist, [D] is the free drug concentration (not bound to the receptor), *R* is the concentration of free receptors, [*RD*] is the concentration of the drug–receptor complex, and $k_{on}$ and $k_{off}$ are the rate constants for the forward and backward processes, respectively.

In contrast, a few drugs form *irreversible* covalent bonds with their receptors. For example, aspirin inhibits platelet aggregation by inhibiting the formation of thromboxane in the platelets. It accomplishes this by binding covalently to and blocking the catalytic activity of cyclooxygenase, the enzyme that produces thromboxane. The effect of a single dose of aspirin will persist long after the drug has been removed from its site of action and will continue until new cyclooxygenase molecules are synthesized, which can then resume the production of thromboxane. Other examples of drugs that bind irreversibly to their receptors include the alkylating agents mentioned above and proton pump inhibitors, such as omeprazole, which block the secretion of gastric acid by binding irreversibly to the $H^+$, $K^+$-ATPase pumps of parietal cells.

The drug–receptor interaction is highly dependent on the chemical structure of both the drug and the receptor and, therefore, small changes in the structure of the drug can reduce or destroy activity. For example, the drug–receptor interaction can distinguish between the *R*- and *S*-isomers of drugs that have chiral carbon atoms. Usually, one isomer is much more active than the other. The *S*-isomer of warfarin, for example, is two to five times more active than the *R*-isomer. The development and promotion of *S*-omeprazole (Nexium) is based on the premise that the *S*-isomer has the higher affinity for the binding site and thus offers therapeutic advantages over preparations containing racemic mixtures (equal quantities of each isomer) of omeprazole, such as Prilosec and its generic equivalents.

Receptors are assumed to exist for all active endogenous compounds (*natural ligands*) such as neurotransmitters and hormones. The interaction between natural ligands and their receptors controls and/or regulates physiological and biochemical processes in the body. In most cases, drugs mimic or antagonize the actions of endogenous ligands by interacting with their cognate receptors. For example, epinephrine is a natural ligand that interacts with $\beta_2$-adrenergic receptors in bronchial smooth muscle to bring about bronchial dilation. Albuterol, a drug, also interacts with this receptor to produce bronchial dilation. Acetylcholine transmits signals through a synapse by interacting with its nicotinic receptor found on postsynaptic neuronal membranes. This interaction, which is mimicked by the drug nicotine, results in the production of a response called an action potential.

It should be noted that there are a few drugs that do not act on receptors but that exert their action by bringing about *physicochemical changes* in the body. For example, conventional

antacids, such as calcium carbonate, act as buffers to reduce acidity in the stomach and polyethylene glycol, an osmotic laxative, acts by preventing the absorption of water in the large intestine.

#### *1.2.1.2 Postreceptor Events*

Drugs almost always bring about some type of change in the *intracellular environment* of cells, but the lipophilic cell membrane presents a physical barrier to most drugs and endogenous ligands. As a result, most receptors are located on the cell membrane itself. The stimulus generated from the interaction of the drug with the membrane bound receptor has to be relayed to the inside of the cell. The relaying of the initial stimulus, known as *coupling* or *signal transduction*, often involves a cascade of different steps during which the initial signal may be amplified or diminished. Some important transduction mechanisms are summarized below (see Figure 1.3).

1. Interaction of a drug with a receptor can lead directly to the opening or closing of an *ion channel* that lies across a cell membrane. In this case, the signal is relayed by changes in the ion concentration within the cell. For example, the interaction of acetylcholine with its nicotinic receptor results in the opening of an ion channel allowing $Na^+$ to move into the cell thus, initiating the production of an action potential.
2. Signal transduction for a large number of drugs involves the *activation of a G-protein* (guanine nucleotide-binding protein). The drug–receptor interaction on the membrane triggers the activation of a G-protein on the cytoplasmic side of the membrane, which then initiates a series of events that culminate in the biological response. Activated G-protein can produce a variety of effects, including stimulation or inhibition of enzymes, and the opening or closing of ion channels. These events usually result in changes in the concentration of an intracellular compound known as the

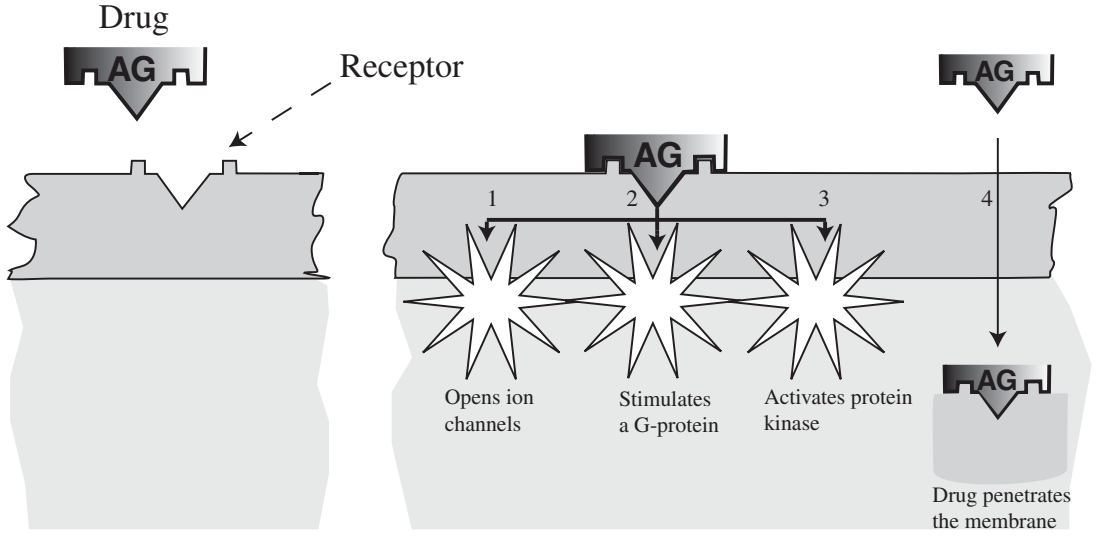


**FIGURE 1.3** Diagrammatic representations of how a drug receptor interaction brings about intracellular events. The intracellular relay of the initial signal resulting from the interaction of a drug with a membrane-bound receptor can be accomplished in one of three ways: (1) the direct opening of ion channels; (2) the activation of a G-protein that may lead to the activation of another enzyme or to a modulation of an ion channel; (3) the activation of protein kinase. Alternatively, (4), some drugs are able to penetrate membranes and directly activate intracellular receptors.

*second messenger*. Examples of second messengers include cyclic adensine-3′,5′-monophosphate (cAMP), calcium, and phosphoinositides. The second messengers then relay the response further through a series of complex steps. For example, the interaction of catecholamines such as norepinephrine with certain β-receptor subtypes involves G-protein activation. This then stimulates adenylate cyclase to convert adenosine triphosphate to cAMP, which acts as the second messenger. Subsequent events include the stimulation of specific protein kinases, activation of calcium channels, and modification of cellular proteins. Other examples of G-protein–coupled receptors are the action of acetylcholine on its muscarinic receptors and the action of serotonin on its 5-HT receptors.

3. The interaction of a drug with its receptor can also result in the stimulation of a receptor-associated enzyme, tyrosine kinase. The activated tyrosine kinase phosphorylates key macromolecules, which are often a part of the receptor itself, to relay the signal. Insulin and peptide growth factors, for example, use this form of signal transduction.

Some drugs are lipophilic enough to penetrate the cell membrane, while others may be transported across the cell membrane by uptake transporters. Drugs that are able to enter a cell can interact directly with intracellular receptors. Examples of drugs that act on intracellular receptors include many steroids such as glucocorticoid steroids, sex hormones, and thyroid hormones. The HMG-CoA reductase inhibitors (commonly known as *statins*) and metformin also act within the cell (hepatocyte) and both are dependent on uptake transporters to deliver them to the intracellular space and their site of action.

### 1.2.2 Agonists, Antagonists, and Concentration–Response Relationships

A drug that mimics the endogenous receptor ligand to activate the receptor is referred to as an *agonist*. The typical relationship between the drug effect and the agonist concentration at the receptor site is shown in Figure 1.4a. Note that as the concentration of the drug increases, the effect increases. At *low concentrations, there is a linear relationship between concentration and effect* (i.e., the response is proportional to the concentration). At higher drug

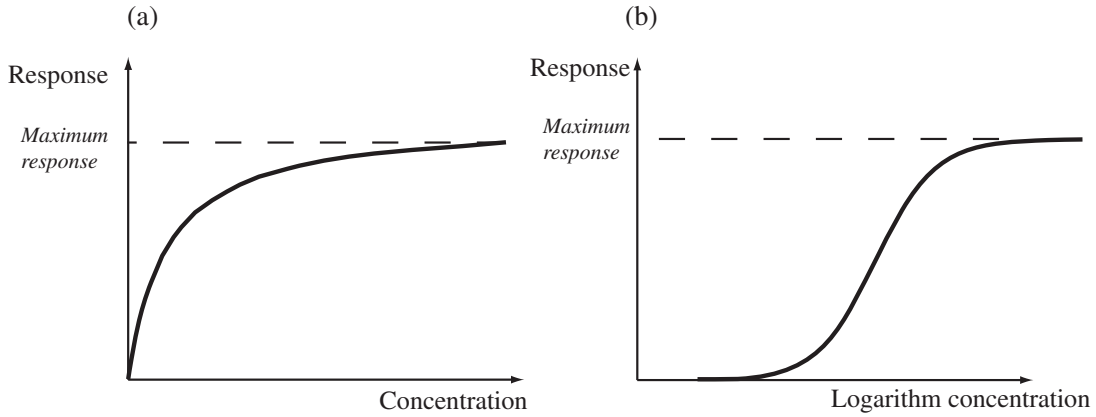


**FIGURE 1.4** Plots of response versus drug concentration: (a) on a linear scale and (b) on a semilogarithmic scale.

concentrations, increases in concentration bring about much smaller changes in effect (the *law of limited returns*). Eventually, at very high concentrations, the effect achieves a maximum value and then remains constant and independent of concentration. In this area of the curve, increases in concentration will not result in further increases in response. This relationship is observed because response is generated by a saturable, capacity-limited process. For example, the response may be limited by the number of receptors that a tissue contains. At low drug concentrations, there are many free receptors and as the drug concentration increases, the drug can bind to the free receptors and response can increase proportionally. At higher concentrations, more and more of the receptors are occupied. As a result, increases in the drug concentration produce much less increase in effect. Eventually, all of the receptors are occupied (or saturated) and a maximum effect is observed. To accommodate a wide range of concentrations, the relationship between effect and concentration is usually plotted on a semilogarithmic scale, which transforms the plot to a sigmoidal shape (Figure 1.4b).

Many agonists are able to produce the system's maximum response without fully occupying all the receptors. In these systems, the maximum response of the drug must be the result of some other saturable, capacity-limited process that occurs after receptor binding. These tissues or systems are said to have *spare receptors*. Experimentally, the presence of spare receptors can be demonstrated by destroying some of the receptors. If an agonist is still able to produce a maximum response, the system must contain spare receptors.

The efficiency with which a drug's interaction with the receptor is converted into the initial stimulus or biosignal is a function of the number of receptors at the site of action and a drug's *intrinsic efficacy*. Intrinsic efficacy can be defined as the magnitude of the stimulus produced per unit receptor occupied. The value of the stimulus that results from a specific concentration of a drug is also a function of the drug's affinity for its receptors. *Affinity* can be defined as the extent or fraction to which a drug binds to receptors at any given drug concentration. Drugs that have high affinity require less drug to produce a certain degree of binding and to elicit a certain response compared to drugs with low affinity. Affinity is one of the factors that determines *potency* (see Chapter 19).

A drug that binds to a receptor but does not activate it is referred to as an *antagonist*. The presence of an antagonist at the receptor site blocks the action of the agonist (Figure 1.5). Higher concentrations of the agonist are needed to displace the antagonist and to produce the effect that is elicited when the antagonist was absent. The antagonist shifts the concentration–response curve of an agonist to the right (Figure 1.6). At sufficiently high concentrations of the antagonist, the agonist's action may be blocked completely and the effect of even high concentrations of the agonist is reduced to zero. Some drugs bind to

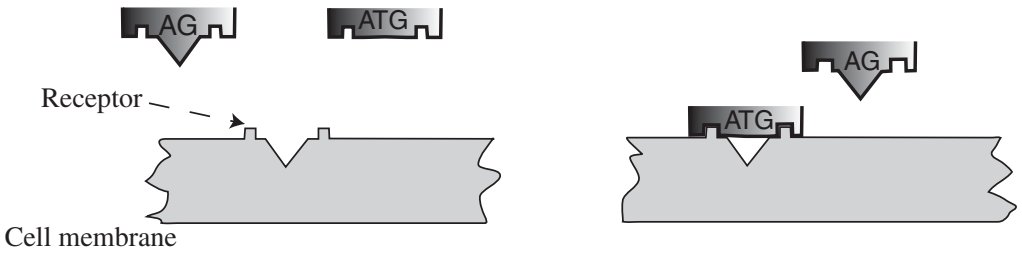


**FIGURE 1.5** Diagrammatic representation of the action of an antagonist. The antagonist (ATG) binds to the receptor but does not produce a signal. Its presence on the receptor blocks the action of agonists (AG), including the natural ligand.

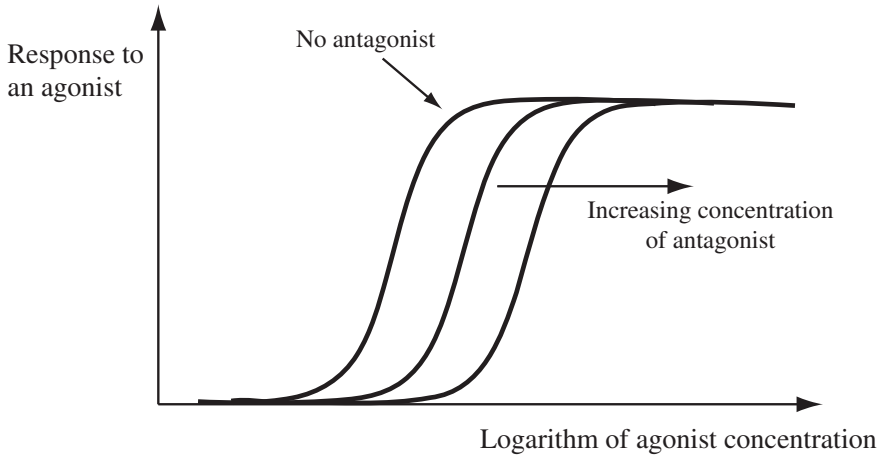


**FIGURE 1.6** Plot of response versus logarithm concentration for an agonist in the absence and presence of increasing concentrations of an antagonist.

receptors, but the binding is less efficient and a full response cannot be achieved even when the drug's concentration is very high and all the receptors are occupied (Figure 1.7). These drugs are referred to as *partial agonists*. A partial agonist will block the effect of a full agonist. In the presence of high concentrations of a partial agonist, the action of a full agonist can be reduced to the maximum response elicited by the partial agonist. Clinically, partial agonists are used to act as buffers to avoid full stimulation of a system. Examples of partial agonists include several β-blockers, including pindolol, and the opioid buprenorphine. The latter is a partial agonist on the μ-opioid receptors and is considered a safer alternative to morphine because it does not produce as much respiratory depression (see Chapter 19).

In summary, drug action is mediated primarily by the interaction of a drug with membrane-bound receptors at its site of action. This produces conformational changes in the receptor, which lead to the generation of an initial signal. The signal is then relayed to the intracellular environment by means of a variety of transduction processes. The response increases with increases in drug concentration until enough receptors are occupied to generate the maximal response. The response to a specific concentration of drug is dependent on drug-specific properties (e.g., intrinsic efficacy and affinity) and tissue-specific properties (e.g., number or density of receptors and amplification or diminution of the initial signal during transduction). An important goal in a study of pharmacodynamics is to derive

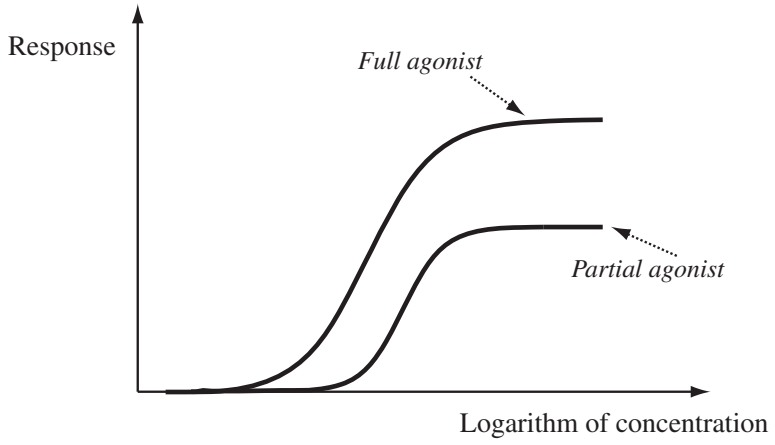


**FIGURE 1.7** Plot of response versus logarithm concentration for a full and a partial agonist.

a mathematical expression for the magnitude of drug response as a function of drug concentration:

$$E = f_{PD}(C) \tag{1.1}$$

where $E$ is the drug effect or response, $C$ is the drug concentration, and $f_{PD}$ is a pharmacodynamic function that links these two variables and contains the drug-specific parameters of intrinsic efficacy and affinity. In equation (1.1), $E$ is the *dependent variable* because it is dependent on all the other components of the equation. The drug concentration at the site of action ($C$) is the *independent variable* because it is independent of all the other components of equation (1.1). This expression would allow the effect to be estimated at any drug concentration and allow the required concentrations for optimum response to be identified.

## 1.3 INTRODUCTION TO PHARMACOKINETICS

*Pharmaco-* comes from the Greek word for "drug," *pharmackon*, and *kinetics* comes from the Greek word for "moving," *kinetikos*. *Pharmacokinetics (PK) is the study of drug movement into, around, and out of the body. By extension, it involves the study of drug absorption, distribution, and elimination* (*metabolism and excretion*) (*ADME*).

Pharmacokinetics involves the study of how drugs enter the body, distribute throughout the body, and leave the body. It is concerned with the driving forces for these processes and the rate at which they occur. Pharmacokinetics is the study of the *time course of drug concentrations in body compartments*. From a therapeutic perspective, the drug concentration at the site of action is by far the most important: Concentrations should be sufficiently high to produce a response but not so high as to produce toxicity. Since it is not possible to routinely measure this concentration clinically, the *plasma concentration* of the drug is the main focus in pharmacokinetics. It is often assumed that the *plasma concentration reflects the drug concentration at the site of action.* This is generally true and the relationship is often linear. Increases or decreases in the plasma concentration will be reflected by proportional increases or decreases at the site of action, respectively. However, as discussed in subsequent chapters, this is not always the case and a more complex relationship between these two concentrations may exist. It is important to note that although changes in the plasma concentration will usually result in proportional changes in the drug concentration at the site of action, the reverse is not true. Because the amount of drug that is delivered to the site of action is usually such a very small fraction of the total amount of drug in the body (in other tissues and the systemic circulation), local changes in the amount of drug at the site of action are generally not reflected by noticeable changes in the plasma concentration.

### 1.3.1 Plasma Concentration of Drugs

As stated above, pharmacokinetics is concerned with the body's exposure to a drug and how drug concentrations change over time. For the most part, drug concentrations in the plasma are the focus in pharmacokinetics. The rationale for this is twofold. First, blood is one of the few body fluids that can be obtained and analyzed repeatedly for drug concentrations at specified times after the administration of a dose. The concentration of drug in whole blood is not commonly used in pharmacokinetics because blood is a complex physical system that consists of red blood cells, white blood cells, and platelets suspended in plasma water. Blood with the cellular elements removed, either by centrifugation (plasma) or clotting