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Pharmacology and Therapeutics for Dentistry

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REMEMBERING JOHN A. YAGIELA, DDS, PhD, AND ENID A. NEIDLE, PhD

Since the publishing of our last edition (6th) of this textbook, we have lost two of our former editors, dear friends, and true giants in the field of dental education: John A. Yagiela and Enid A. Neidle. Both had been editors through all of the previous editions of this textbook, and both were very instrumental in providing the initial focus and establishing its content. This is the first time since 1980 that the names of these two outstanding individuals will not appear on the book as editors. John and Enid have left a lasting legacy. We dedicate this edition to their memory as we carry on the tradition of providing a current and thorough treatment of pharmacology for dental students and the dental profession.

John Allen Yagiela was born in Washington, DC, but grew up in Los Angeles.

He received his dental degree from UCLA in 1971 and his PhD in pharmacology from the University of Utah in 1975 and completed a residency in anesthesiology from the UCLA School of Medicine in 1983. Dr. Yagiela used his expertise in pharmacology and anesthesiology to make this textbook the standard reference for all dental students. His contributions to critical chapters in principles of pharmacology and dental anesthesia were immensely important for the foundation of basic pharmacologic principles for dental students and professionals. Moreover, as the lead editor, he was tireless in his effort to make certain all chapters were accurate and current. John applied his vast knowledge and abundant energy to all the things that are required to insure a quality textbook. He was always helpful to contributors and often helped authors who needed assistance with certain aspects of their chapters. This included everything from providing expert advice on the text, to providing figures to authors, down to simply explaining when to correctly use a dash. We always found him supportive and willing to provide information and advice on many areas of pharmacology. The field of dental anesthesiology and dental education in general, as well as this text, will be forever in his debt. John was active as a clinician in the area of dental anesthesiology. Indeed, he was a key and devoted advocate for the field of dental anesthesiology and was largely responsible for spearheading the recognition of anesthesiology as a specialty of dentistry. John spent the majority of his academic carrier at UCLA School of Dentistry where he held several leadership positions, including professor (later Professor Emeritus) and Chair, Department of Diagnostic and Surgical Sciences. He was also in demand as a keynote speaker and has received many academic awards. On a personal note, he was a kind, fun, and an ever-inquisitive man who delighted in the wonders of the universe.

Enid Anne Neidle received her PhD from the Department of Physiology at Columbia University.

Her first faculty position was in the Department of Pharmacology at the Jefferson Medical College in 1950, but she moved to New York University in 1955 to become an Instructor in the Department of Physiology, which began a long career in the College of Dentistry. Dr. Neidle was the initial force behind this text and has had a key role in the previous editions. It was her insight that brought to fruition the first thorough textbook of pharmacology and therapeutics designed for the dental profession. As the textbook's first lead editor, she was dedicated to finding key people to contribute to the text and deciding on its focus to better serve the dental community. She was also a major contributor to dental education. Dr. Neidle was professor (later Professor Emeritus) and Chair, Department of Pharmacology, New York University School of Dentistry. Her initial research contributed to the field of cholinergic and anticholinergic drugs and later to dental education. She spent 33 years of her career at New York University, and she held several positions in organized dentistry, including Assistant Executive Director of Scientific Affairs for the America Dental Association for 6.5 years. One of her passions was to further the cause of women in dentistry. She received several honors for her work and dedication, including a national scholarship named in her honor. Enid was also in demand as a public speaker and was an early advocate of evidence-based dentistry. Those of us who knew her from the first edition of this textbook remember Enid for her abundant organizational skills and devotion to academic dentistry. (From those early years on, I found her most supportive and instructive. – FD)

HONORING BART JOHNSON, DDS, MS

We are deeply saddened by the recent passing of Bart Johnson, one of the three editors of this textbook. Bart was an editor not only of this edition but also the sixth edition as well as an author over the previous three editions. In 2015, Dr. Johnson was diagnosed with stage 4 colon cancer. Nonetheless, he remained an editor until this edition was finished.

Barton Johnson received his DDS degree in 1985 from UCLA. He continued on at UCLA in a general practice residency, and later earned an MS degree in Oral Biology. He was a faculty member at the University of Washington School of Dentistry from 1991 to 2007, and directed its General Practice Residency program during that time. Bart held many prominent leadership positions including President of the American Association of Hospital Dentists. He had been Director of the Swedish General Practice Residency from 2009 to 2016. Dr. Johnson specialized in special care dentistry, serving the needs of patients with significant underlying medical issues. He also contributed his knowledge and experience as editor and author. His expertise included pharmacology, internal medicine, medical emergencies, hospital dentistry, and basic and advanced cardiac life support.

We deeply appreciate all the wonderful work he did with the book, especially with the battle he had and with his extensive clinical responsibilities. He made several critical editorial contributions to the book. He was a trusted colleague who offered expert advice, and is the sole author of two chapters in the book. We are all grateful and proud of his many contributions to dental pharmacology. It has been a joy to work with Bart and to witness his courage and positive attitude while dealing with his disease. We appreciate his dedication to the book and his professionalism even when it was a special challenge.

It is with the utmost respect and gratitude that we honor Bart.

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HOW TO APPROACH PHARMACOLOGY

Although pharmacology can be considered a basic science, the ultimate purpose of pharmacology in the health science setting is to apply basic principles to clinical practice. This book, which is targeted to the dental student and dental practitioner, is designed to meet that need. Pharmacology is important to the dentist not only because of the drugs that he or she prescribes or uses in the dental office but also because of other drugs that the patient takes. Every drug can affect the entire body. Moreover, when more than one drug is given concurrently, there is a potential for drug interactions that could have adverse consequences.

This book is designed to make specific dental applications to each drug class. Included in this information are the benefits and risks associated with those drug classes.

In the study of pharmacology, it is important to learn drugs by their classes on the basis of similarity of mechanism of action rather than individual stand-alone medications. Thus armed with the knowledge of the properties of a class of drugs and examples of drugs within that class, one can streamline the learning process. Organization of drug information can then be arranged around the following subcategories (these will be useful in studying most drugs):

1. Name of drug class and examples
2. Mechanism of action
3. Pharmacokinetics
4. Indications
5. Adverse effects
6. Contraindications
7. Miscellaneous information, including drug interactions
8. Implications for dentistry

Some devices can help in the learning of drug names. The nonproprietary (generic) names for drugs within a given class often have similarities. Being familiar with a list of suffixes of generic drug names can be helpful in identifying an individual drug. Such a list is given next.

SUFFIXES AS CUES FOR REMEMBERING DRUG CLASSES

Suffix	Drug Class	Example
"azole"	Azole-type antifungal drug or antibacterial-antiparasitic drug	Fluconazole Metronidazole
"caine"	Local anesthetic	Lidocaine
"coxib"	Cyclooxygenase-2 (COX-2) inhibitor	Celecoxib
"dipine"	Dihydropyridine Ca^{++} channel blocker	Amlodipine
"ilol" or "alol"	β-Adrenergic receptor blocker that also blocks the α_1-adrenergic receptor	Carvedilol, labetalol
"mab"	Monoclonal antibody	Infliximab
"olol"	β-Adrenergic receptor blocker	Metoprolol
"onium" or "urium"	Quaternary ammonium compound, usually used as a peripheral competitive skeletal muscle relaxer	Pancuronium, atracurium
"osin"	α_1-Adrenergic receptor blocker	Prazosin
"pam" or "lam"	Benzodiazepine antianxiety agent or sedative hypnotic	Diazepam, triazolam
"pril" or "prilat"	Angiotensin-converting enzyme (ACE) inhibitor	Captopril
"sartan"	Angiotensin II receptor blocker	Losartan
"statin"	HMG CoA reductase inhibitor antilipid drug	Lovastatin
"triptan"	Serotonin $5\text{-}HT_{1B/1D}$ agonist antimigraine drug	Sumatriptan
"vir"	Antiviral drug	Acyclovir

Application of information to clinical cases can increase retention and appreciation of pharmacology. The cases presented in this book help to make that application. The dentist will encounter drugs prescribed by a physician that have adverse effects on the oral cavity. Knowledge of a drug is essential in determining the likelihood of a drug causing adverse oral effects, and what strategies can be used to reduce these effects without compromising the intended therapy. On the other hand, a drug administered by the dentist could impact therapy by the physician. Here again, the dentist will need to have knowledge of that drug to determine whether or not it is advisable to use it in a given patient. These situations require knowledge of how drugs act, including the receptors involved, and what responses are linked to these receptors.

The landscape of pharmacology is ever expanding with the constant development of new drugs, new drug classes, and new information on older drugs. Furthermore, the growth in our knowledge in areas such as pharmacogenetics and pharmacogenomics promises to lead to the practice of tailoring drug therapy to the individual.

All in all, pharmacology is an exciting and dynamic discipline. This book covers the major areas of pharmacology and provides an intellectual framework on which to use drugs in a rational manner.

Frank J. Dowd
Barton S. Johnson
Angelo J. Mariotti

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The competing demands of academia in the modern health science setting make the writing of textbooks such as *Pharmacology and Therapeutics for Dentistry* a challenging task. In this effort, we have been aided greatly by our contributing authors, past and present, who have given their time and expertise to ensure that the information provided herein is both accurate and current. We wish to especially acknowledge Dr. John Yagiela and Dr. Enid Neidle, past chief editors of this textbook, for the foundations they set. (Separate tributes to each of them are given earlier.) We specifically acknowledge the contributors to this text who have devoted time and expertise to advancing dental pharmacology. We also must express gratitude to our families, Pat Dowd, Bridgette Mariotti, and Kim Franz, for their forbearance in dealing with our distractions and preoccupations on everything pharmacologic.

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Frank J. Dowd
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INTRODUCTION

Pharmacology may be defined as the science of drugs and how they affect living systems. The term derives from *pharmakon,* the Greek word for drug or medicine, and *logia,* the Latin suffix traditionally used to designate a body of knowledge and its study. As an organized discipline, pharmacology is of recent origin, but the study of medicinal substances is as old as civilization itself.

HISTORY

Sir William Osler (1849 to 1919) once said, "The desire to take medicine is perhaps the greatest feature which distinguishes man from animals." This serves to illustrate the historical relationship between drugs and human beings. The use of natural products to cure disease and alter mentation dates back to the dawn of time. By the writing of the Ebers papyrus (c. 1550 BCE), more than 700 prescriptions for various ailments were known. Many of the ingredients incorporated in these preparations—lizard's blood, virgin's hair, fly excreta—are humorous by modern standards, but also included were many compounds recognized today as pharmacologically active. A summary of folk remedies and other medicinals that have withstood scientific scrutiny would list such substances as opium (morphine), belladonna (atropine), squill and foxglove (digitalis), cinchona bark (quinine and quinidine), coca leaves (cocaine), and ma huang (ephedrine). The empirical study of plant derivatives and animal products must have been extensive to be so fruitful.

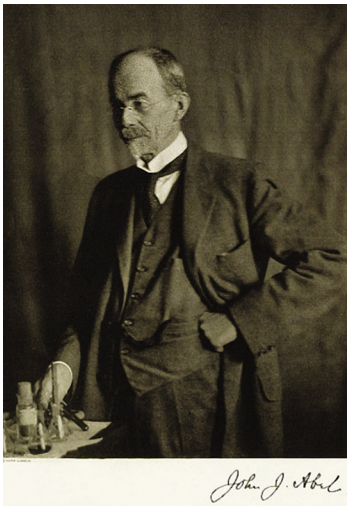
A major hindrance to the effective use of these drugs, however, was the large number of materials usually present in apothecary formulations. For example, the most popular drug of the 15th century, triaca, contained more than 100 separate components. Aureolus Paracelsus (1493 to 1541) was the first to recognize that the indiscriminate mixing of numerous substances did little but dilute whatever effective compounds may have been present initially. The focus of Paracelsus on single agents was refined by Felice Fontana (1720 to 1805), who deduced from his own experiments that each crude drug contains an "active principle" that, when administered, yields a characteristic effect on the body. One of the greatest scientific achievements of the 19th century was the isolation and objective evaluation of such "active principles."

In 1803, a young German pharmacist, Frederick Sertürner (1780 to 1841), extracted the alkaloid morphine from opium. This singular achievement not only marked the beginning of pharmaceutical chemistry, but it also led to a revolution in experimental biology. The availability of newly purified drugs and the standardization of existing biologic preparations encouraged pioneers like Francois Magendie (1783 to 1855) and Claude Bernard (1813 to 1878) to use pharmacologic agents as probes in the study of physiologic processes. The use of curare by Bernard for the elucidation of the neuromuscular junction is but one example of the successes obtained with this approach. Perhaps because drugs became associated with several biologic sciences and were, of course, considered under the domain of the various medical specialties, the development of pharmacology as a separate discipline was delayed.

*(Photos in this introduction are as follows: From Wellcome Library, London L0074448, Sir William Osler (1849 to 1919), Canadian physician, aged 63. Copyrighted work available under Creative Commons Attribution only license CC BY 4.0 http://creativecommons.org/licenses/by/4.0/. *Paracelsus,* © Musée du Louvre, © Direction des Musées de France, 1999; *Claude Bernard,* public domain; *John Jacob Abel,* public domain; *Agonist concentration-response curve; Dioscorides' Material Medica,* public domain; *aspirin tablets,* photo © istock.com).

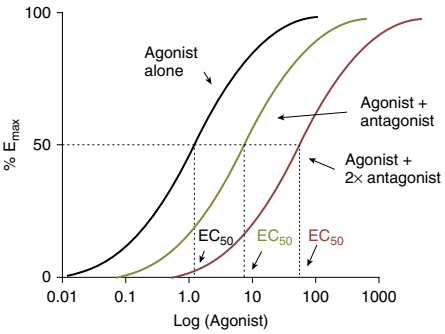
Rudolf Buchheim (1820 to 1879) and Oswald Schmiedeberg (1838 to 1921) were the two individuals most responsible for establishing pharmacology as a science in its own right. Buchheim organized the first laboratory exclusively devoted to pharmacology and became the first professor of his discipline. A student of Buchheim's, Schmiedeberg founded the first scientific journal of pharmacology. More importantly, through his tutelage Schmiedeberg helped spread acceptance of pharmacology throughout the world. One protégé of Schmiedeberg was John J. Abel (1857 to 1938), generally regarded as the father of American pharmacology.

Once an obscure experimental science, pharmacology has expanded its purview to such an extent that the subject has become an important area of study for all health professionals and holds certain interests for the lay public as well. In dentistry, the impact of pharmacology was formally recognized by the American Dental Association in 1934 with publication of the first edition of *Accepted Dental Remedies.*



SCOPE OF PHARMACOLOGY

Pharmacology is one of the few medical sciences that straddles the division between the basic and the clinical. The scope of pharmacology is so extensive that several subdivisions have come to be recognized. *Pharmacodynamics* is the study of the biologic activity that a drug has on a living system. It includes a study of the mechanisms of action of the drug and the exact processes that are affected by it. The influence of chemical structure on drug action (the structure–activity relationship) is also a concern of this branch of pharmacology. *Pharmacokinetics* deals with the magnitude and time course of drug effect, and it attempts to explain these aspects of drug action through a consideration of dosage and the absorption, distribution, and fate of chemicals in living systems.



Pharmacotherapeutics is the proper selection of an agent whose biologic effect on a living organism is most appropriate to treat a particular disease state. It requires a consideration of, among many other things, dose, duration of therapy, and side effects of drug treatment. The practice of *pharmacy* involves the preparation and dispensing of medicines. Although pharmacists today are rarely called on to actually prepare drug products, they are a useful source of drug information for both the clinician and the patient. *Toxicology* is that aspect of pharmacology dealing with poisons, their actions, their detection, and the treatment of conditions produced by them. The importance of toxicology to modern life is continually underscored by new discoveries of chemical hazards in the environment. As the various disciplines of science and medicine have continued to evolve, fruitful areas of inquiry have emerged from the union of fields with overlapping interest. For example, study of the interrelationships between drugs and heredity, aging, and the immune system has led to the respective development of *pharmacogenetics, geriatric pharmacology,* and *immunopharmacology.* A final subdivision of pharmacology, *pharmacognosy,* has gained new relevance. Essential at a time when most drugs were derived from plants, it literally means "drug recognition" and deals with the characteristics of plants and how to identify those with pharmacologic activity.

Although most drugs today are synthesized chemically, phytochemistry, especially the synthesis of complex chemical structures by plants, remains of interest. Furthermore, herbal medicine as a discipline of pharmacognosy has gained significant importance since 1994. The use of products in this area has spurred interest in the active components of herbal medicines, their clinical efficacy, and their potential liabilities.

After a description of how the study of drugs is classified, it is appropriate to discuss what is meant by the word *drug.* To the pharmacologist, a drug is any chemical agent that has an effect on the processes associated with life. This definition is obviously broad and ill-suited for many parties who define the term more restrictively to better serve their particular needs. The therapist, for example, considers drugs as those chemicals that are effective in treating disease states. To the lay public, drugs generally connote those substances that cause mental and psychological alterations. Finally, governmental agencies are concerned with the revenue derived from the taxes levied against the sale of certain substances or with public health problems associated with their use. Some of these agents, such as tobacco and alcohol, are legally sequestered—that is, by law they are considered "nondrugs."

Although pharmacologists have long recognized these agents as potent drugs, they are exempted from the usual governmental restraints and are not subject to normal scrutiny by the U.S. Food and Drug Administration. There are other substances that have gained such special status not by historical accident, as did some of those previously mentioned, but by considerations of public health. Examples of these include chlorine and fluoride added to community water supplies and iodides mixed with table salt. Lawsuits over the question of whether these public measures constitute an illegal form of "mass medication" have been resolved by the courts, at least in part through the categorization of these chemicals as legal nondrugs when they are used in a specific manner for the public good.

Drugs discussed in this book almost exclusively include only those substances with a known therapeutic application. Even so, the potential number of agents for consideration is large: several thousand drugs marketed in a multiplicity of dosage forms and, in some instances, in a bewildering variety of combinations. To limit confusion, emphasis is placed on single, prototypical agents that represent their respective drug classes. By this approach, an understanding of the properties of related agents can be more readily achieved; at the same time, differences that may exist between them can be highlighted. Finally, it is important to recognize that there are certain generalizations that apply to all drugs. These principles of drug action are the subject of the first four chapters in this book. A mastery of the concepts presented in these chapters is necessary for a thorough understanding of pharmacology, for the rational use of therapeutic agents, and for the objective evaluation of new drugs.

NEW TO THE 7TH EDITION

The 7th Edition of *Pharmacology and Therapeutics for Dentistry* is substantially different from previous editions. Some of the chapters from the previous edition (e.g., those not directly related to, or only narrowly focused upon, dental practice) have been removed. Furthermore, the chapters in this edition have focused on content that is pertinent to the dental student. This has resulted in a reduction in chapter and book length. Appendices have been expanded to provide additional reference information. Other changes to the 7th Edition include the following:

(1) updated pharmacologic information
(2) revised and expanded illustrations
(3) dentally related case studies and subsequent discussions
(4) outlines at the beginning of each chapter
(5) bolded words and phrases in the text to focus the reader on key concepts and drugs
(6) color use for the first time

It is our hope that this concise, contemporary, and authoritative edition of *Pharmacology and Therapeutics for Dentistry* will be a great benefit to the pharmacology student and faculty member.

1

Pharmacodynamics: Mechanisms of Drug Action*

Frank J. Dowd and Peter W. Abel

KEY INFORMATION

- Most drugs bind to, and act through, receptors.
- The vast majority of drug receptors are proteins.
- Five different families of receptors are presented.
- Binding of a drug to a receptor is selective, and the affinity of the binding is measured by its K_d.
- The effect of the drug after binding to a receptor is called signal transduction. This occurs through a number of steps.
- Drug agonists at a given receptor can be distinguished based upon affinity of binding, potency (EC_{50}), and intrinsic activity (maximal effect, also called ceiling effect or E_{max}).
- Partial agonists have lower E_{max} values than full agonists.
- Antagonists are drugs that bind to receptors and block the effects of agonists.
- Antagonists whose blockade of the receptors can be overcome by adding higher concentrations of an agonist are called competitive antagonists.
- Conversely, receptor blockade by a noncompetitive antagonist is not surmountable by adding higher concentrations of the agonist.
- Tolerance to a drug (reduced response to a drug despite continued treatment) can occur by a number of mechanisms, which include desensitization and downregulation of the receptors.
- Receptors are not static structures and can cycle through more than one configuration.

CASE STUDY

Joe B, your dental patient, takes medication for chronic asthma. He has been given a drug preparation which includes salmeterol, a bronchodilator, and the adrenal corticosteroid fluticasone. His physician has indicated to Joe that he may need a rescue inhaler at times, but the rescue inhaler should not be used unless necessary to reverse an acute asthma attack. In reading about this drug combination, you see there is a "black box" warning that it may increase the risk of death from asthma. Why does it have this warning, and why was Joe warned about the frequency of use of a rescue inhaler?

DRUGS, RECEPTORS, AND SIGNAL TRANSDUCTION

Pharmacodynamics, which is the heart of pharmacology, is the study of how drugs act to achieve a response. Drugs are chemical substances that are administered to alter or modify existing physiologic or pathologic processes. In conventional doses, most therapeutic agents are generally selective in their action and influence a narrow spectrum of biologic events. How does this happen? Tissue elements to which drugs bind are called **receptors**. They have highly ordered physiologic/biochemical properties that permit only a very few particular compounds to combine with them, while prohibiting all others from doing so. Once bound, the receptor/drug complexes initiate other events to occur at the cellular level.

The existence of receptors that respond to exogenously administered drugs implies that drugs often mimic or inhibit the actions of endogenous ligands (chemicals that bind) for these receptors. These receptors existed long before drugs were developed. They originally evolved to respond to specific endogenous ligands such as hormones and neurotransmitters. Their great specificity of binding to both endogenous ligands and exogenous drugs suggests that simple molecular modifications of a drug may drastically affect the activity of the drug. This can be beneficial or detrimental to the clinical use of the drug.

Receptor Classification

For many years after their postulation more than a century ago, receptors remained an enigma to pharmacologists. Little was known about them other than the probability that they were complex macromolecules possessing a ligand-binding site to interact with specific drugs and an effector site to initiate the pharmacologic response. With the development of biochemical methods for the isolation and characterization of proteins, enzymes became available as model systems for the early study of drug–receptor interactions. Enzymes exhibit many of the properties that are ascribed to receptors. They are macromolecules having measurable biologic functions that possess specific reactive sites for selected substrates. The close association between enzymes and receptors was underscored in the early 1940s when it became apparent that some enzymes serve as drug receptors. The list of drugs that alter known enzymatic activities is extensive and includes such examples as angiotensin-converting enzyme inhibitors, anticholinesterases, protease inhibitors, reverse transcriptase inhibitors, statin cholesterol synthesis inhibitors, and various antimetabolites used in cancer chemotherapy, among others.

In addition to enzymes (including coenzymes), other receptors have been identified that are of clinical significance. The most common receptors are those located on and within the various membranes of the cell. Their study has been greatly aided in recent years by

* The authors wish to recognize Dr. John A. Yagiela for his past contributions to this chapter.

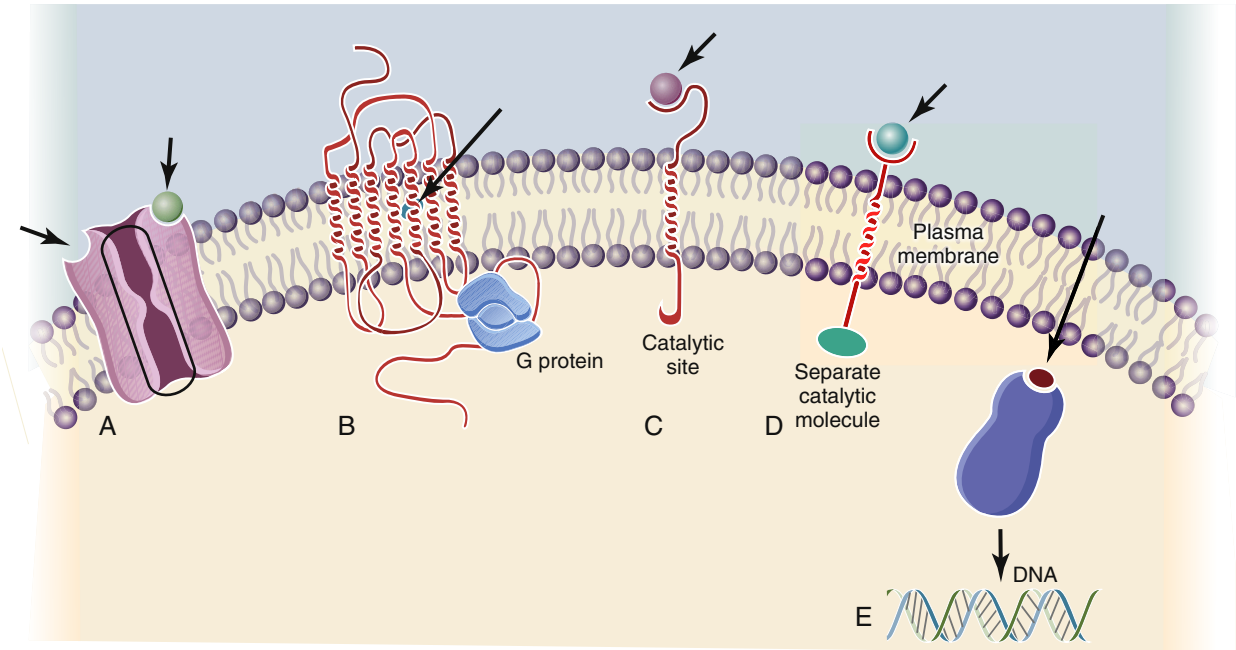


FIG 1-1 Examples of five major classes of receptors. *Arrows* denote the receptor ligand-binding sites. **A**, Ion channel–linked receptors. Drugs such as nicotine can activate ligand-gated ion channels, leading to depolarization (or hyperpolarization) of the plasma membrane. **B**, G protein–coupled receptors. Many drugs can activate G protein–linked receptors, causing release of the α and βγ subunits of the G protein. **C**, Transmembrane receptors that have enzymatic cytosolic function. Agents such as insulin and epidermal growth factor activate this type of receptor. **D**, Transmembrane receptors that bind a separate cytosolic enzyme. Cytokines bind to this type of receptor. **E**, Intracellular receptors. Lipophilic substances (dark oval) such as steroids can cross the plasma membrane and activate intracellular receptors.

developments in genomics and proteomics. Many integral membrane proteins function as receptors for endogenous regulatory ligands, such as neurotransmitters, hormones, and other signaling molecules. In addition, membrane transporter proteins and metabolic enzymes, described in Chapter 2 for their influence on drug disposition, are also targets of drug action.

Nucleic acids serve as receptors for a limited number of agents. Certain antibiotics and antineoplastic compounds interfere with replication, transcription, or translation of genetic material by binding, sometimes irreversibly, to the nucleic acids involved. Other drugs, including thyroid hormones, vitamin D analogues, sex steroids, and adrenal corticosteroids, also modify transcription, but here the affected DNA becomes activated or inhibited as a consequence of drug interaction with a separate receptor protein in the cytosol or nucleus of the cell, as will be described subsequently.

Receptors involved in physiologic regulation can be grouped by molecular structure and functional characteristics into several superfamilies. Most of these receptors are membrane bound and have one or more extracellular ligand-binding domains linked by one or more lipophilic membrane-spanning segments to an effector domain often, but not always, located on the cytoplasmic side of the membrane. This arrangement is ideal for the translation of an extracellular signal into an intracellular response. Usually, the endogenous ligand "signal" (upon binding to the receptor) is hydrophilic and incapable of passive diffusion through the cell membrane. The same is true for most drugs that bind to these same receptors. For lipophilic regulatory ligands, such as thyroid hormone and various steroids, a separate superfamily of intracellular receptors exists. Commonly, when these drugs bind, they expose a DNA-binding site on the receptor protein, allowing the receptor to interact with DNA and alter transcription. These five major classes of receptors are illustrated in Figure 1-1 and described in the following text.

Ion channel–linked receptors

There are two general classes of ion channels: voltage-gated and ligand-gated (see Figure 1-1, *A*). **Voltage-gated ion channels** are activated by alterations in membrane voltage. Voltage-gated Na^+ channels open when the membrane is depolarized to a threshold potential and contribute to further membrane depolarization by allowing Na^+ influx into the cell. As described in Chapter 14, local anesthetics such as lidocaine bind to voltage-gated Na^+ channels, leading to blockade of neuronal depolarization. Specific voltage-gated ion channels also exist for several other ions, particularly K^+, Ca^{2+}, H^+, and Cl^-.

In contrast, ligand-gated ion channels (see Figure 1-1, *A*) are activated in response to the binding of specific ligands or drugs. Another name for ligand-gated ion channels is **ionotropic receptors**. (This term should not be confused with inotropic.) Many neurotransmitters, drugs, and some cytoplasmic ligands activate membrane-bound ligand-gated ion channels. These include several types of glutamate receptors, at least one 5-hydroxytryptamine ($5\text{-}HT_3$) receptor promoting Na^+, K^+, or Ca^{2+} movements, and certain γ-aminobutyric acid and glycine receptors promoting Cl^- influx. Depending on the ionic charge and the direction of flow, ligand-gated ion channels can either depolarize or hyperpolarize the cell membrane.

The nicotinic receptor, the first membrane-bound drug receptor to be fully characterized, is an important example of a ligand-gated ion channel (see generic example in Figure 1-1, *A*). An oligomeric structure, the polypeptide constituents of the nicotinic receptor subunits are arranged concentrically to form a channel through which small ions can traverse the plasma membrane when the receptor is activated

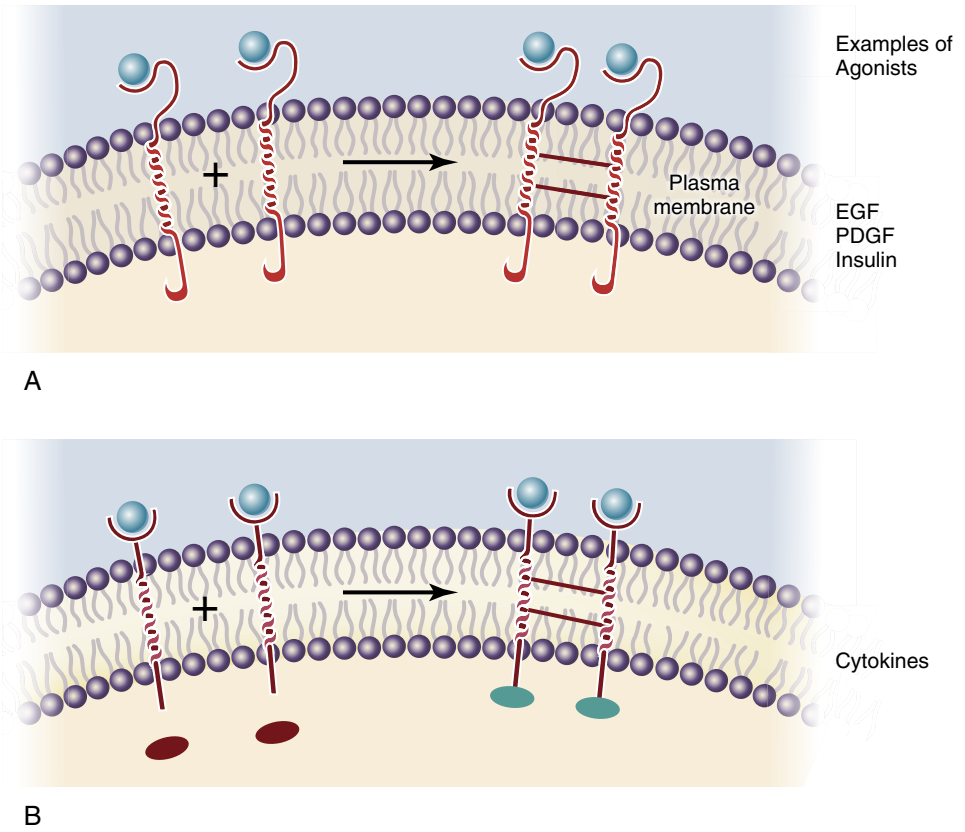


FIG 1-2 Dimerization of two membrane-bound receptor types that activate cytosolic enzymatic activity. Drugs (*blue spheres*) bind to the receptors, leading to dimerization and activation of enzymatic activity on the cytoplasmic side of the receptor (illustrated by conversion of the enzyme from *red* to *green ovals* in **B**). Examples of drugs and other ligands that work through these receptors are shown. **A**, The receptor contains enzyme activity as part of the cytoplasmic end of the receptor. *EGF*, Epidermal growth factor; *PDGF*, platelet-derived growth factor. **B**, The receptor binds and activates a separate enzyme located in the cytoplasm.

by the binding of two acetylcholine (ACh) molecules. As is the case with other ion channels, numerous subtypes of nicotinic receptors exist expressing differing affinities for specific ligands.

G protein–coupled receptors

G protein–coupled receptors, sometimes referred to as metabotropic receptors, constitute the largest superfamily of integral membrane proteins, and collectively serve as targets for approximately half of all non-antimicrobial prescription drugs (see Figure 1-1, *B*). The basic structure of these receptors includes a common seven-membered transmembrane domain. Generally, metabotropic receptors greatly amplify extracellular biologic signals because they activate G proteins, which activate ion channels or, more commonly, other enzymes (e.g., adenylyl cyclase), leading to the introduction or formation of a host of internal second messengers for each extracellular signal molecule detected.

G proteins are heterotrimers consisting of α, β, and γ subunits. After receptor activation, guanosine diphosphate (GDP, attached to the α subunit) is replaced by guanosine triphosphate (GTP), and the heterotrimer splits into the α monomer and βγ dimer. Many, but not all, of the observed cellular actions are caused by the α subunit. As an example, $G_{\alpha s}$, the specific α subunit for the G protein associated with β-adrenergic receptors, activates adenylyl cyclase, which catalyzes the synthesis of cyclic adenosine 3′,5′-monophosphate (cAMP). cAMP activates protein kinase A, which catalyzes the phosphorylation of serine and threonine residues of certain intracellular proteins, leading to a complex alteration in cellular function.

The G protein system is very complex. One receptor subtype may activate different G proteins, several receptor subtypes may activate the same G protein, and the ultimate target proteins can exist in tissue-specific isoforms with differing susceptibilities to secondary effector systems. The different G protein pathways can also interact with one another. The complexity of G protein signal transduction provides a sophisticated regulatory system by which cellular responses can vary, depending on the combination of receptors activated and the cell-specific expression of distinct regulatory and target proteins. Several specific membrane-bound G proteins are discussed beginning in Chapter 5 and continuing thereafter with regard to several clinical drugs discussed in the text.

Transmembrane receptors that have enzymatic cytosolic function

Enzyme-linked receptors have only one transmembrane domain per protein subunit, with an enzymatic catalytic site on the cytoplasmic side of the receptor (see Figure 1-1, *C*). For many of these receptors, dimerization activates the receptor to provide the conformational change required for expression of enzymatic activity. The most important cytoplasmic sites have one of the following functions: (1) tyrosine kinase activity, (2) tyrosine phosphatase activity, (3) serine or threonine kinase activity, or (4) guanylyl cyclase activity. For types 1 and 3, autophosphorylation of the receptor also occurs at tyrosine sites and at serine/threonine sites, respectively. Figure 1-2 shows how some of these receptors dimerize after a drug agonist binds.

TABLE 1-1 Receptor Types, Examples, and Approximate Time Until a Noticeable Response Occurs After Receptor Stimulation

Receptor Type	Some Receptor Examples	Time
Ion channel	Nicotinic cholinergic $GABA_A$ Glycine	Milliseconds
G protein–linked	Muscarinic cholinergic Adrenergic (α and β) Opioid Histamine	Seconds
Transmembrane with cytosolic enzyme domain	Epidermal growth factor Platelet-derived growth factor Insulin	Minutes to hours
Transmembrane that binds to a separate cytosolic enzyme	Cytokines (e.g., interleukins, interferons, tumor necrosis factors)	Minutes to hours
Intracellular (nuclear target)	Thyroid Estrogen Vitamin D	Hours to days

Many forms of cancer seem to involve mutant variants of enzyme-linked receptors in which the catalytic site or associated nonreceptor protein kinase is continuously activated. Approximately half of all oncogenes discovered to date encode for continuously activated protein kinases.

Transmembrane receptors that bind to a separate cytosolic enzyme

Another type of transmembrane receptor is one that has a noncatalytic domain that activates a separate cytosolic tyrosine kinase, called Janus kinase (JAK), that phosphorylates separate cytosolic proteins. This receptor dimerizes after binding to the kinase (see Figure 1-2) and is the type of receptor to which cytokines bind (see Figure 1-1, *D*).

Intracellular receptors

Lipophilic substances capable of crossing the plasma membrane may activate intracellular receptors (see Figure 1-1, *E*). Sex steroids, mineralocorticoids, glucocorticoids, thyroid hormones, and vitamin D derivatives all activate specific nuclear receptors that influence DNA transcription. When a drug (or hormone) binds to the receptor, it folds into the active configuration and dimerizes with a partner receptor. The conformational change results in a dramatic increase in binding to specific DNA sequences. Binding of thyroid hormone to its receptor produces more than a tenfold increase in receptor affinity for binding to DNA. DNA binding of the activated receptor often initiates transcription, leading to increased production of specific proteins. Because this type of signal transduction requires protein synthesis, drugs that activate intracellular receptors typically have a delay of several hours before the onset of their pharmacologic effect. (This is the reason glucocorticoids cannot be used as primary drugs for the management of anaphylaxis.) In some systems, the binding of the drug-receptor complex inhibits transcription. Regardless of the specific mechanism involved, however, the intensity and duration of drug effect are temporally independent of its plasma concentration.

Table 1-1 indicates the relative speed of response for the various types of receptors.

In addition to these intracellular receptors, other enzymes and proteins involved in cell function and gene expression are receiving increasing scrutiny as potential targets for drug therapy. Nitric oxide, which stimulates guanylyl cyclase directly to form cyclic guanosine 3′,5′-monophosphate (cGMP), and sildenafil, which inhibits the breakdown of cGMP by cGMP-specific phosphodiesterase-5, are two examples of currently available agents acting intracellularly on regulatory enzymes. Finally, structural proteins such as tubulin, which are assembled to form microtubules, are targets for several drugs used in the treatment of cancer, gout, and fungal infections.

Drug-Binding Forces

Implicit in the interaction of a drug with its receptor is the chemical binding of that drug to one or more specific sites on the receptor molecule. Multiple bond formation often accompanies the interaction between a drug and receptor. Four basic types of binding are pictured in Figure 1-3. Drug-binding forces vary in strength. Hydrophobic binding is often very weak, whereas covalent binding can be quite strong (e.g., the acetylation of a receptor shown in Figure 1-3).

Most drugs reversibly bind to their receptors. As described in Chapter 2, the duration of action of drugs is related to how long an effective drug concentration remains in the vicinity of the drug receptors. This time may vary from a few minutes to many days, but usually it is on the order of minutes to hours. If a drug irreversibly binds to a receptor, new receptor synthesis is usually required to reverse the effect of the drug.

Structure–Activity Relationships

Examination of structure–activity relationships (SARs) is a time-honored method of studying drug–receptor interactions. In SAR investigations, specific features of the structure of a drug molecule are identified and then altered systematically to determine their influence on pharmacologic activity. SAR studies of closely related agents (congeners) led to an understanding of the chemical prerequisites for pharmacologic activity and, on a practical level, made possible the molecular modification of drugs to provide enhanced or even novel therapeutic effects, while reducing the incidence and severity of toxic reactions. In addition, SAR studies serve to illustrate how the combined action of the various binding forces described earlier are necessary for maximal drug activity. This yields certain clues concerning the physicochemical properties of the receptor sites involved that are of value to investigators seeking to unravel the exact structure of these sites. X-ray crystallography techniques have shed light on not only the structure of receptors but the different functional conformations of the receptor and their relation to drug binding. All of the drug-binding forces shown in Figure 1-3, as well as drug size and conformation(s) (see following), are important contributors to drug structure–activity relationships.

Drug Size, Shape, and Isomerism

Most clinically useful drugs are organic compounds that have molecular weights less than 1000 and greater than 100. Exceptions include drugs such as the inorganic compound lithium carbonate and some of the newer biologic proteins, which can have molecular weights in the range of 150,000. Selectivity of a drug for a receptor is dependent on the three-dimensional structure of the drug. Thus, conversion of a *cis-* to a *trans-* conformation of a drug can have dramatic effects on affinity. Optical isomers of drugs often have very different affinities for the same receptor. Norepinephrine, for instance, is supplied in a dextrorotary (*d*) and a levorotary (*l*) form. (The two are often combined.) The *l* conformation has a tenfold higher affinity for adrenergic receptors than the *d* conformation, reflecting the importance of the three-dimensional structure as seen in mirror images.

Events Following Drug Binding: Signal Transduction

The combination of a drug with its receptor represents the first event in a series of reactions that culminate in a pharmacologic effect. An

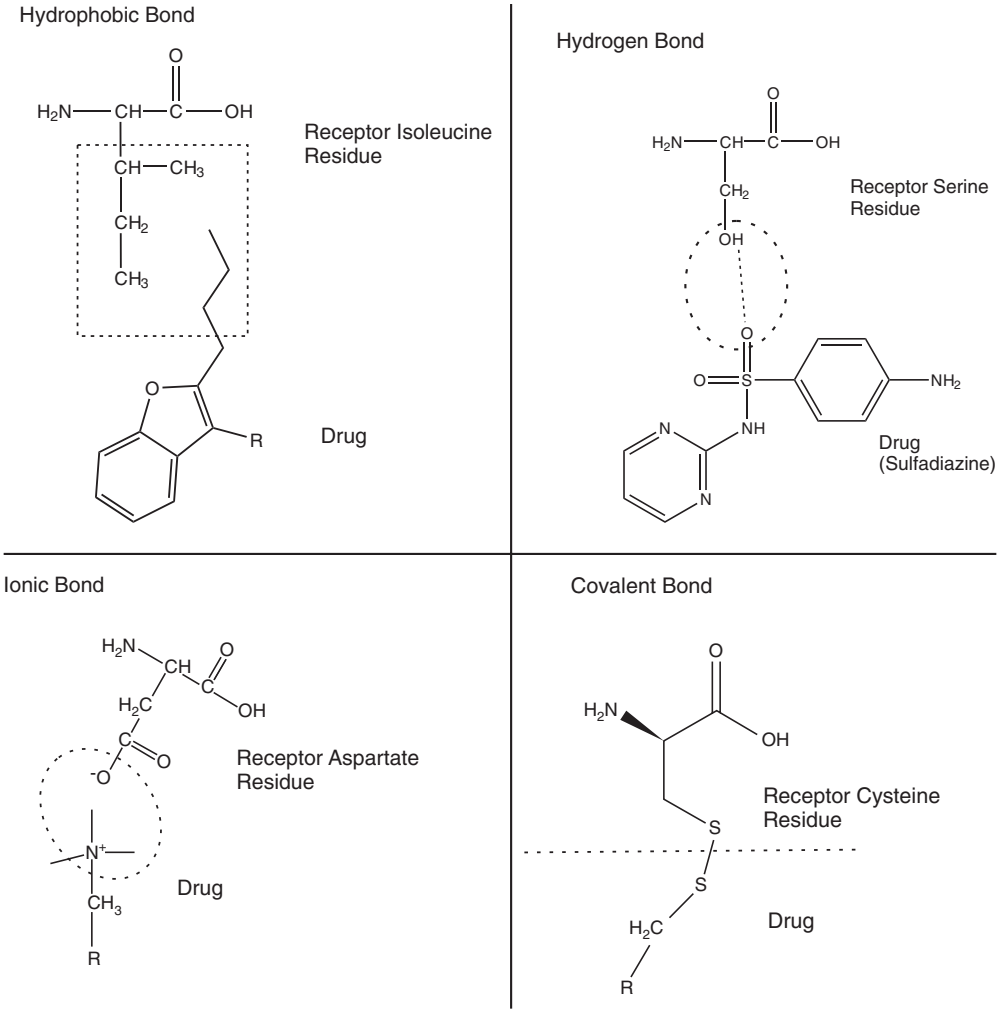


FIG 1-3 Four chemical bonds associated with drug–receptor interactions. Dotted areas indicate the region of the bonds.

important second step in this chain is the receptor response to drug binding. Drugs generally are not highly reactive compounds in the chemical sense; they exert their influences indirectly by altering, through their receptor attachment, the activity of an important regulator of a biologic process. The mechanism of action of a drug refers to this perturbation of normal function.

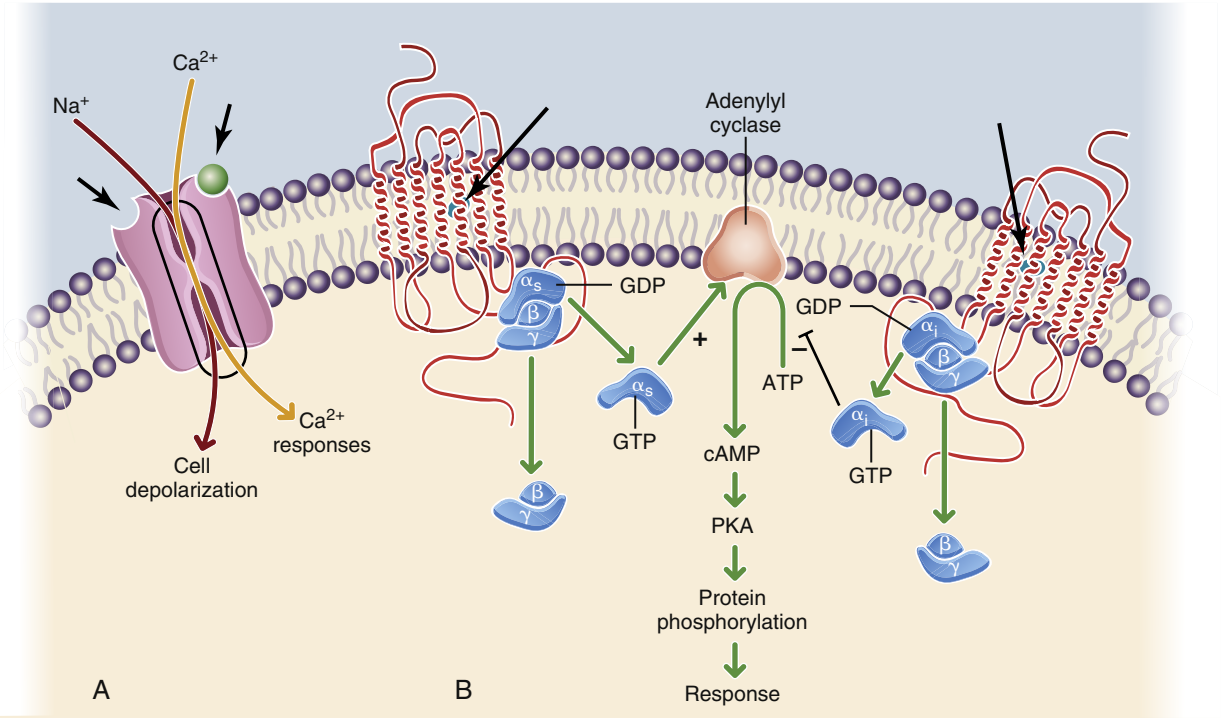
Activation of a receptor by a drug leads to a cascade of events that eventually results in an observable pharmacologic effect. These events constitute the **signal transduction pathway**, which is also called **stimulus–response coupling**. Individual receptor types have different signal transduction pathways (Figure 1-4).

Ion channel receptors

Ion channel receptors react to drugs by either increasing or decreasing their conductance. Channels are usually selective for a single ion. The increase or decrease in conductance of an ion leads to a cell event such as depolarization of the cell, hyperpolarization of the cell, or calcium signaling (see Figure 1-4, *A*). Nicotinic receptors and chloride channel receptors are examples of this class of receptors.

G protein–linked receptors

G protein–linked receptors encompass a variety of signaling pathways. G proteins are classified based on the nature of their α subunit. Three different types of G protein–coupled receptors are shown in Figure 1-4, *B* and *C*. The G protein complex is inactive when GDP is bound to the α subunit, which happens when the receptor is not stimulated by an agonist. Receptor stimulation leads to dissociation of GDP from the α subunit and the replacement binding of GTP (Figure 1-4, *B* and *C*). When this happens, the α subunit dissociates from the βγ subunit complex and then affects the activity of a nearby enzyme. In the case of $G\alpha_s$ the effect is to stimulate the enzyme adenylyl cyclase. Alpha subunits possess GTPase activity, which allows the G protein subunits to reassociate and return to an inactive state when the receptor is no longer stimulated. The activated function of adenylyl cyclase is to convert ATP to cyclic AMP (cAMP), which leads to activation of cAMP-dependent protein kinases (PKA) and resulting cell changes. The opposite effect, (i.e., inhibition of adenylyl cyclase) occurs when a different type of G protein–linked receptor releases α_i, bound to GTP. A third type of G protein–linked receptor involves the release of α_q. $Alpha_q$ activates phospholipase C (PLC), which converts phosphatidylinositol-bisphosphate (PIP_2) to inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). Both are important for calcium signaling. IP_3 causes the release of calcium from intracellular stores, and DAG stimulates protein kinase C (PKC). In several cases the βγ subunit also participates in signal transduction, for instance, by affecting ion channels. Drugs that act through α_s are said to act through G_s (the G protein containing α_s) and include drugs that stimulate the β-adrenergic receptor. Likewise, drugs that act through G_i include drugs



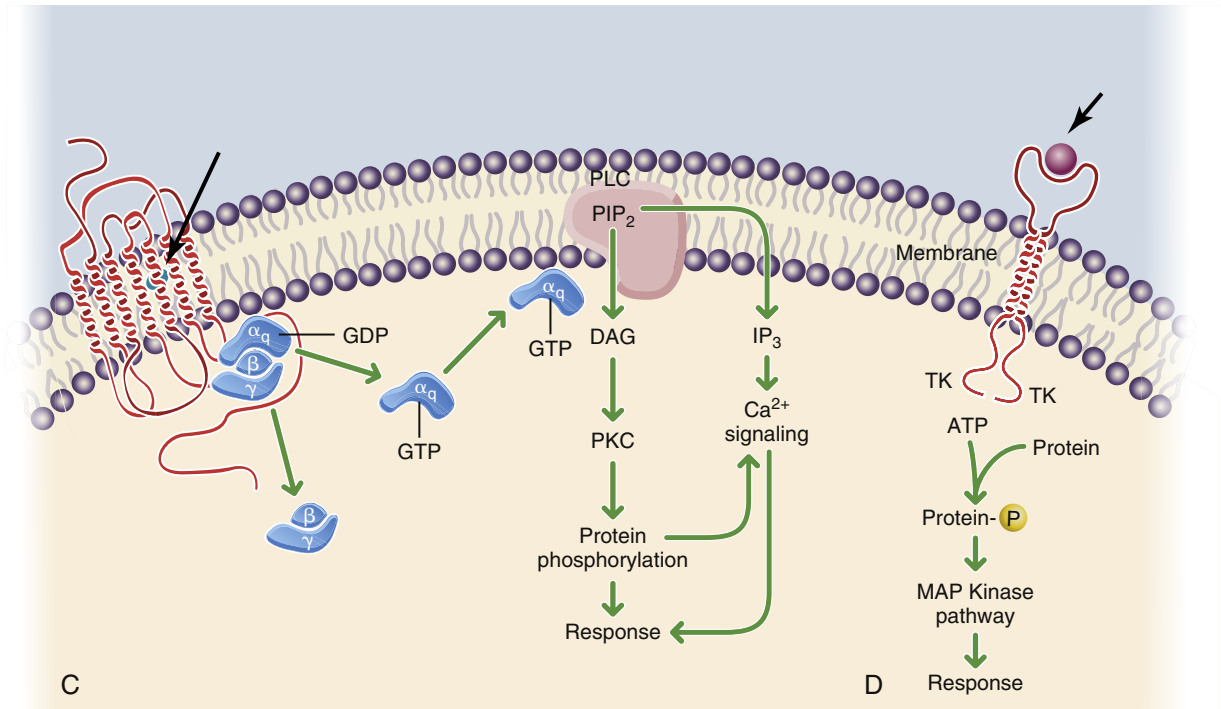


FIG 1-4 Signal transduction pathways. **A**, Ion channel receptors react to drugs by either increasing or decreasing their conductances. Although the conductances for Na^+ and Ca^{2+} are shown in the same channel, typically channels are more selective for one type of ion. Channels vary as to their selectivity for cations or anions. Drug-binding sites are indicated by *arrows* on either side of the channel. **B and C**, Three different types of G protein–coupled receptors are shown: receptors coupled to G_s, G_i, and G_q. The pathways are explained in the text. *Arrows* indicate the sites of drug binding on the receptor. *GDP*, Guanosine diphosphate; *GTP*, guanosine triphosphate; *PLC*, phospholipase C; *PIP_2*, phosphatidylinositol-bisphosphate; *IP_3*, inositol 1,4,5-trisphosphate; *DAG*, diacylglycerol; *PKA*, cyclic AMP-dependent protein kinase; *PKC*, protein kinase C. **D**, Transmembrane receptors that have enzymatic cytosolic activity. In the example given, tyrosine kinase causes the phosphorylation of a separate substrate (as well as autophosphorylation, not pictured). *TK*, Tyrosine kinase.

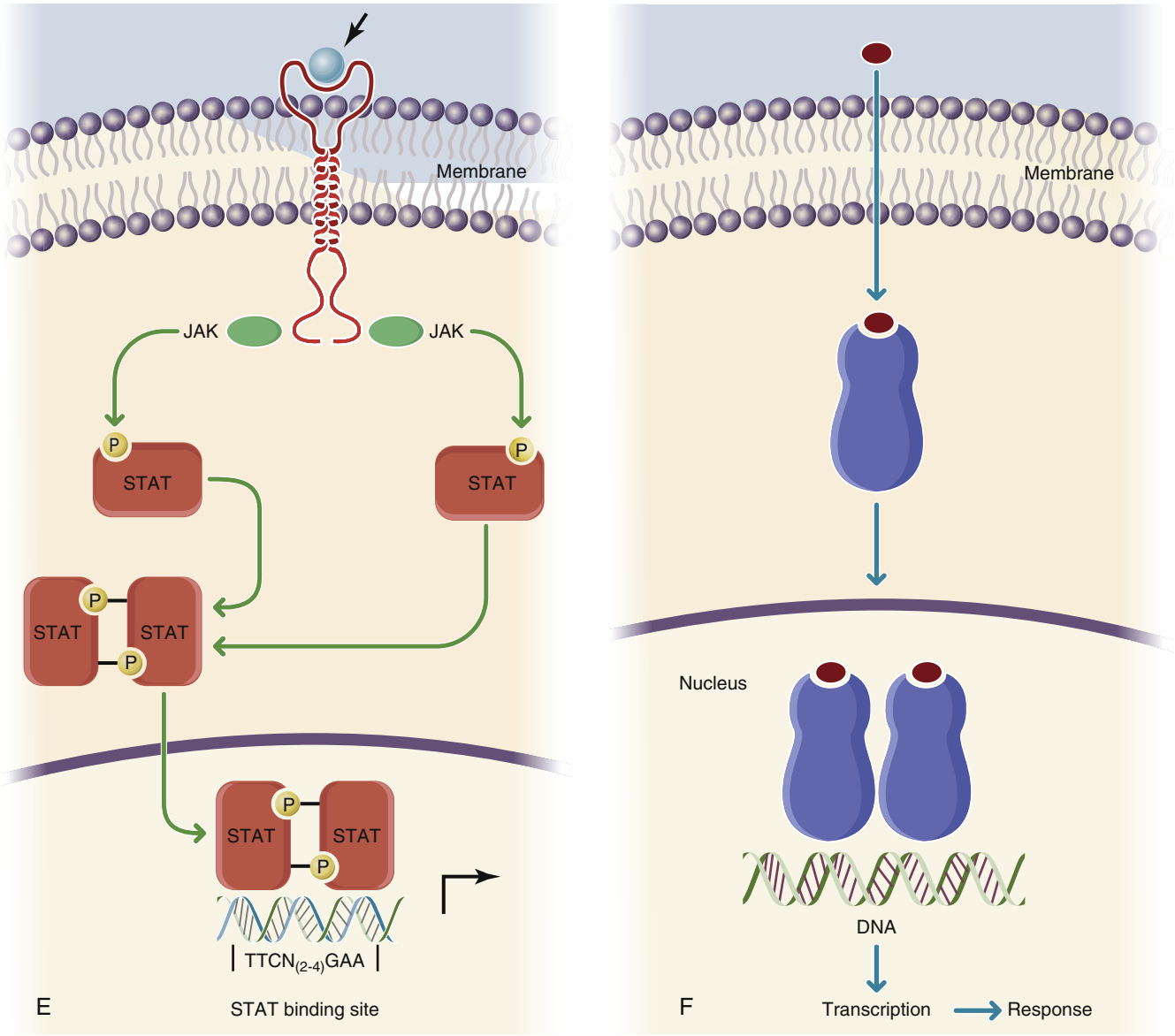


FIG 1-4, cont'd **E**, Transmembrane receptors resembling those that have enzymatic activity (e.g., tyrosine kinase) but are lacking enzymatic activity on the receptor. A separate cytosolic tyrosine kinase, JAK, is shown, which causes phosphorylation of STATs. Activated STATs dimerize and migrate to the nucleus to induce transcription. $TTCN_{2-4}GAA$ is the DNA consensus binding element for STAT. *JAK*, Janus kinase; *STAT*, signal transducer and activator of transcription. **F**, Nuclear receptors. Drugs (*dark ovals*) bind to receptors in the cytoplasm; the complex translocates to the nucleus and causes changes in transcription.

that stimulate the α_2-adrenergic receptor. Drugs that act through G_q include those that stimulate the muscarinic cholinergic receptor.

Epinephrine provides a useful illustration of the complex downstream consequences of drug binding. Incorporated into local anesthetic solutions to prolong the duration of pain relief, epinephrine mimics the action of the neurotransmitter norepinephrine. As a result of epinephrine attachment to α_1-adrenergic receptors on vascular smooth muscle cells, the G protein known as G_q is activated, phospholipase C_β activity is stimulated, and the membrane lipid phosphatidylinositol-4,5-bisphosphate is broken down to yield the second messengers diacylglycerol and inositol-1,4,5-trisphosphate (IP_3). Diacylglycerol initiates a cascade of metabolic events that support muscle contraction. IP_3 causes the release of Ca^{2+} from intracellular storage sites, which induces the activation of actomyosin and initiates vasoconstriction.

Transmembrane receptors that have enzymatic cytosolic activity

Insulin and several growth factors act through this type of receptor. Enzymatic activity on the cytosolic aspect of the receptor catalyzes changes that lead to the characteristic cell changes. In the example given in Figure 1-4, *D*, after insulin binds extracellularly, intracellular tyrosine kinase causes the phosphorylation of a separate substrate (as well as autophosphorylation, not pictured). Activation of several subsequent pathways such as the MAP kinase pathway follows, leading to further changes such as transcription in the nucleus.

Transmembrane receptors that bind to a separate cytosolic enzyme

Various cytokines act through these receptors. These receptors require a separate cytosolic tyrosine kinase to complete their function as receptors (see Figure 1-4, *E*). Typically, this enzyme is a JAK, which phosphorylates a group of proteins called signal transducers and activators of transcription (STATs). Activated STATs dimerize and migrate to the nucleus to induce transcription of selective genes. As can be surmised, many other steps are involved in the complex array of secondary signaling pathways.

Intracellular (nuclear) receptors

Steroid hormones, vitamin D, and thyroid hormone act through this type of pathway. Drugs that bind to these receptors diffuse into the cell and bind to intracellular receptors (see Figure 1-4, *E*). Dimerization with a co-receptor protein usually occurs after drug binding, followed by movement of the entire complex into the nucleus and induction of transcription of selective genes by binding to specific response elements (promotors/enhancers) on the DNA. Other steps are involved in the signaling pathways, and several other proteins, including co-activators and co-inhibitors, are involved in shaping the final transcription process.

CONCENTRATION–RESPONSE RELATIONSHIPS

A fundamental aspect of drug action is the relationship between the dose administered and the effect obtained. As one would expect, the magnitude of a chemical's effect on a system is positively correlated with the quantity or concentration of that chemical. For example, to increase the saltiness of a food, more salt must be added. Within certain limits, the addition of salt yields a graded and (nearly) linear response. However, with repeated additions of salt, the increase in saltiness becomes less and less until finally, further additions do not increase the sensation of greater saltiness. The dose–effect relationship of a drug is similar and is not a linear function throughout the entire dose range. Below a minimum threshold, there will be no observable effect. Above a certain ceiling, even a large dose would exert no additional effect because the maximal effect has already been reached.

Occupation Concept

Clark attempted in the 1920s to quantify drug effects through application of the law of mass action. Out of his efforts, and the contributions of others, emerged the occupation concept of drug action. The occupation concept holds that the magnitude of a pharmacologic response elicited by a drug that reversibly combines with its receptor is directly proportional to the number (or fraction) of receptors occupied by the drug. The relationship can be written as follows:

$$D + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} DR \rightarrow \text{Effect}$$

where *D* is the drug, *R* is the receptor, and k_1 and k_2 are rate constants. At equilibrium $k_2/k_1 = K_d$ (the dissociation constant). The $\boldsymbol{K_d}$ is a measure of the **affinity** of the drug for the receptor: the smaller the K_d, the greater the affinity.

After binding (DR) has occurred, an effect (*E*) follows, usually after several intervening signal transduction steps following binding, as described earlier. These intervening steps are represented by a single arrow in the preceding equation. A derivative of the Michaelis-Menton equation can be used to quantify drug effects as follows:

$$E = \frac{E_{max} \times [D]}{K_d + [D]}$$

(where E_{max} = maximal effect or ceiling effect)

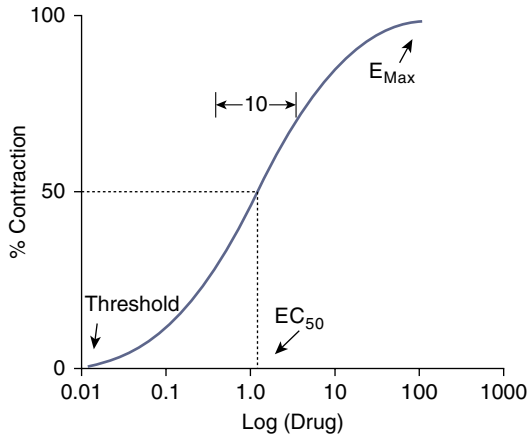


FIG 1-5 Theoretical concentration-response curve (log scale) for a smooth muscle stimulant. As shown, the linear portion of the sigmoid curve, extending from approximately 25% to 75% of the maximal effect, is encompassed by a tenfold concentration range. A range of 10,000 times is required, however, to depict the curve in its entirety (from 1% to 99% of the maximal effect). The concentration yielding 50% of the maximal response (EC_{50}) is also shown. E_{max}, ceiling effect = intrinsic activity.

Based upon this equation, the effect of the drug is predictably and quantitatively dependent on the drug concentration. Moreover, a geometric relationship (rectangular hyperbola) exists when graphing E versus [D]. The drug concentration is usually expressed in $\log_{10}$ units. This mathematic relationship between the concentration of a drug and its response may be shown visually by an experiment in which an isolated muscle is exposed to increasing concentrations of a drug while the force of contraction is measured (Figure 1-5).

When a drug is introduced into a tissue, it binds to its receptor in accordance with the K_d for that drug at that receptor. Each muscle cell may require a minimal number of receptors to be occupied before it contracts. The lowest concentration to elicit a measurable response is termed the **threshold concentration**. As higher concentrations are used, the number of receptors occupied increases, as does the intensity of response. An increase in the fraction of receptors occupied necessarily reduces the number available for subsequent binding so that at high concentrations each increment of drug produces progressively smaller additions to the magnitude of contraction. At very high concentrations, the receptor population becomes saturated, and further drug administration no longer influences contraction. A maximal muscle response for the drug, termed the **ceiling effect**, or $\boldsymbol{E_{max}}$, is achieved.

The useful concentration range for a drug falls between the threshold and the ceiling (E_{max}). By expressing data as the logarithm of the concentration versus the degree of response, this important and normally hyperbolic segment of the concentration–effect relationship becomes a sigmoid curve with the linear central portion typically extending over a tenfold concentration range. The concentration of a drug that produces a half-maximal response ($\mathbf{EC_{50}}$) is often used to compare potencies of various drugs. The EC_{50} depends in part on the K_d, but it is not necessarily equal to the K_d. When data from several experiments are expressed on a single graph with the log concentration of the drug, this value can be accurately determined for each drug from the linear portion of the respective curve. Notice that the log concentration of the drug is plotted against a graded response in the tissue. A graded response is one in which the magnitude of the response increases incrementally as the drug concentration is increased. The curves generated are therefore called **graded log concentration**

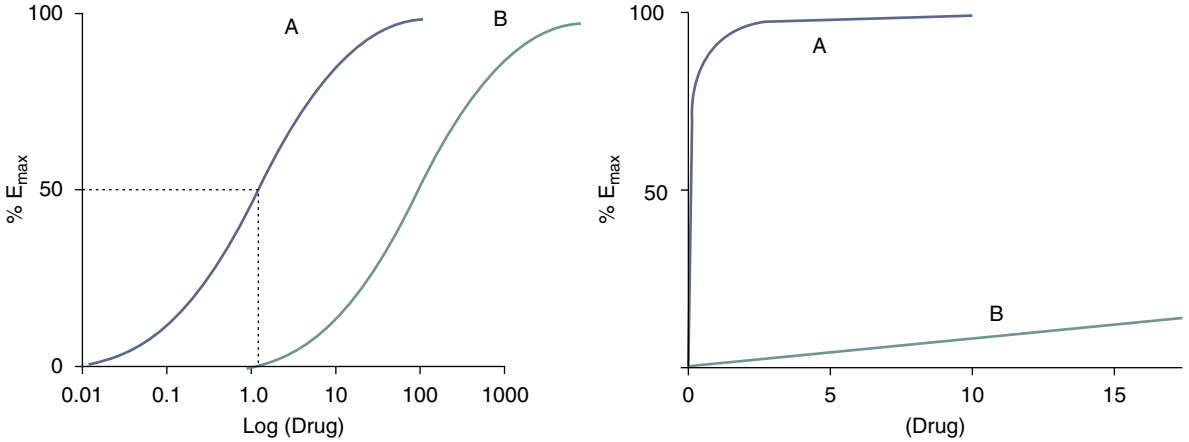


FIG 1-6 Concentration-effect curves for two drugs differing in receptor affinity by a factor of 100. *Left*, A log scale. Note the identical shapes of the two concentration–effect relationships. *Right*, An arithmetic scale. The lack of correspondence between the two curves hinders the drug comparison of the two drugs. Note that the units on the ordinate are percentages of E_{max}.

response curves. If the concentration data were not logarithmically transformed, graphical analysis would become more complex. Figure 1-6 illustrates the difficulties encountered if two drugs differing only in receptor affinity are examined on an arithmetic scale. The curve for drug A is so compressed that the concentration yielding the EC_{50} cannot be easily ascertained; for drug B, it cannot even be represented on the same page.

Agonists

Drugs, or other ligands, that bind to a receptor and elicit a response from a tissue are known as **agonists**. Agonists that produce ceiling effects—effects that are not exceeded by other drugs—are called **full agonists**, and drugs whose maximal effects are less than those of full agonists are referred to as **partial agonists**. The distinction between full and partial agonists is unrelated to differences in receptor affinity; rather, it is due to differences in their abilities to activate signal transduction changes after binding. The difference between these two classes of agonists lies in their unequal **intrinsic activities**. E_{max} is the measure of the **intrinsic activity** of a drug. Intrinsic activity is the ability of a drug to activate a receptor after the drug–receptor complex has formed. Incorporating intrinsic activity into the concentration- effect equation yields:

$$E = \text{intrinsic activity} \cdot \frac{E_{max}[D]}{K_d + [D]}$$

Thus, drugs with a low intrinsic activity are **partial agonists**. The log concentration-response curve of a partial agonist has a lower maximum and a reduced slope compared to that of a full agonist (Figure 1-7).

Two drugs (A and B) with the same intrinsic activity are shown in Figure 1-7, in which two agonists of muscle contraction are compared. The muscle was removed from the animal, placed in a bath containing an oxygenated physiologic salt solution, and attached to a strain gauge to measure contractions. In such experiments, conditions can be manipulated to ensure that each drug tested has equal access to the receptor in question. This condition greatly simplifies the interpretation of experimental results and cannot readily be duplicated in whole-animal investigations.

In addition to intrinsic activity, one other term is important in Figure 1-7: **potency**. Potency is the concentration (or dose) of the drug needed to achieve a given level or amount of response. The potency of drugs is reflected in their position on a concentration-response curve; the further

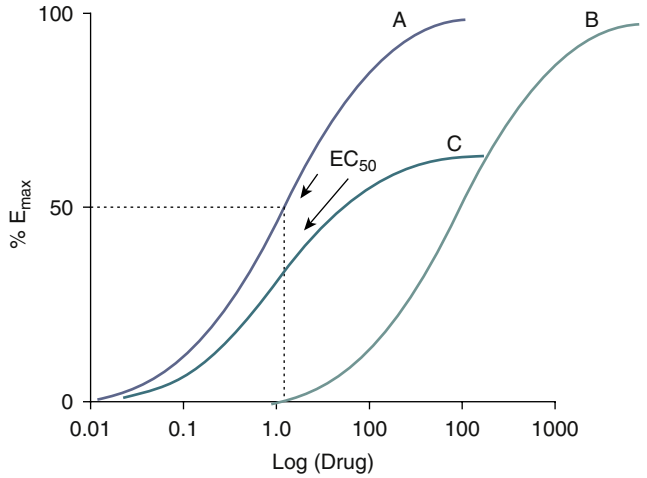


FIG 1-7 Theoretical concentration-response curves for three agonists acting at the same receptor. Drugs A and B have the same intrinsic activity (E_{max}), but B has less potency than A. Drug C has a lower intrinsic activity than either A or B, but it has the same potency as drug A (as measured by the EC_{50}.).

to the left the drug response curve lies, the more potent the drug. The potency of a drug is usually expressed as the concentration of the drug required to achieve a half-maximal stimulation of the response ($\mathbf{EC_{50}}$). The lower the EC_{50}, the greater the potency. In Figure 1-7, drug C has a lower intrinsic activity than either A or B; however, its potency is the same as that of drug A (because the EC_{50} values for both A and C are equal). The potency of drug C is greater than that of drug B. Because drug C has a lower intrinsic activity than either drug A or B, drug C is termed a **partial agonist**.

The terms affinity, intrinsic activity, and potency are conceptualized in Figure 1-8. This figure shows the equation linking a drug to an effect, and how affinity, intrinsic activity, and potency are related. Potency is related to affinity but is not the same as affinity. Affinity relates only to binding to a receptor; potency requires binding and achieving a response. Clinically however, the potency of a drug is also influenced by additional factors such as the drug's ability to reach the receptor (determined by the rate of absorption and the patterns of distribution and elimination). Since the concentration of a drug at the receptor is not known, clinical potencies are based on dose and are usually measured as the $\mathbf{ED_{50}}$ (effective dose to achieve 50% of the maximal response).

Notice that the term affinity relates only to the binding of the drug to its receptor, whereas intrinsic activity and potency **encompass both binding and subsequent signal transduction events leading to a response. Full agonists** are those that have an E_{max} that is the highest for any agonist at that receptor. **Partial agonists** have lower E_{max} values and therefore have lower intrinsic activity.

Figures 1-5, 1-6, and 1-7 show tissue responses to drugs and therefore are the types of graphs from which intrinsic activity and potency can be derived. On the other hand, the K_d of a drug is derived solely from binding data such as that obtained from a radioligand binding experiment, in which experiments are conducted using a radiolabeled drug in the presence of a receptor. Analysis of responses to drugs is often complicated by the fact that more than one drug molecule may bind simultaneously to a given receptor, one binding event may influence another, and the pharmacologic response may not be proportional to the number of receptors occupied by an agonist.

Indirect agonists

The discussion about agonists (full or partial) has to this point been about drugs that act directly on receptors: **direct agonists**. **Indirect agonists** are those that increase the level of direct agonists often by reducing the rate of metabolism of the direct agonist. A good example is the use of cholinesterase inhibitors to increase endogenous levels of acetylcholine, thereby increasing the effect of acetylcholine at its receptors.

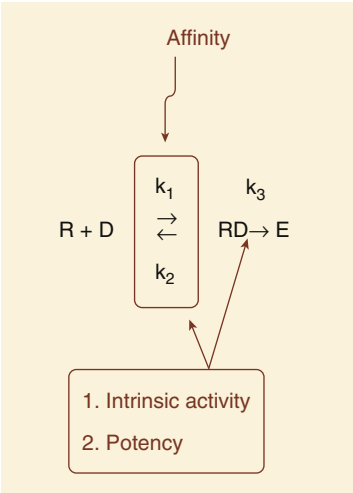


FIG 1-8 Depiction of drug characteristics. Affinity relates solely to drug binding, whereas intrinsic activity and potency encompass both binding and the events that follow leading to an effect.

Antagonists

Drugs that inhibit the effects of agonists are called **antagonists**. Pure antagonists have an intrinsic activity of zero because they bind to receptors but do not activate signal transduction pathways. Antagonists that bind reversibly to a receptor at the same site as the agonist are **competitive antagonists**. By making receptors less available for agonist binding, a competitive antagonist depresses the response to a given dose or concentration of agonist. The result is a parallel shift to the right of the agonist concentration-response curve (see Figure 1-9). An important aspect of this type of inhibition is that it is completely surmountable by a sufficiently high concentration of agonist. The presence of a competitive antagonist produces an apparent reduction in the affinity of an agonist for its receptor. The affinity of a competitive antagonist is measured as the K_i, which is equivalent to the K_d for an agonist. Competitive antagonists are common in pharmacology, and numerous examples are cited in succeeding chapters: antihistamines versus histamine, naloxone versus morphine, propranolol versus epinephrine, to name a few. By virtue of its small intrinsic activity, a partial agonist can also serve as a competitive antagonist of a full agonist. The aggregate receptor–stimulated event from the combination depends on the relative drug concentrations, receptor affinities, and intrinsic activities of the two agents.

Another type of antagonism commonly encountered is **noncompetitive**. The noncompetitive blockade is insurmountable in that the ceiling effect of an agonist can never be reattained, regardless of the concentration of the agonist that is administered. One way a noncompetitive antagonist can act is to decrease the effective number of receptors by irreversibly binding to the receptor site. The result of noncompetitive inhibition is a downward displacement of the agonist log concentration-response curve. Figure 1-9 reviews the dissimilarities between the two classic types of drug blockade. Competitive antagonists increase the EC_{50} of the agonist but do not affect the intrinsic activity of the agonist. Noncompetitive antagonists decrease the apparent intrinsic activity of the agonist with little effect on its EC_{50}.

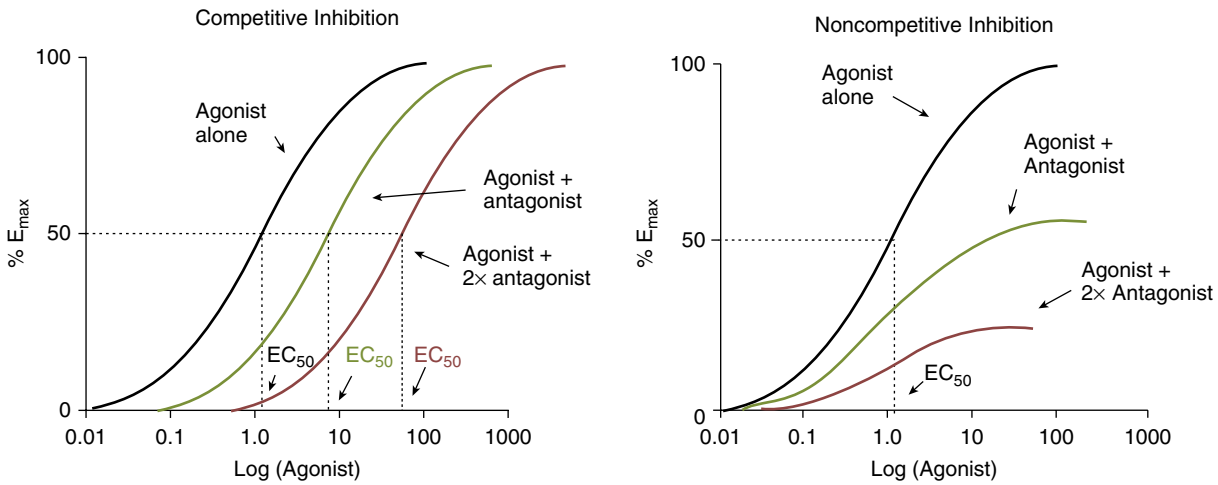


FIG 1-9 Effect of drug antagonism on a concentration response profile of an agonist. The left panel shows the effect of a competitive antagonist. Note that the EC_{50} values for the agonist increase with increasing concentrations of the antagonist. The right panel shows the effect of a noncompetitive antagonist. Note that the EC_{50} values for the agonist do not change with the antagonist.

Allosteric effects

Drugs that bind to receptors and affect the function of the receptor but do so at a site that is different from the usual ligand are said to act at an **allosteric** site. Drugs that act allosterically can either increase or decrease the receptor response. Allosteric inhibitors are another mechanism of noncompetitive inhibition.

Spare receptors

It is quite common for full agonists to achieve their maximal effect without occupying all of the relevant receptors of a cell. This is because extra receptors are present. This phenomenon is called the **spare receptor** concept or **receptor reserve**. It is demonstrated experimentally by achieving the E_{max} at a concentration of a drug that does not bind all of the receptors. It is also demonstrated by the effect of a noncompetitive antagonist. Instead of the predictable decrease in E_{max} when the noncompetitive antagonist is added, there is a shift to the right of the agonist response curve until all spare receptors have been bound by the noncompetitive antagonist. At that point, adding more antagonist generates the predictable decrease in E_{max} of the agonist.

Receptor Diversity

In addition to the fact that pharmacologic responses are often not linearly related to receptor occupancy, situations exist in which the receptors for a drug are not identical to one another. A repeating theme in the elucidation of the autonomic nervous system has been the division of receptor classes into an increasing array of types and subtypes with differing drug sensitivities. Part of the explanation for the unusual pharmacology of tamoxifen was made clear by the discovery that there were two subtypes of estrogen receptors in various tissues that responded differently to this agent. Individuals may even harbor differences in receptor structure based on single point mutations. An important example is the β_2-adrenergic receptor, for which numerous single nucleotide polymorphisms have been identified that may alter drug responsiveness in diseases such as asthma.

Pharmacodynamic Tolerance

The preceding discussion of concentration–response relationships is further complicated by the fact that the drug effect on the receptor can change with the passage of time. **Pharmacodynamic tolerance** is a general term for situations in which drug effects dissipate with time despite the continued presence of the agonist at a fixed concentration. At the receptor level, various processes in addition to the primary drug effect are often invoked that subsequently limit pharmacologic responses. In the case of the β-adrenergic receptor, phosphorylation of specific amino acid constituents leads to a loss of drug action or a large decrease in drug response, a process termed **desensitization** (Figure 1-10).

The loss of drug action can be measured by a lack of increase in cyclic AMP or some other reduction in the signaling pathway. In this example, agonist-induced phosphorylation by a G protein–coupled receptor kinase (*GRK*) of the β-adrenergic receptor induces binding of a protein, β-arrestin, which prevents the receptor from interacting with G_s. Removal of the agonist for a short time (e.g., several minutes) allows dissociation of β-arrestin and removal of phosphate from the receptor by phosphatase, resulting in restoration of the receptor's normal responsiveness to the agonist. A separate mechanism, internalization, can occur in which endocytotic membrane trafficking of the receptors takes place. This is also promoted by β-arrestin and takes place after longer exposure to an agonist. After internalization, receptors can either be shuttled back to the plasma membrane or destroyed by lysosomal enzymes. Internalization accounts for **downregulation** of the receptors.

Pharmacodynamic tolerance may also occur independently of any change in the drug receptor or stimulus–response system. As an illustration of this point, consider a drug that increases blood pressure by causing vasoconstriction in selected vascular beds. In response to the increase in blood pressure, various cardiovascular reflexes are evoked that reduce blood pressure, including activation of the parasympathetic nervous system, which causes bradycardia. The buildup of lactate and other metabolites in the affected tissues also limits vasoconstriction. Eventually, additional changes, such as decreased salt and water retention, may also reduce drug-mediated increases in blood pressure responses even further. These and other mechanisms of drug tolerance are described more fully in Chapter 3.

Multistate Model of Drug Action

Receptors may exist in more than one conformation. According to the multistate model of drug action, these forms of receptors are in equilibrium, and drugs act by altering their relative distributions. Figure 1-11 illustrates a simple two-state version in which the receptor can exist in an active or inactive conformation.

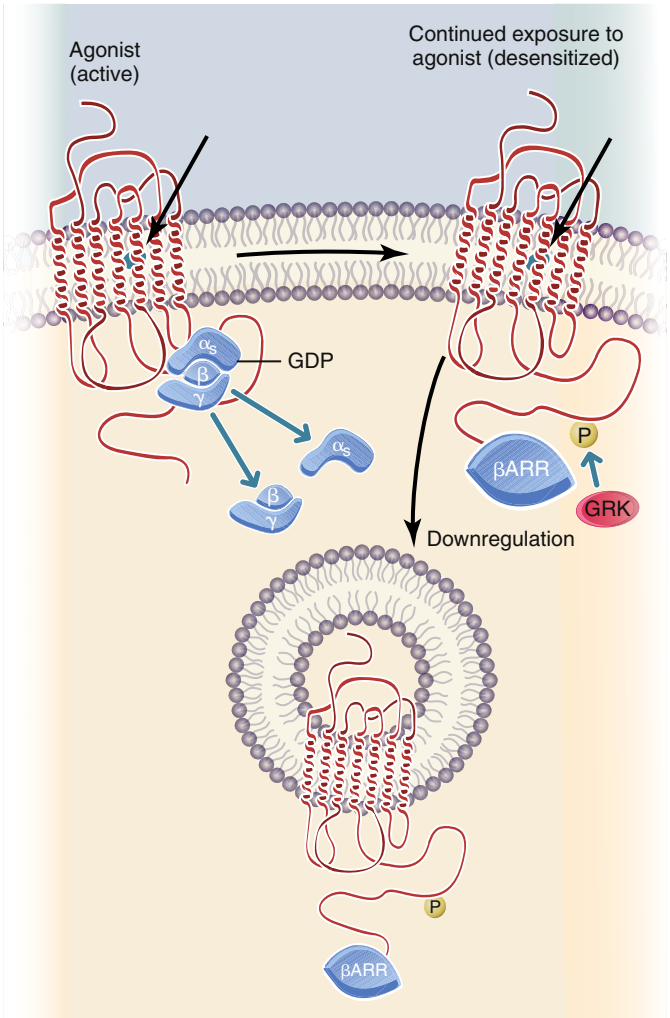


FIG 1-10 Rapid desensitization and long-term downregulation of the β-adrenergic receptor. Both events lead to a lack of a response when the receptor is stimulated by an agonist. *GDP*, Guanosine diphosphate; *GTP*, guanosine triphosphate; Ⓟ, phosphorylation on carboxyl terminal hydroxyl groups; *GRK*, G protein–coupled receptor kinase; *βARR*, β-arrestin which prevents the receptor from interacting with G_s. Refer to text above for further details.

In this model, full and partial agonists increase the proportion of receptors that exist in the active state. Receptors, in the absence of a ligand, tend to be in the inactive state. The degree to which they exist in the active state without an agonist corresponds to a level of activity which is called **constitutive activity**. Drug agonists bind to the receptor, converting the receptor to the active state. This is reflected in the difference in sizes of the reaction arrows (see Figure 1-11). Partial agonist binding produces an insufficient active form of the receptor to yield a maximal response (Figure 1-12). Competitive antagonists associate with receptors regardless of—and without influencing—their conformational state. Therefore Figure 1-12 shows no change in the active form of the receptor as a result of binding of a competitive antagonist. Noncompetitive antagonists limit the ability of agonist binding to elevate the number of receptors in the active state by reducing the total number of available receptors.

The major attractions of the multistate model are that it gives a solution for differences in the magnitude of the response between structurally related drugs, and that it affords a simple mechanism for the pharmacologic response elicited by drug binding. It also provides an explanation for drugs known as **inverse agonists**. An inverse agonist causes an effect opposite to that of the agonist, in contrast to a competitive antagonist, which simply blocks the agonist (or the inverse agonist) but has no inherent effect by itself (see Figure 1-12). In a tonically active pathway, in which the receptor has constitutive activity (without drug), a drug that preferentially binds to the inactive configuration or induces its formation would behave as an inverse agonist. In other words, inverse agonists inhibit endogenous activity of a receptor. For example, flumazenil, a competitive antagonist of the benzodiazepine receptor, reverses the effects of both agonists and inverse agonists. Additional examples of inverse agonism have been shown for various G protein–coupled receptors overexpressed in cells experimentally or after neoplastic transformation. Inhibition of constitutionally active oncogenes by inverse agonists may provide a new strategy for cancer chemotherapy.

A final advantage of the multistate model is that it can accommodate desensitization and time-dependent actions of drugs such as nicotine. Nicotine exhibits a complex pharmacologic profile. Initially, this natural alkaloid acts like an agonist: it stimulates ACh receptors at autonomic ganglia and in skeletal muscle. The stimulation is temporary, however, and in minutes the action of nicotine transforms from that of excitation to one of antagonism. This metamorphosis can be adequately explained if one assumes that a third, or "desensitized," configuration of the receptor exists to which active receptors are slowly converted and from which they even more slowly recover. Nicotine, by increasing the proportion of active receptors, causes an initial stimulation and a subsequent prolonged loss of activity as receptors are progressively trapped in the desensitized state. Ion channel desensitization is a different mechanism of desensitization from that depicted in Figure 1-10.

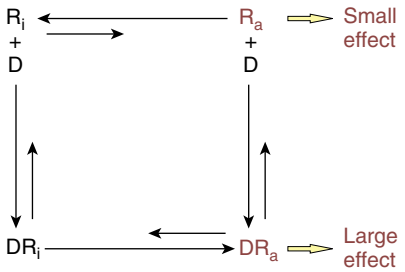


FIG 1-11 Two-state model of drug–receptor interaction. The receptor can exist in an active (R_a) or inactive (R_i) state. Unless the receptor mediates a tonically active process, without any drug, only the inactive state is present. Drugs (D) may bind to R_a, R_i, or both. Agonist binding favors the formation of DR_i and DR_a. The ratio of DR_a/DR_i influences the degree of response to the drug. The level of R_a corresponds to the degree of constitutive activity of the receptor.

RECEPTOR-INDEPENDENT DRUG ACTIONS

No description of drug action would be complete without a consideration of agents that exert pharmacologic effects through receptor-independent mechanisms. Aside from the fact that these drugs act without the benefit of receptor intermediaries, there are no common traits serving to link this miscellaneous array of compounds. It has also proved impossible to derive a quantitative description of drug responses akin to that presented for receptor-based agents. The very diversity of these drugs precludes any unifying relationship between concentration and effect. Nevertheless, concentration-effect curves similar to those previously discussed are often obtained with these drugs, and general concepts such as potency and efficacy still apply. For the sake of discussion, these drugs are grouped arbitrarily into three categories: chemically reactive agents, physically active agents, and counterfeit biochemical constituents.

Chemically Reactive Agents

Chemically reactive drugs include a wide variety of compounds, some of which interact with small molecules or ions, whereas others attack proteins and other macromolecules. Gastric antacids and metallic ion chelators are two kinds of drugs that combine with inorganic substances within the body. Of particular importance to dentistry are the systemic and topical fluorides used to increase tooth resistance against dental caries. Also of interest is dimercaprol, a chelating agent capable of forming coordination complexes with mercury and other heavy metals. Drugs affecting macromolecules

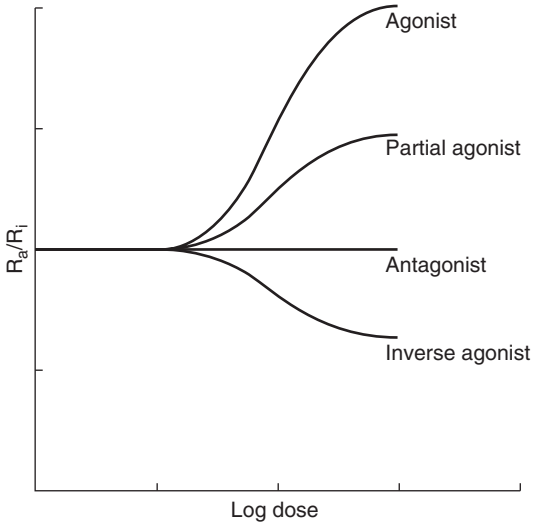


FIG 1-12 Concentration–effect relationships according to the two-state model. In this example, a tonically active process (constitutive activity) is depicted. Full agonists give the maximal ratio of active to inactive receptors (R_a/R_i). Notice that what is being plotted is the log concentration of the drug versus the ratio, R_a/R_i. Partial agonists also increase the ratio, but to a lesser degree. Antagonists bind without disturbing the existing R_a/R_i ratio, and inverse agonists exert an opposite effect by reducing the R_a/R_i ratio and inhibiting a normally partially active pathway. In this example, all the drugs are assumed to have the same receptor affinity.

include most germicides and the antineoplastic alkylating agents. Sodium hypochlorite solutions provide antisepsis and facilitate canal debridement during endodontic therapy because they release hypochlorous acid, a potent chemical disrupter of biologic matter. Generally, these compounds can be readily distinguished from drugs whose effects are receptor mediated. With the exception of certain chelating agents, they lack specificity and may individually react with various substances, organic or otherwise. Minor structural modifications also do not usually influence activity of these drugs. Finally, the reactions of these drugs rely heavily on covalent bonding or on strong ionic attachments; they do not usually depend on hydrophobic or weak electrostatic interactions.

Physically Active Agents

Physically active agents, in contrast, are often useful therapeutically because they are chemically inert and can safely be used for their colligative properties. Magnesium sulfate is an effective cathartic because it is not absorbed from the gastrointestinal tract and exerts an osmotic effect, causing retention of large amounts of water within the intestinal lumen. The colon becomes distended and is stimulated to undergo expulsive contraction. Through a similar osmotic mechanism, mannitol helps reverse cerebral edema in a patient with traumatic brain injury. A totally unrelated physical mechanism is evoked by hydrogen peroxide. Although highly reactive, hydrogen peroxide is useful in wound debridement because of its effervescent action. The release of gas bubbles promotes the physical removal of debris from injured tissues.

The physically active agents generally exhibit a surprising lack of structural specificity. For many agents, the major requirements for activity seem to be a certain pharmacologic inertness coupled with the ability to be administered in high concentrations (compared with most other drugs) without causing undue toxicity.

Counterfeit Biochemical Constituents

Counterfeit biochemicals are those that are incorporated into specific macromolecules by the cell. They are artificial analogues of natural substrates. The resulting drug effects arise from an altered biologic activity of the affected macromolecules or from their increased susceptibility to destruction. The 2′-deoxycytidine analogue cytarabine is representative of this group. When incorporated into a cell's DNA, cytarabine inhibits the reparative and replicative functions of DNA polymerase. Affected cells may undergo apoptosis or terminal differentiation. Agents of this type are used therapeutically in the treatment of several neoplasias and microbial infections.

CASE DISCUSSION

Salmeterol is an agonist at β_2-adrenergic receptors. By stimulating these receptors, it causes bronchodilation. Salmeterol is used chronically and has a long duration of action. Rescue inhalers act on the same receptors but are more effective in providing a quick and more pronounced effect than salmeterol. However, repeated administration of a rescue inhaler can cause these receptors to desensitize and downregulate, a mechanism discussed earlier. This results in a reduced ability of the drug to cause bronchodilation, which is one reason there is the warning against overuse of the rescue inhaler. The warning against overuse of salmeterol is based on a similar but less pronounced effect on the β_2-adrenergic receptors. Therefore, a glucocorticosteroid (e.g., fluticasone) is usually given with salmeterol to reduce the risk of a breakthrough asthma attack. Nonetheless, salmeterol administration needs to be given for as limited duration as possible.

GENERAL REFERENCES

1. Ariëns EJ, Simonis AM, van Rossum JM: Drug-receptor interactions: interaction of one or more drugs with one receptor system. In Ariëns EJ, editor: *Molecular pharmacology: mode of action of biologically active compounds*, New York, 1964, Academic Press.
2. Bhattacharya S, Hall SE, Li H, et al.: Ligand-stabilized conformational states of human β2 adrenergic receptor: insight into G-protein-coupled receptor activation, *Biophys J* 94:2027–2042, 2008.
3. Clark AJ: The reaction between acetyl choline and muscle cells. Part II, *J Physiol* 64:123–143, 1927.
4. Heng BC, Aubel D, Fussenegger M: G Protein-coupled receptors revisited: therapeutic applications inspired by synthetic biology, *Annu Rev Pharmacol Tox* 54:227–249, 2014.
5. IUPHAR/BPS Guide to Pharmacology (contains receptor classifications and nomenclature) (on the web) http://www.guidetopharmacology.org/ (accessed 2015).
6. Katritch V, Cherezov V, Stevens RC: Diversity and modularity of G protein-coupled receptor structures, *Trends Pharmacol Sci* 33:17–27, 2012.
7. Kenakin T: Principles: receptor theory in pharmacology, *Trends Pharmacol Sci* 25:186–192, 2004.
8. Kobilka BK: Structural insights into adrenergic receptor function and pharmacology, *Trends Pharmacol Sci* 32:213–218, 2011.
9. Rosenbaum DM, Rasmussen SG, Kobilka BK: The structure and function of G protein-coupled receptors, *Nature* 459:356–363, 2009.
10. Urban JD, Clarke WP, von Zastrow M, et al.: Functional selectivity and classical concepts of quantitative pharmacology, *J Pharmacol Exp Ther* 320:1–13, 2007.
11. Wenthur CJ, Gentry PR, Mathews TP, Lindsley CW: Drugs for allosteric sites on receptors, *Annu Rev Pharmacol Tox* 54:165–184, 2014.

2

Pharmacokinetics: The Absorption, Distribution, and Fate of Drugs*

Frank J. Dowd

KEY INFORMATION

- Drugs are able to penetrate membrane barriers by several mechanisms.
- The more lipid-soluble a drug is, the more likely it is to penetrate the lipid environment of membranes.
- Distribution of weak acids and weak bases depends on pH and the pK_a of drugs.
- Drug transporters play notable roles in the small intestine, liver, kidneys, and capillaries.
- Each route of drug administration has its own absorption characteristics.
- The blood–brain barrier is effective in keeping many drugs out of the brain.
- Drug distribution in saliva reflects plasma concentrations for several drugs.
- The liver is the most important organ for drug metabolism, employing many key enzymes, most notably the cytochrome P450 enzymes.
- Many factors, including drug inhibitors and drug inducers, can affect cytochrome P450 enzymes.
- The kidneys are the most important organs for excreting drugs.
- First-order kinetics refers to a process (e.g., elimination of a drug) in which a constant percentage of drug is eliminated per unit time.
- Zero-order kinetics refers to a process (e.g., elimination of a drug) in which a constant amount of drug is eliminated per unit time.
- Drugs differ from one another in their volumes of distribution, elimination half-times, and clearances.
- Four equations can be used to calculate drug transit in the body: volumes of distribution, half-times, clearance values, and steady-state plasma concentrations (for multiple dosing).

CASE STUDY

As a result of oral surgery that you performed on your patient, you prescribe acetaminophen plus codeine #3 (300 mg acetaminophen with 30 mg codeine), two tablets initially and one tablet every 4 hours thereafter (6 doses maximum) as needed for pain. Your patient mentions that due to gastric reflux, he also intends to begin using an over-the-counter histamine-2 blocker. He mentions that he has a bottle of Tagamet (cimetidine) with more pills in it from a previous use. Assuming the cimetidine is not out of date, would you offer any advice to your patient based on this information?

We learned in chapter one (Pharmacodynamics), that the magnitude of the effect of a drug is directly related to the concentration of the drug at the relevant receptors. When a drug is administered to a patient, however, several factors contribute to achieving the drug concentration at the receptors. Drug concentrations are rarely static; they increase and decrease as dictated by the processes of absorption, distribution, metabolism, and excretion. This chapter examines these processes (**pharmacokinetics**, Fig. 2-1) and how they influence the passage of drugs through the body.

PASSAGE OF DRUGS ACROSS MEMBRANES

For a drug to be absorbed, reach its site of action, and eventually be eliminated, it must cross one or more biologic membrane barriers. Because such barriers to drugs behave similarly, the cell membrane can serve as an example for all. The cell membrane is composed of a bimolecular sheet of lipids (primarily phospholipids and cholesterol) with proteins interspersed throughout and extending beyond the lipid phase of the membrane (Fig. 2-2). The presence of protein molecules spanning the entire thickness of the membrane provides a necessary link between the extracellular environment and the cell interior, which is consistent with the concept that drug activation of a membrane-bound receptor on the external surface of a cell can be directly translated into an intracellular response. Specific transmembrane proteins also provide important pathways for the uptake and extrusion of drugs.

Passive Diffusion

The passage of drugs across biologic membranes can involve several different mechanisms. Of these, passive diffusion is the most commonly encountered. The defining characteristic of passive diffusion is that the drug moves down its electrochemical gradient when crossing the membrane. The gut epithelial barrier is a good example of how drugs can permeate cell barriers.

Simple diffusion

One way that hydrophilic drugs may penetrate a cell barrier is by aqueous diffusion, by permeating between epithelial tight junctions or through aqueous pores. This avoids the lipid barrier of the cell membrane, but it is limited by drug size and other restrictions. More commonly, lipophilic drugs will diffuse directly through the lipid barrier of the cell membrane (**lipid diffusion**). The rate of transfer of nonelectrolytes across a membrane is directly proportional to the lipid/water partition coefficient. (The partition coefficient is a measure of the relative solubility of an agent in a fat solvent, such as olive oil or octanol, vs its

* The author wishes to recognize Dr. John A. Yagiela for his past contributions to this chapter.

solubility in water [Fig. 2-3].) A drug with a high partition coefficient (i.e., a *lipophilic* drug) readily enters the lipid phase of the membrane and passes down its concentration gradient to the aqueous phase on the other side. More molecules are then free to enter the membrane and continue the transfer process. With poorly lipid-soluble compounds, however, only a few molecules enter the membrane per unit of time, and the rate of passage is depressed.

The absence of an ionic charge is one major factor favoring lipid solubility. Conversely, drugs with an ionic charge, such as those containing a quaternary nitrogen atom, permeate membranes slowly if at all. The term **hydrophobic bonding**, introduced in Chapter 1, refers to the tendency for water-insoluble molecules to be drawn together; this behavior is responsible for the preferential tendency of lipid-soluble drugs to penetrate cell membranes by way of the lipid components. Many other therapeutic agents are weak electrolytes; depending on the pH of their aqueous environment, they can exist in ionized and neutral forms. Because charged molecules penetrate membranes with considerable difficulty, the rate of movement of these drugs is governed by the **partition coefficient** of the neutral species versus the **ionized species**. As illustrated in Figure 2-4, acidic conditions favor the transport of weak acids, and the opposite holds true for basic compounds.

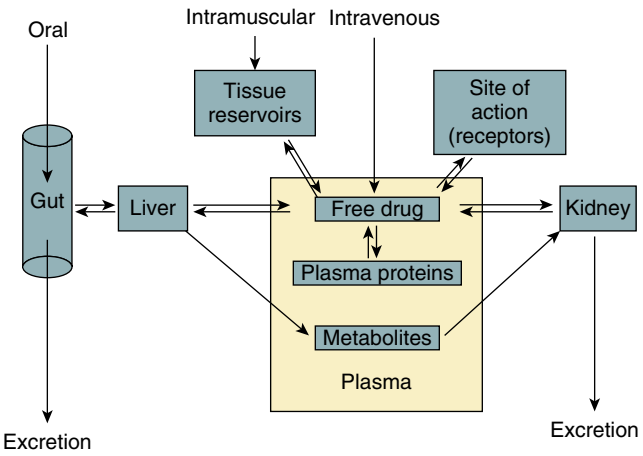


FIG 2-1 Outline of the major pathways of absorption, distribution, metabolism, and excretion of drugs. Compounds taken orally must pass through the liver before reaching the systemic circulation. When in the bloodstream, agents are distributed throughout the body and come in contact with their respective sites of action. Drugs are filtered by the kidney, only to be reabsorbed if lipid soluble. Metabolism of many drugs occurs primarily in the liver, after which the metabolites are excreted in bile or via urine. Some agents eliminated in the bile are subject to reabsorption and may participate in an enterohepatic cycle.

The same concept of water interaction used to explain the aqueous solubility of ions also applies to many nonionic molecules. Although unsubstituted aliphatic and aromatic hydrocarbons have little or no tendency to react with water, affinity for water molecules is not restricted to structures with a formal charge. Organic residues possessing electronegative atoms such as oxygen, nitrogen, and sulfur can interact with water through the formation of hydrogen bonds to provide some degree of aqueous solubility.

Figure 2-3 shows that lipid solubility is not the only factor influencing the simple diffusion of uncharged drugs across cell membranes; molecular size is also important. Water, glycerol, and some other very small molecules permeate much more readily than would be predicted from their respective partition coefficients. Figure 2-3 also shows that some large organic molecules diffuse more slowly than expected, indicating that some degree of water solubility is necessary for the passive diffusion of drugs across membranes. No matter how lipid soluble an agent is, it will never cross a membrane if it cannot first dissolve in the extracellular fluid and be carried to the membrane structure. Benzocaine, an active local anesthetic when applied directly to nerves, is ineffective after injection because its water insolubility precludes significant diffusion away from the administration site and toward its locus of action within the neuronal membrane.

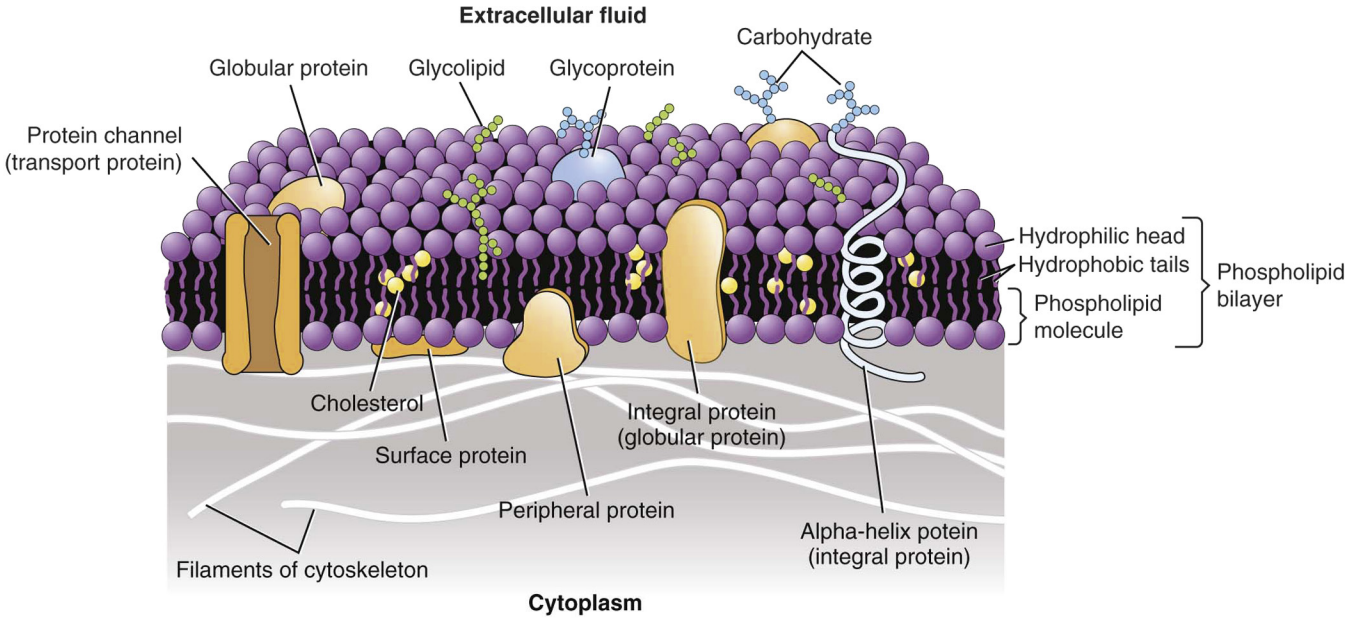


FIG 2-2 Cells are surrounded by a plasma membrane composed of a phospholipid bilayer, cholesterol, proteins, and carbohydrates. Modified from VanMeter KC, et al.: *Microbiology for the Healthcare Professional,* St Louis, ed 2, 2016, Mosby.

Similarly, when inside a membrane, a drug with an extremely high partition coefficient may be so soluble in the lipid phase that it has little tendency, despite moderate solubility in water, to diffuse out of the membrane down its concentration gradient. This is commonly called "lipid trapping."

Simple diffusion across capillary walls warrants special comment. In addition to the transcellular pathway of drug diffusion just described for lipid-soluble agents, an aqueous **paracellular pathway** formed by 10-nm to 15-nm clefts between the endothelial cells of most capillaries permits the aqueous diffusion of water-soluble drugs between the plasma and extracellular space. Hydrophilic molecules up to small proteins in size can use this route; fixed negative charges along the diffusion pathway tend to promote the movement of positively charged macromolecules while restricting movement of those with net negative charges.

Facilitated diffusion

Water, small electrolytes, and hydrophilic molecules of biologic importance generally move across plasma membranes much more readily than would be predicted by simple diffusion. In these instances, transmembrane proteins serve to circumvent the lipid bilayer and facilitate diffusion. The simplest mechanism involves a transmembrane pore (porin), such as aquaporin 1. Discovered in 1991, aquaporin 1 is a 28-kDa polypeptide that forms a 3-Å channel through which water can enter or leave cells. More than 10 variants of aquaporins have been discovered in mammalian tissues and are especially prominent in cells and organs involved with the transcellular movement of water: kidneys, capillaries, secretory glands, red blood cells, choroid plexus, brain glia, eyes, and lungs. Some aquaporins are selective for water only, increasing membrane permeability by a factor of up to 100 times; others permit the passage of glycerol and several other small molecules in addition to water.

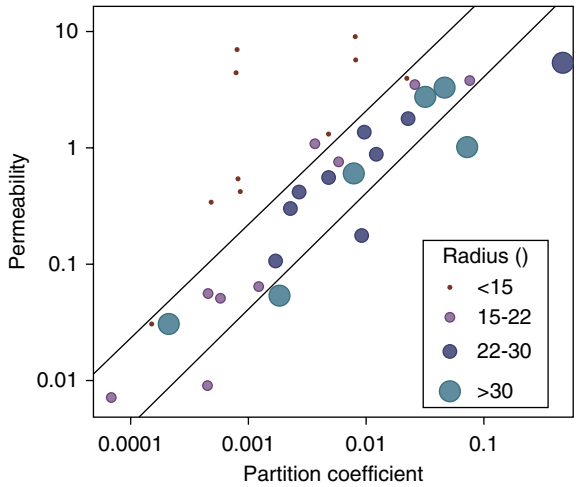


FIG 2-3 Relationship between membrane permeability and lipid (olive oil)/water partition coefficient in *Chara certatophylla*. Each *circle* represents a single nonelectrolyte with a molecular radius as indicated in the key. Small compounds permeate more readily than their partition coefficient would indicate; the reverse is true for large molecules. (Adapted from Collander R: The permeability of plant protoplasts to small molecules, *Physiol Plantarum* 2:300-311, 1949.)

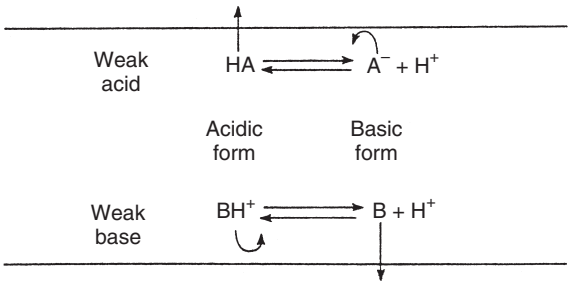


FIG 2-4 Membrane penetration by weak electrolytes. The nonionic species of drugs (*HA, B*) permeate membranes much more efficiently than do the charged forms (A^-, BH^+). Acidic conditions shift the dissociation curves to the left, favoring the diffusion of weak acids. An increase in pH favors the loss of hydrogen (H^+) and the diffusion of weak bases.

The movement of specific ions (e.g., Na^+, K^+, and Ca^{++}) across the cell membrane is facilitated by the presence of transmembrane channels, such as the nicotinic receptor described in Figure 7-4 and the Na^+ channel illustrated in Figure 14-4. The opening of these gated channels (in contrast to porins, which are always open) is regulated by the electric potential across the membrane or by the presence of specific ligands, such as neurotransmitters. When a channel is open, passive diffusion of an ion capable of traversing it depends on the electric potential across the membrane and the chemical gradient of the ion. Boosting the electrochemical gradient by manipulating the voltage across the cell membrane is an effective method of increasing ionic flow. Even in the absence of specific ion channels, the transport of fixed ions and weak electrolytes across tissue barriers can be facilitated by the appropriate use of electric current (as in iontophoresis, discussed subsequently).

Numerous lipid-insoluble substances are shuttled across plasma membranes by forming complexes with specific membrane constituents called **carriers** or **transporters**. Carriers are similar to receptors in many ways; they are proteins, often quite selective about the agents with which they combine, and subject to competitive inhibition. Because the number of transporter molecules is finite, carrier-mediated diffusion can be saturated at high drug concentrations. The GLUT family of glucose transporters is representative of carrier proteins that facilitate the movement of hydrophilic solutes across cell membranes. The initial step in the facilitated diffusion of glucose is its binding to the exposed active site of the transporter protein. This binding sequentially causes an external barrier or gate to close and interior gate to open, after which the glucose is released into the cell. The release of glucose causes the internal gate to close and the external gate to open, re-exposing the active site and completing the cycle.

Active Transport

Active transport is the term given to the carrier-mediated transfer of a drug against its electrochemical gradient. In addition to exhibiting selectivity and saturability, active transport requires the expenditure of energy and may be blocked by inhibitors of cellular metabolism. Active transport permits the efficient absorption of substances vital for cellular function (and certain drugs that resemble them structurally) and the selective elimination of waste products and foreign chemicals, including many drugs. Approximately 2000 genes—7% of the total human genome—code for transporters and associated proteins. Two superfamilies of transporters are of special significance to pharmacokinetics: **ATP-binding cassette (ABC) transporters** and **solute carrier (SLC) transporters**.

ABC transporters hydrolyze adenosine triphosphate (ATP) to provide the energy directly needed for molecular transport and are referred to as **primary active transporters**. The most extensively researched representative is **P-glycoprotein** ("P" for altered permeability). Originally identified in 1976 for its ability to expel numerous antineoplastic drugs from mutated cells that overexpress it,

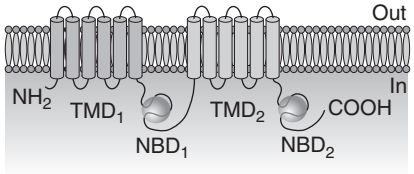


FIG 2-5 Two-dimensional topology of P-glycoprotein. Two transmembrane domains (*TMDs*) provide the transport mechanism and are powered by the nucleotide-binding domains (*NBDs*) that hydrolyze ATP. (Adapted from Sarkadi B, Homolya L, Szakács G, et al.: Human multidrug resistance ABCB and ABCG transporters: participation in a chemoimmunity defense system, *Physiol Rev* 86:1179-1236, 2006.)

P-glycoprotein is a complex 170-kDa glycoprotein with transmembrane domains that form the pump itself and a nucleotide-binding domain that hydrolyzes ATP to power the transport (Fig. 2-5). P-glycoprotein preferentially promotes the cellular extrusion of large (300 to 2000 Da) hydrophobic substances and neutral or positively charged amphiphilic molecules. Transported drugs include numerous anticancer agents (e.g., doxorubicin, vinblastine, and paclitaxel), antiviral compounds (e.g., ritonavir), Ca^{++}-channel blockers (e.g., diltiazem), digoxin, antibiotic and antifungal drugs (e.g., erythromycin and ketoconazole), hormones (e.g., testosterone), and immunosuppressants (e.g., cyclosporine).

Drug binding to active transporters occurs within the plasma membrane near the cytoplasmic surface, limiting transport to drugs with good lipid solubility or sufficient length to reach the active site. P-glycoprotein is expressed in various cells, but the highest concentrations are located in intestinal epithelial cells; renal proximal tubular cells; canalicular membranes of hepatocytes; the capillary endothelium of the brain, choroid plexus, testes, and placenta; placental trophoblasts; adrenocortical cells; and stem cells. Other ABC transporters important in pharmacokinetics include the multidrug resistance-associated protein (MRP) family. Collectively, the MRP transporters are also widespread and involved in the vectorial (one-way) movement of drugs and other xenobiotics. In contrast to P-glycoprotein, the MRP transporters pump amphipathic molecules with at least one negative charge. These substrates include bile salts, nucleotide analogues, and conjugates of glutathione, glucuronic acid, and sulfate.

In contrast, SLC transporters do not directly use ATP as an energy source for transport and are referred to as **secondary active transporters**. These transporters require an electrochemical gradient down which solutes can move. The Na^+ pump (Na^+,K^+ -ATPase) a **primary active transport** process, is the main driving force for secondary active transport. By maintaining a large electrochemical gradient for Na^+ across the plasma membrane, movements of molecules that are energetically coupled to Na^+ (or another ion with a strong electrochemical potential difference across the membrane) can occur against their own concentration gradients. Secondary active transporters that move the coupled substances in the same direction as the linked ion are termed **cotransporters** or **symporters**. In contrast, **antiporters or exchangers** move the coupled substances in the opposite direction. Many SLC transporters (including the GLUT family described previously) allow the transmembrane movement of specific chemicals down their own electrochemical gradients and therefore support facilitated diffusion. In contrast to the ABC transporters, SLC transporters can facilitate bidirectional movement of substrates based on their existing concentrations across the cell membrane.

Organic anion transporters (OATs) and organic anion–transporting polypeptides (OATPs) are important subfamilies of SLC transporters involved in pharmacokinetics. As a group, they promote the cellular uptake of acidic drugs into the liver, kidney, intestine, lung, and brain, as well as their excretion via the bile and urine. An analogous family of organic cation transporters (OCTs) provides similar handling of positively charged drugs.

Endocytosis and Exocytosis

The processes of endocytosis and exocytosis are together the most complex methods of drug transfer across a biologic membrane. The term *endocytosis* refers to a series of events in which a substance is engulfed and internalized by the cell. (A similar term, *phagocytosis* or "cell eating," is a variant of endocytosis associated more with the removal of particulate matter by macrophages than with drug transport.)

Endocytosis usually begins with the binding of a compound to be absorbed, usually a macromolecule, by its receptor on the membrane surface. Several mechanisms exist. A good example is the attachment of low-density lipoprotein (LDL) to its respective receptor. With time, the bound agent–receptor complex is concentrated in an indentation of the membrane called a coated pit. *Clathrin*, a cytoplasmic protein that attaches to the internal surface of the plasma membrane, serves to capture the receptors within the pit while excluding other surface proteins. Internal rearrangement of its structure deepens the pit, forming a coated bud. A second protein, termed *dynamin*, is believed to congregate around the collar of the invaginated bud and initiate separation from the membrane. When released, the vesicle loses its clathrin coat and fuses with a cytoplasmic organelle called the endosome. Some of the captured contents, such as the LDL receptors, are recycled back to the plasma membrane by transport vesicles; the remainder undergo lysosomal processing and release into the cytoplasm.

The complementary process of exocytosis occurs when vesicles, such as those produced by the Golgi apparatus, fuse with the plasma membrane and discharge their contents outside the cell. Exocytosis is the primary method by which cellular products such as regulatory hormones are secreted by the cell. The term *transcytosis* is descriptive of a coupled form of endocytosis and exocytosis leading to the transfer of drug from one epithelial surface of a cell to another.

ABSORPTION

Absorption refers to the transfer of a drug from its site of administration into the bloodstream. The particular route of administration selected greatly influences the rate and perhaps the extent of drug absorption.

Oral Ingestion

Oral ingestion was the first, and is still the most commonly used, method for the administration of therapeutic agents. The major advantages of the oral route lie in three areas: convenience, economics, and safety (Table 2-1). The bulk of drug absorption occurs in the small intestine with lesser amounts being absorbed in the stomach. Sudden high blood concentrations are not nearly as likely to be achieved by the ingestion of drugs as they are by parenteral injection. Allergic reactions are also less likely to occur, especially serious reactions. The oral route does have some drawbacks, however. Because self-administration is the rule, patient compliance is required for optimal therapy. Drug absorption is likely to be delayed (on a clinical average of 30 to 60 minutes) and may be incomplete. Metabolic inactivation or complex formation may also occur before the drug has a chance to reach the systemic circulation. These limitations to the oral route translate into an increased variability in patient response (Table 2-1).

TABLE 2-1 Characteristics of Routes of Drug Administration

Route of Administration	Absorption Characteristics	Advantages	Disadvantages
Oral	Variable; depends on rate of gastric emptying; dosage forms affect rate	Convenient, economical, self-administration, low cost, relatively safe	Requires patient compliance; unsuitable for poorly absorbed drugs; rapid inactivation for some drugs
Sublingual, buccal	Rapid for some drugs	Avoids first-pass metabolism; predictable effect for some drugs	Drug must be kept in contact with absorption site
Intravenous	Immediate	Ideal for emergencies; rapid titration is possible; the fastest way to achieve predictable plasma drug concentrations; large volumes can be given over time	Adverse effects appear rapidly and are difficult to reverse; suspensions cannot be given; pain, vasculitis, extravasation may occur; not usually for self-administration
Intramuscular	Rapid for aqueous solutions; slow for suspensions or depot forms	More predictable response than for oral drugs; rate of absorption can be manipulated; useful for noncompliant patients	Painful; may cause muscle damage; bleeding risk with patients on anticoagulants; may interfere with some diagnostic tests that measure organ or tissue damage
Inhalation	Rapid absorption for anesthetics; some inhaled drugs (e.g., antiasthma drugs) stay in the respiration tract	Useful for bronchodilators and inhaled steroids; useful for gaseous or volatile liquid anesthetics, titration of anesthetic	Coughing; bronchodilator and steroid self-administration require patient education
Subcutaneous	Rapid for aqueous solutions; slow for suspensions or depot forms	Aqueous or depot forms can be used	Pain, tissue necrosis

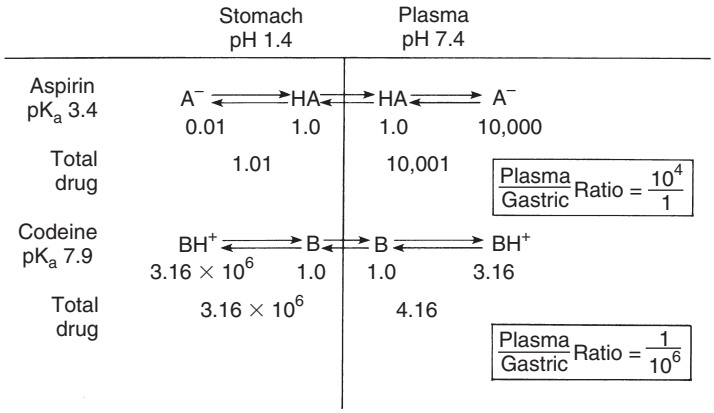


FIG 2-6 Gastric absorption of aspirin, a weak acid, and codeine, a weak base. The absorption of aspirin is promoted by ion trapping within the plasma; the low pH of stomach fluid favors gastric retention of codeine. (The actual 3.49 pK_a of aspirin is truncated to 3.4 for purposes of illustration.)

Influence of pH

Absorption is favored when the drug ingested is lipid soluble. For weak electrolytes, the pH of the surrounding medium affects the degree of ionization and drug absorption. Because the H^+ concentrations of the stomach and small intestine diverge widely, the two structures seem to be qualitatively dissimilar in their respective patterns of drug absorption. Figure 2-6 illustrates this difference and its effect on the analgesic combination of aspirin plus codeine. Aspirin is an organic acid with a pK_a (negative log of the dissociation constant) of 3.49. In gastric juice (pH 1 to 3), aspirin remains largely nonionized, and its passage across the stomach mucosa and into the bloodstream is favored. The plasma has a pH of 7.4, however, and upon entering this environment, the aspirin becomes ionized to such an extent that return of the drug to the gastrointestinal tract is prevented by the low lipid solubility of the anionic species. When equilibrium is established, the concentration of nonionized aspirin molecules on both sides of the membrane is the same, but the total amount of drug (ionized plus neutral forms) is much greater on the plasma side. The relative concentration of drug in each compartment can be calculated with the Henderson-Hasselbalch equation, as follows:

$$\text{Log}\ \frac{\text{base}\ (A^-)}{\text{acid}\ (HA)} = \text{pH} - pK_a$$

This unequal distribution of drug molecules based on the pH gradient across the gastric membrane is an example of ion trapping. The biologic process that sustains this partitioning is the energy-consuming secretion of H^+ by the gastric parietal cells. Because few organic acids have a pK_a low enough to permit significant ionization at stomach

pH, almost all acidic drugs should theoretically be effectively absorbed across the gastric mucosa.

For bases such as codeine (pK_a 7.9), the opposite applies. Codeine is almost completely ionized in the acidic environment of the stomach; absorption is negligible, and virtually all the drug remains within the stomach. Only very weak bases are nonionized at gastric pH and available for absorption. In this case, the ion trapping occurs before absorption within the gastric lumen. (Interestingly, this is sometimes useful in forensic medicine. Many drugs subject to abuse are organic bases (e.g., heroin, cocaine, and amphetamine). Even when injected intravenously, they tend to accumulate in the stomach by crossing the gastric mucosa in the reverse direction. Questions of intravenous overdosage can often be answered from the analysis of stomach contents.)

When the acidic gastric fluid passes into the small intestine, it is quickly neutralized by pancreatic, biliary, and intestinal secretions. The pH of the proximal one-fourth of the intestine varies from 3 to 6, but it reaches neutrality in more distal segments. Under these more alkaline conditions, aspirin converts to the anionic form, whereas a significant fraction of the codeine molecules give up their positive charge. Although basic drugs are favored for absorption over acids in the small intestine, ion trapping is not as extensive because the pH differential across the intestinal mucosa is small. Differences in intestinal absorption based on pH are more concerned with the rate of uptake than with its extent. As one might expect, neutralization of gastric contents by the administration of antacids or ingestion of food temporarily removes the qualitative disparity in electrolyte absorption normally observed between the stomach and the small intestine.

Mucosal surface area

A second major difference between absorption in the stomach and absorption in the small intestine relates to the intraluminal surface areas involved in drug uptake. Aside from certain mucosal irregularities (rugae), the stomach lining approximates that of a smooth pouch with a thick mucus layer. In contrast, the mucosa of the small intestine is uniquely adapted for absorption. Contributions by the folds of Kerckring, villi, and microvilli combine to increase the effective surface area 600-fold. Assuming a small intestine 280 cm in length and 4 cm in diameter, approximately 200 m^2 are available for drug absorption. The surface/volume ratio in the small intestine is so great that drugs ionized even to the extent of 99% may still be effectively absorbed. Many studies have shown that acidic drugs with a pK_a greater than 3.0 and basic compounds with a pK_a less than 8.0 readily pass from the intestinal fluid into the plasma. As a result, although pH considerations favor the gastric absorption of aspirin, as much as 90% of the drug is actually absorbed from the small intestine in vivo. Experimentally, nonelectrolytes such as ethanol are also absorbed from the intestine many times faster than from the stomach.

Gastric emptying

Because almost any substance that can penetrate the gastrointestinal epithelium is best absorbed in the small intestine, the rate of gastric emptying can significantly affect drug absorption, particularly for organic bases that are not absorbed at all from the stomach. Gastric emptying is accomplished by contraction of the antrum of the stomach. A cyclical pattern of activity occurs in fasting patients where periods of quiescence (about 1 hour each) are followed by contractions that increase in intensity over a 40-minute period before terminating in a short burst of intense contractions that migrate from the stomach to the distal ileum. Ingesting a tablet or small volume of liquid may result in gastric retention of the drug for 1 hour or longer. After eating a meal, sustained antral and pyloric contractions help break up the ingested food and permit the extrusion of liquid into the duodenum while retaining particles more than 1 mm in diameter within the stomach. A mixed meal of solids and liquids usually begins to enter the duodenum in about 30 minutes and requires about 4 hours to leave the stomach completely. Conversely, a glass of water ingested on an empty stomach is moved into the small intestine in a more rapid fashion, with half of the water expelled from the stomach in 15 minutes, and essentially all of the liquid removed by 1 hour.

A major variable in delaying gastric emptying is the presence of fat. Normally, most oral medications should be taken in the absence of food but with a full glass of water. This procedure speeds drug entry into the small intestine and provides maximum access to the gastrointestinal mucosa. Occasionally, the presence of a fatty meal promotes the absorption of a drug that has a high lipid but low water solubility. The protease inhibitor saquinavir and the fat-soluble vitamins are examples of substances that are better absorbed in the presence of lipids. In these instances, the delay in gastric emptying produced by the high fat content of the chyme is compensated for by a more complete absorption. Because gastric emptying is often a limiting factor in the rate of drug absorption, many unrelated drugs exhibit latency periods (the lag phase between oral ingestion and onset of drug effect) of a similar magnitude.

Influence of dosage form

Although the times required for gastric emptying and for diffusion across the mucosal barrier undoubtedly contribute to the delayed onset of action of drugs taken orally, situations exist in which these events are not rate limiting. Most drugs intended for oral use are marketed in the form of capsules or solid tablets. In contrast to solutions, these preparations must first dissolve in the gastrointestinal fluid before absorption can occur. If dissolution is designed to be very slow, it can become the controlling factor in drug absorption.

The first step in the dissolution process is the disintegration of the tablet (or the capsule and its granules) to yield the primary drug particles. The dissolution process may be considered rate limiting whenever a drug solution produces a systemic effect faster than a solid formulation of the same agent. Sometimes discrepancies in absorption between dosage forms are of such magnitude that clinical differences are noted. With aspirin, the concentration of drug in the plasma 30 minutes after administration can be twice as high for a solution as for a solid tablet. Although it is unclear whether this difference results solely from drug dissolution or from other factors, such as the more rapid gastric emptying typical of liquids, dissolution is probably at least partially responsible.

The influence of dosage form on drug absorption is often taken advantage of by drug manufacturers. To avoid release of certain drugs within the stomach, they are often prepared in the form of enteric-coated tablets. An enteric coat consists of a film of shellac or some polymeric substitute. The covering is insoluble under acidic conditions, but it does break down to permit tablet disintegration in the more alkaline environment of the small intestine. Although these preparations are often beneficial, their usefulness nevertheless is negatively affected by an increased variability in patient response. Because drug absorption cannot begin until the tablet passes into the duodenum, the time required for gastric transit becomes an important variable. The passage of a single insoluble tablet from the stomach into the intestine is a random event that can take several minutes to more than 6 hours.

Sustained-release preparations represent another method of capitalizing on the influence of formulation on drug absorption. These products are usually designed to release a steady amount of drug

within the gastrointestinal tract for 12 to 24 hours. Some preparations also provide an initial loading dose that is readily available for absorption. Sustained release may be accomplished by using a porous matrix, with the drug located in the interior spaces and on the external surface. An alternative is to make spheres of drug that dissolve at different rates because of various coatings.

The sensitivity of gastrointestinal absorption to variations in drug formulation is best exemplified by the concern over **bioavailability**. In many instances, chemically identical drugs have proved in the past to be biologically nonequivalent because of differences in formulation. In one study of tetracycline hydrochloride, nine preparations from different manufacturers were compared with an aqueous solution of the same drug. Although seven brands produced blood concentrations ranging from 70% to 100% of the reference solution, two products exhibited relative bioavailabilities of only 20% to 30%. Differences in bioavailability are more clinically important with drugs that are poorly absorbed, have low margins of safety, and are inactivated by capacity-limited processes. Since 1977, federal law has required that bioequivalence testing be performed on all new drugs, and the FDA has mandated such testing of existing products for which a problem of nonequivalence is known to exist. Bioavailability considerations related to drug selection are considered further in Chapter 42.

Active transport

Most drugs intended for oral use are absorbed by passive diffusion. Active transport systems do exist, however, for specific dietary constituents that sometimes increase the absorption of certain drugs. The absorption of levodopa and baclofen from the intestine is enhanced because they are amino acid analogues that are actively transported into intestinal cells by the large neutral amino acid transporter (an SLC transporter). Valacyclovir is, likewise, much better absorbed than is its congener acyclovir because it is a substrate for PepT-1, another SLC transporter.

Active transport mechanisms can also inhibit drug absorption. P-glycoprotein is highly expressed along the luminal surface of intestinal epithelial cells, where it exports xenobiotics that would otherwise be absorbed. This function is in concert with the "chemoimmunity defensive" role P-glycoprotein plays in protecting cells from exposure to potentially toxic compounds. Although P-glycoprotein may delay the absorption of many drugs and prevent altogether the uptake of pharmaceuticals of low absorptive potential, it is probably of minor significance regarding the extent of absorption of most drugs intended for oral use, whose concentrations in the chyme are sufficient to overwhelm the capacity of P-glycoprotein to export them. Figure 2-7 depicts the active transport of drugs into and out of intestinal cells and at other important sites.

Drug inactivation

A shortcoming of oral ingestion is the inactivation of drugs before they reach the systemic circulation. The destruction of some agents (e.g., epinephrine and insulin) is sufficiently great to preclude their administration by this route. With other drugs (e.g., penicillin G), losses may be smaller but still large enough to make oral administration inefficient. Gastric acid is one of the principal causes of drug breakdown within the gastrointestinal tract, but degradation also results from enzymatic activity. Vasopressin, insulin, calcitonin, and other polypeptides are subject to hydrolysis by pancreatic and intestinal peptidases. Intestinal cells also contain intracellular enzymes for metabolizing drugs. Of particular importance are the presence of monoamine oxidase for the inactivation of biogenic amines and the presence of CYP3A4/5 enzymes (described later) for the oxidation of numerous compounds. Enteric bacterial enzymes may also destroy certain ingested agents, such as chlorpromazine. Finally, intestinal contents can alter the effectiveness of many orally administered drugs. Binding to constituents of chyme, chelation with divalent cations, or formation of insoluble salts may decrease the amount of drug available for absorption.

A special fate exists for substances that are successfully absorbed from the gastrointestinal tract. The venous drainage of the stomach, small intestine, and colon is routed by the hepatic portal system to the liver. A **first pass** of high drug concentration through this enzyme-laden organ can significantly reduce the quantity of agent reaching the systemic circulation. For example, lidocaine is metabolized so rapidly in the liver that virtually all of an oral dose is destroyed during its first pass. Although less pronounced, disparities in opioid analgesic and antibiotic efficacies observed between the oral route and other modes of administration are of clinical importance to the practice of dentistry.

Other enteral routes

The oral and rectal mucosa are occasionally used as sites of drug absorption. Sublingual administration, in which a tablet or troche is allowed to dissolve completely in the oral cavity, takes advantage of the permeability of the oral epithelium and is the preferred route for a few potent lipophilic drugs, such as nitroglycerin and oxytocin, and even the commonly used oral sedative triazolam. One reason for selecting the sublingual route is to avoid drug destruction. Because gastric acid and intestinal and hepatic enzymes are bypassed, sublingual absorption can be more efficient overall for certain drugs than intestinal uptake. The onset of drug effect may also be quicker than with oral ingestion. In dentistry, triazolam generally reaches peak effect in 20 to 30 minutes sublingually, as compared to 30 to 45 minutes orally.

Rectal administration may be used when other enteral routes are precluded, as in an unconscious or nauseated patient. Although a significant fraction of absorbed drug enters the circulation without having to pass through the liver, uptake is often unpredictable. For many patients, aversion to rectal introduction of drugs prohibits administration by this route.

Inhalation

The alveolar membrane is an important route of entry for some drugs and many noxious substances. Although the alveolar lining is highly permeable, it is accessible only to agents that are in a gaseous state or are inhaled in sufficiently fine powders or microdroplets to reach the deepest endings of the respiratory tree. Gaseous agents include the therapeutic gases, carbon monoxide, inhalation anesthetics, and numerous volatile organic solvents. The second category of alveolar membrane penetrants is collectively known as **aerosols**. This term refers to liquid or solid particles small enough (usually ≤10 μm in diameter) to remain suspended in air for prolonged periods. Any such finely divided material, when inhaled, reaches some portion of the respiratory tree and is affected by the processes of sedimentation and inertial precipitation. Most aerosols contain a mixture of particle sizes.

Therapeutic use of aerosols is not widespread, but some emergency medications are prepared in this form. Because the onset of effect is extremely rapid after inhalation of an aerosol drug, this route can provide a means of quick self-medication for individuals in danger of acute allergic reactions to venoms or drugs. Epinephrine is one such emergency agent that is marketed as an aerosol. Many respiratory drugs are also prepared in aerosol form because they are highly effective by this route while minimizing systemic exposure. The rapidity and efficiency of alveolar membrane absorption can occasionally pose problems for therapy, however, as illustrated by the use of aerosols containing isoproterenol. Although 97% of an isoproterenol spray is swallowed under normal conditions and inactivated by various enzymes,

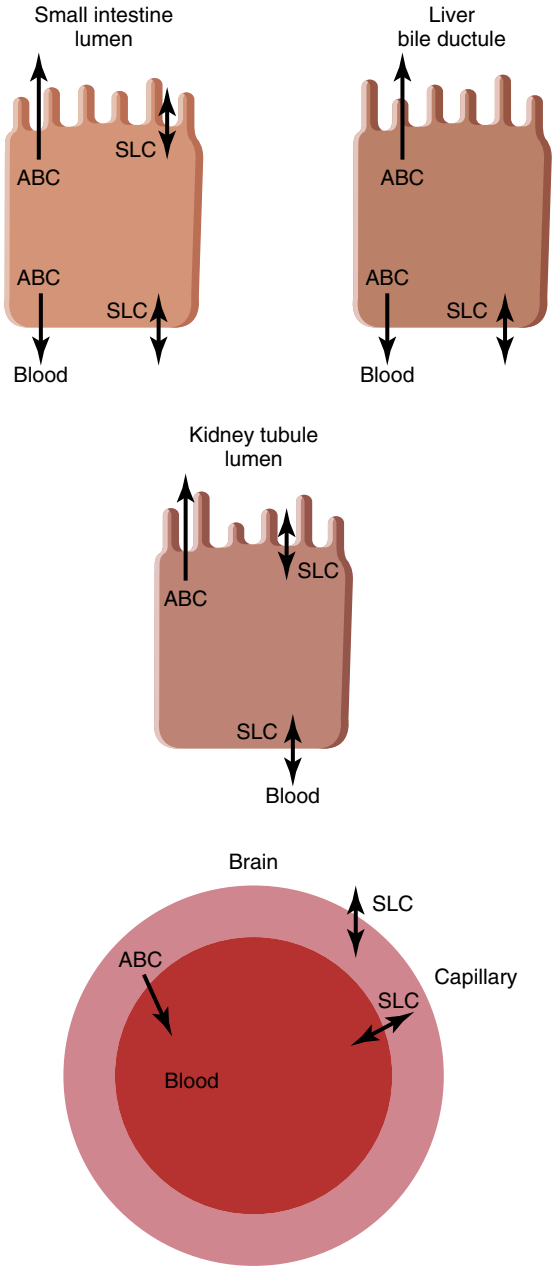


FIG 2-7 Transepithelial or transendothelial transport of drugs across the small intestine and the liver (absorption), brain capillaries (distribution), and liver and kidneys (elimination). *ABC,* ATP-binding cassette transporter; *SLC,* solute carrier transporter.

overmedication can produce toxic effects. This reflects the hazards of aerosols when abused and provides a caveat for uncontrolled self-medication with any potentially dangerous drug. Concern over aerosols is also related to questions of toxicology, such as the absorption of heavy metal dusts by industrial workers.

Parenteral Injection

Drugs are frequently given by parenteral injection when oral ingestion is precluded by the patient's condition, when a rapid onset of effect is necessary, or when blood concentrations greater than those obtainable with the enteral route are required. The method of injection selected varies with the particular drug and therapeutic need of the patient (Table 2-1).

Intravenous route

The administration of drugs by infusion or injection directly into the bloodstream is particularly useful when immediate effects or exact blood concentrations are desired. Also, through the technique of titration, the intravenous route provides an avenue for the controlled administration of drugs that have a very narrow margin of safety between therapeutic and toxic concentrations. The infusion of lidocaine to prevent ventricular arrhythmias and the incremental injection of antianxiety drugs during intravenous sedation are two examples in which titration is used to achieve a desired effect while avoiding adverse reactions. Most IV drugs should be administered over a period of 1 minute, which approximates the circulation time of blood through the body. This procedure avoids high, transient concentrations and permits discontinuance if any

untoward effect is observed during the course of injection. Other characteristics of intravenous injections are given in Table 2-1.

Intramuscular route

The intramuscular route is often selected for drugs that cannot be given orally because of slow or erratic absorption, high percentage of drug inactivation, or lack of patient cooperation (Table 2-1). The rate of absorption from an intramuscular site is governed by the same factors influencing gastrointestinal uptake, such as lipid/water partition coefficient, degree of ionization, and molecular size. Many drugs are absorbed at approximately the same rate, however, regardless of these factors. Muscles with high blood flows (e.g., deltoid) provide faster absorption rates than muscles with lesser flows (e.g., gluteus maximus). Generally, 5 to 30 minutes is required for the onset of drug effect, but this latency period can be controlled to some extent. Exercise markedly speeds absorption by stimulating local circulation. Conversely, uptake may be minimized by the application of ice packs or (in an emergency) tourniquets.

Subcutaneous route

Injection of drugs into the subcutaneous connective tissue is a widely used method of administration for agents that can be given in small volumes (≤2 mL) and are not locally damaging. Subcutaneous absorption is similar to that of resting muscle, and onset times are often comparable. As with the intramuscular route, absorption can be delayed by diminishing blood flow, either through the application of pressure or by surface cooling. Pharmacologic interruption of circulation with vasoconstrictors is also a common strategy, especially in local anesthesia. Because of the ease of subcutaneous implantation, compressed pellets of drugs, sometimes mixed with insoluble matrix material, can be inserted to provide nearly constant drug release for weeks or months. Testosterone and several progestational contraceptive agents (e.g., levonorgestrel) have been successfully administered by this approach.

When subcutaneous administration is chosen for a systemic effect, the hastening of drug absorption is sometimes advantageous. Toward this end, warming the tissue promotes drug uptake by improving local circulation. Massage of the injection site, in addition to stimulating blood flow, helps spread the drug and provides an increased surface area for absorption.

Other parenteral injection routes

Intraarterial injections are occasionally performed when a localized effect on a particular organ or area of the body is desired. Injections of radiopaque dyes for diagnostic purposes and antineoplastic agents to control localized tumors are the most commonly encountered examples. Intrathecal administration is used when the direct access of drug to the central nervous system (CNS) is necessary. Indications for injection into the subarachnoid space include the production of spinal anesthesia with local anesthetics and the resolution of acute CNS infections with antibiotics. The intraperitoneal infusion of fluids is a useful substitute for hemodialysis in the treatment of drug poisoning. Although intraperitoneal injection is commonly used in animal experimentation, the risk of infection usually precludes such use in humans. Last, intraosseous (anterior tibial) injection of emergency drugs can be used when intravenous access cannot be obtained quickly.

All these specialized injection techniques are potentially dangerous to the patient. They should be performed only when expressly indicated and then only by qualified personnel.

Topical Application

Drugs are often applied to epithelial surfaces for local effects and less frequently for systemic absorption. Penetration of drugs across the epithelium is strongly influenced by the degree of keratinization.

Skin

The epidermis is a highly modified tissue that isolates the body from the external environment. The outer layer of skin (stratum corneum) is densely packed with the protein keratin. This layer is impervious to water and water-soluble drugs, and its relative thickness and paucity of lipids in contrast to other biologic membranes retard even the diffusion of even some lipophilic agents. However, certain compounds may readily penetrate the skin to cause systemic effects. These drugs include organic solvents, organophosphate- and nicotine-based insecticides, and some nerve gases. Severe poisoning has also resulted from the excessive application of sunburn creams containing local anesthetics. Even lipid-insoluble substances such as inorganic mercury can diffuse across skin if exposure is prolonged.

The benefits of improving and sufficiently controlling percutaneous absorption to make it a reliable route of drug administration have prompted several marketing strategies. A "transdermal therapeutic system" has been developed to provide continuous systemic uptake of nitroglycerin, scopolamine, fentanyl, and nicotine for prophylaxis of angina pectoris, prophylaxis of motion sickness, management of chronic pain, and assistance with smoking cessation, respectively. The system is a complex patch that consists of an outer impermeable backing, a reservoir containing the drug in a suspended form, a semipermeable membrane, and an inner adhesive seal. Another approach to improving drug penetration through the epidermis is the use of occlusive dressings. These dressings retain moisture and break down the horny layer through the process of maceration. A final technique, iontophoresis, is discussed subsequently.

Mucous membranes

The topical application of drugs to mucous membranes offers several potential advantages for local therapy as was discussed with sublingual or buccal administration. The tissues can often be visualized by the clinician, permitting accurate drug placement. The use of this route generally minimizes systemic effects while providing an optimal concentration of drug in the area being treated. In contrast to the case with skin, drugs have little trouble permeating mucous membranes to affect localized conditions. Systemic absorption of lipophilic drugs from mucous membranes readily occurs. Before this fact was widely appreciated, the topical application of tetracaine to the pharyngeal and tracheal mucosa was a leading cause of local anesthetic overdosage. In dentistry, the use of corticosteroids to ameliorate inflammatory conditions has also led to systemic responses, such as the suppression of adrenocortical function by triamcinolone. Although these effects are generally mild and transient, they can create problems for patients with hypertension, diabetes mellitus, or peptic ulcer. Local therapies can also affect systemic health by serving as antigenic stimulants and, in the case of antibiotics, by disturbing the normal microbial ecology and promoting the emergence of resistant microorganisms.

The nasal mucosa offers a suitable avenue for the uptake of certain agents. Desmopressin, used in the treatment of diabetes insipidus, and butorphanol, a potent analgesic, are examples of drugs that can be given intranasally.

Iontophoresis

Iontophoresis is the electric transport of positively or negatively charged drugs across surface tissues. The technique involves passing a direct electric current of appropriate polarity through the drug solution and patient. Permeation of mucous membranes, skin, and hard tissues is possible with this approach, yet the total dose delivered is small, and systemic toxicity is unlikely. In dental therapeutics today, iontophoretic applications of drugs are rarely used, although many of

our chronic pain patients have narcotic delivery systems that use this technique of administration.

DISTRIBUTION

Distribution refers to the movement of drugs throughout the body. The rate, sequence, and extent of distribution depend on many factors: the physicochemical properties of the drug, cardiac output and regional blood flow, anatomic characteristics of membranes, transmembrane electric and pH gradients, binding to plasma proteins and tissue reservoirs, and carrier-mediated transport. For all but the very few drugs that act intravascularly, the capillary membrane constitutes the first tissue barrier to be crossed in the journey of a drug from the bloodstream to its site of action.

Capillary Penetration

After a drug gains access to the systemic circulation, it becomes diluted by the plasma volume of the entire vascular compartment. For a compound administered intravenously, this process requires only several minutes for completion; for drugs given by other routes, intravascular distribution occurs concurrently with absorption. The transfer of drugs out of the bloodstream is governed by the same factors that control its entrance. Lipophilic drugs diffuse across the capillary membrane extremely rapidly. The transfer is so expeditious that equilibrium with interstitial fluid is practically instantaneous. Under these conditions, the rate of drug uptake is determined by the blood flow through the tissue under consideration. Well-perfused organs are saturated with drug long before many other tissues have had a chance to reach even a fraction of the equilibrium concentration. Water-soluble drugs diffuse through gaps located between adjacent endothelial cells. With these agents, transcapillary movement is slower than for drugs that have high lipid/water partition coefficients and is inversely proportional to molecular weight. As molecular size increases beyond 20 to 30 kDa, aqueous paracellular diffusion ceases to be quantitatively important. Current evidence suggests that caveolae-based transcellular movement takes over as the primary transport method for large drugs. Convection may also be important in vascular beds with large gaps between endothelial cells, and it assumes special prominence when inflammatory signals cause paracellular pathways to widen.

Entry of Drugs into Cells

As previously discussed, the cell membrane acts as a semipermeable barrier, admitting some drugs into the cell, while excluding others. Nonpolar, lipid-soluble compounds distribute evenly across plasma membranes, but distribution of weak electrolytes at equilibrium is more complex. The intracellular pH is approximately 7.0, differing slightly from the 7.4 pH of extracellular fluid. Acids with a pK_a less than 8.0 tend to remain outside the cell, whereas basic drugs with a pK_a greater than 6.0 tend to accumulate within it. Because the concentration differential across the cell membrane based on a pH gradient of 0.4 can equal 2.5:1, the acid–base status of a patient can significantly affect the dose response of weak electrolytes acting intracellularly. (The influence of pH on the distribution of local anesthetics across nerve membranes is described in Chapter 14.) Ions, unless very small in size (molecular weights of ≤60 Da) or transported by membrane-bound carriers, penetrate cell membranes with difficulty, if at all. Charged drugs that do gain access to the cell by passive diffusion are distributed at equilibrium according to their electrochemical gradient across the membrane.

Restricted Distribution

In some tissues or organs, anatomic relationships and membrane transporters sequester interstitial or transcellular fluids from the general extracellular space and restrict intracellular access to drugs. The most important examples for therapeutics include the CNS and the fetal circulation.

Central nervous system

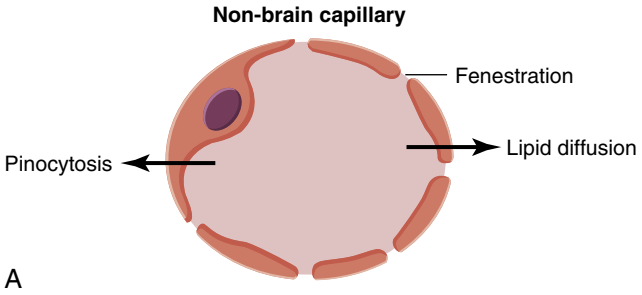
Entry of drugs into the CNS is unusually dependent on lipid solubility. Most drugs with high lipid/water partition coefficients are taken up very quickly, as exemplified by the immediate onset of general anesthesia after the intravenous injection of thiopental. The rapid distribution of lipophilic drugs into the brain and spinal cord arises from the fact that the CNS receives approximately 15% of the cardiac output yet composes only 2% of total body weight. Despite this favorable blood supply, drugs that are sparingly lipid soluble are largely excluded from the extracellular space of the brain. There are four reasons why there is an added barrier in the brain constituting the **blood–brain barrier**. These are shown in Figure 2-8. First, the capillaries of the brain do not have fenestrations and are characterized by tight junctions. Transcytosis is not characteristic of these capillaries. Second, a cellular sheath composed of processes extending from connective tissue astrocytes surrounds the capillaries. Third, P-glycoproteins actively transport drugs out of the brain. Fourth, choroid plexus cells provide an avenue to pump drugs out of the cerebrospinal fluid.

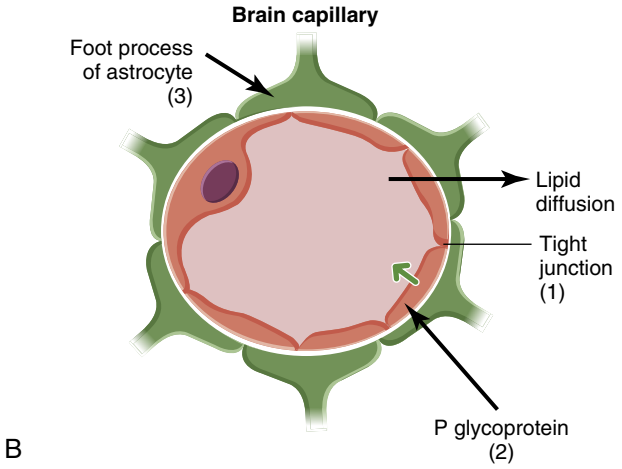
The selective distribution of compounds into the CNS has several important therapeutic ramifications. Some alkaloids intended for peripheral nervous system effects may cause central disturbances on entry into the brain. Conversion of such drugs (e.g., scopolamine) to positively charged quaternary ammonium derivatives (e.g., methscopolamine) prevents CNS influences yet allows essential peripheral nervous system activity. Conversely, drugs used for their central effects may benefit by molecular modifications that enhance their entry into the brain. Lower total doses can be given and peripheral effects minimized.

Sometimes the blood–brain barrier is a hindrance to therapy. Penicillin G, a water-soluble organic acid with a pK_a of 2.6, diffuses slowly into the CNS and is subject to active removal by the choroid plexus. For patients with bacterial encephalitis, this lack of drug penetration can complicate treatment. (Fortunately, capillary permeability in the brain often increases during meningeal inflammation.) A clever approach to circumventing the blood–brain barrier is embodied in the treatment of parkinsonism. This condition is associated with a deficiency of dopamine within selected portions of the brain. Replacement therapy with dopamine is ineffective because the drug is excluded by the blood–brain barrier. To avoid this problem, levodopa, the amino acid precursor of dopamine, is used instead. Levodopa readily enters the brain, where it is subsequently decarboxylated to the active drug.

Placental transfer

Fetal blood vessels projecting into sinuses filled with maternal blood are covered by a single syncytium of cells called **trophoblasts**. The movement of drugs across the placenta is limited by the trophoblastic membrane, which is qualitatively similar to plasma membranes elsewhere. Although trophoblasts are known to secrete amino acids and other vital nutrients actively into the fetal circulation, the entry of most drugs depends on passive diffusion across the lipid barrier. For highly lipophilic drugs such as thiopental, distribution is retarded only by the rate of maternal blood flow through the placenta and by peculiarities in the fetal circulation that limit tissue perfusion. Even so, it has been calculated that 40 minutes are required for fetal tissues to attain 90% equilibration with a constant maternal arterial concentration. Limited by a sluggish transmembrane diffusion, the transfer of water-soluble compounds is so inefficient that virtually no drug from





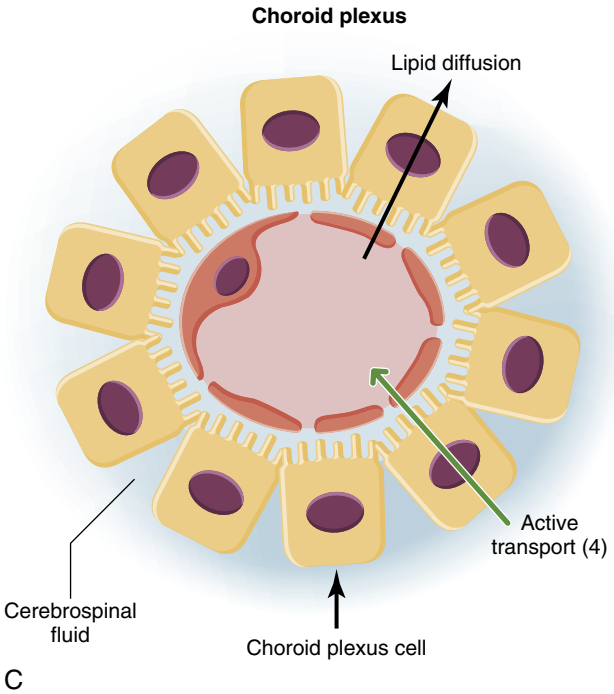


FIG 2-8 The contributors to the blood–brain barrier. The following four factors are shown. A brain capillary is compared to capillaries elsewhere in the body. (1) Tight junctions characterize the capillaries in the brain. (2) Astrocytes (glial cells) surround brain capillaries, providing an additional lipid barrier. (3) P-Glycoproteins pump drugs out of capillary cells. The third illustration shows cells of the choroid plexus surrounding a capillary. (4) These cells have SLC pumps that transport drugs from the CSF into the capillary lumen. *SLC*, Solute carrier transporters; *CSF*, cerebrospinal fluid.

a single administration may gain access to the fetus. As in the CNS, P-glycoproteins located in the trophoblastic plasma membrane facing the maternal blood tend to prevent potentially dangerous substances from entering the fetal circulation. Nevertheless, even sparingly lipid-soluble agents eventually accumulate in the fetus if administered to the mother in multiple doses.

Concern over the placental transfer of drugs arises from the possibility of inducing toxic manifestations in the newborn and developmental defects in the embryo and fetus. These topics are discussed further in Chapter 3.

Volume of Distribution

Drugs are not distributed equally throughout the body. Although lipophilic substances tend to penetrate all tissue compartments (provided that they have a modicum of water solubility for blood transport and are not actively ejected), hydrophilic compounds are often disseminated more restrictively. The **volume of distribution (V_d)** is a useful indicator of how drugs are dispersed among the various body compartments. In its simplest form, the V_d is calculated from the equation:

$$D = V_d \times Cp_0$$

where D is the quantity of drug administered in a single dose, and Cp_0 is the plasma concentration of the drug extrapolated to zero time, as shown later in Figure 2-14. Solving for V_d: $V_d = D/Cp_0$. In summary, the V_d is the **hypothetical** amount of water by which a particular dose would have to be diluted to produce a given plasma concentration, assuming that no drug has been lost through incomplete absorption or by metabolism or excretion.

As a practical matter, drugs confined within the blood have a V_d of approximately 3 L. This value represents the total plasma volume of a 70-kg man of average build. Most compounds pass readily from the vascular tree into the interstitial compartment, however. At equilibrium, these drugs are distributed in an extracellular volume of 12 L, which includes the vascular and interstitial fluids. Ionic drugs (e.g., aminoglycosides) are generally contained in this V_d. Molecules that can freely penetrate all membranes are diluted by the water of the entire body, which is approximately 41 L. Clearly, a difference of 3 versus 12 versus 41 L is significant. Figure 2-9 depicts the major body fluid volumes, and Table 2-2 provides a list of agents with representative V_d values.

It is apparent from Table 2-2 that the V_d of many compounds does not correspond to any definable anatomic fluid compartment. Accepting that the measurements were made correctly, and that problems in drug absorption and elimination were successfully avoided, several explanations remain for these results. The V_d equation provides only an **apparent distribution**, partly because it assumes that drugs are evenly dispersed. To illustrate this point, Na^+ is present in all body fluids (with an actual V_d of 41 L), but the apparent (calculated) V_d for Na^+ is only 18 L. This discrepancy arises because Na^+ is actively but incompletely extruded from intracellular water. Dissimilarities between true and calculated V_d values based on unequal compartment concentrations arise whenever ions are distributed across electrically polarized membranes, weak electrolytes are present in fluids of different pH, or drugs are actively transported into or out of a water space.

TABLE 2-2 Volumes of Distribution of Various Agents

Agent	V_d (L)*	Corresponding Fluid Compartment
Evans blue	3	Plasma water
Iodine 131–albumin	3	
Mannitol	12	Extracellular water
Amoxicillin	15	
Na^+	18	
Enalapril	40	
Urea	41	Total body water
Lidocaine	77	
Tetracycline	100	
Atropine	120	
Meperidine	300	
Chlorpromazine	1500	
Propofol	4000	
Chloroquine	13,000	

*For a 70-kg male.

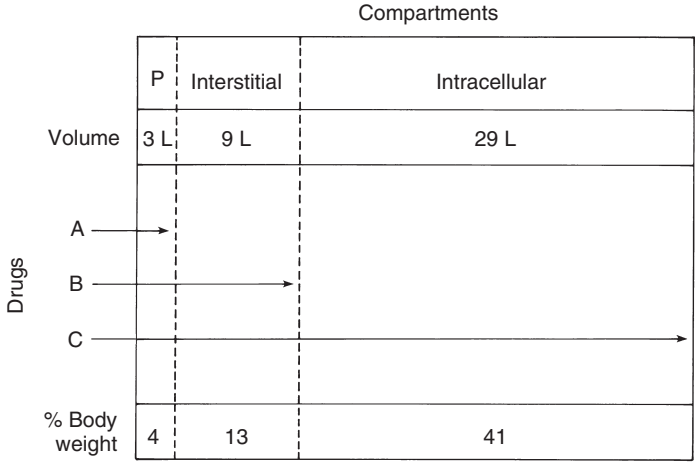


FIG 2-9 Body water compartments. The membrane barriers that separate plasma from interstitial fluid and interstitial fluid from intracellular water are indicated by *dashed lines*. The upper set of figures represents the respective volumes for a 70-kg man; the lower set are percentages of total body weight. Of the drugs shown, *A* is restricted to the plasma, *B* is distributed within the extracellular compartment (plasma + interstitial fluid), and *C* is disseminated throughout the total body water.

The enormous V_d values recorded for drugs such as propofol and chloroquine generally result from tissue binding. The sequestration of compounds within cells or certain tissues necessarily reduces the concentration of drug in the plasma, leading to an abnormally high calculation of V_d. (No drug can have a true V_d >41 L in the typical adult.) Plasma protein binding can also affect V_d determinations. Because the total drug in plasma is usually measured, binding artificially inflates the drug concentration and depresses V_d. If free drug is measured, significant binding by plasma proteins has the same effect as binding at extravascular sites. The point of the V_d is to help understand how drugs sequester and cluster in the body based on many influences.

Drug Binding and Storage

The sojourn of drugs in the body is considerably influenced by binding to proteins and other tissue components. Reducing the concentration of free solute causes a decrease in the rate of passage across membrane barriers and may alter drug distribution at equilibrium, as reflected in V_d determinations. Drug sequestration can also affect the processes of absorption, metabolism, and elimination.

Plasma protein binding

Numerous drugs become associated with plasma proteins, especially albumin. The predominant protein in plasma, albumin contains roughly 200 ionized functional groups per molecule and has the capacity to bind many different substances concurrently. A second plasma protein, α_1-acid glycoprotein (also known as orosomucoid), is a major "acceptor" of basic, or cationic, agents. Transcortin (which is specific for corticosteroids and a few other agents), other globulins, and various lipoproteins play more limited roles in drug binding.

The reversible attachment of drugs to plasma proteins is reminiscent of drug-receptor combinations in that the reaction obeys the law of mass action, as follows:

$$\text{Drug} + \text{Protein} \rightleftharpoons \text{Drug-protein complex}$$

The percentage of bound drug usually does not change over the dosage ranges used clinically, and assigning most drugs a fixed value is permissible (e.g., 99% for diazepam). Drugs differ tremendously in their affinity for plasma proteins; the percentage of binding of individual agents ranges from 0% to approaching 100%.

The binding of agents within the vascular compartment removes available free drug and therefore reduces the concentration gradient of free drug across the capillary membrane and slows egress from the plasma into the extravascular space. As free molecules leave the circulation, the bound drug begins to dissociate according to the law of mass action and becomes available for further egress.

Glomerular filtration and passive hepatic uptake involve only free drug; significant binding may depress the metabolism and excretion of drugs. When compounds are actively or otherwise rapidly taken up by organs of elimination, however, the instantaneous reversibility of binding can lead to a faster-than-normal elimination rate. Penicillin G is secreted into the urine so efficiently that blood flowing through the kidney is almost completely cleared of the antibiotic in a single pass. Because albumin binding presents the kidney with more total drug per unit time, secretion is quicker than would be the case if the drug were more evenly distributed throughout the body.

Two potential clinical concerns related to plasma protein binding involve patient variability in binding efficacy and the possibility for drug interaction. Individual differences in drug binding affect the concentration of free drug within the bloodstream and may lead to insufficient therapy in one patient and overdosage in another. The unusual susceptibility to diazepam exhibited by patients with hypoalbuminemia should be considered when the drug is used for intravenous sedation. Inasmuch as the attachment of drugs to plasma proteins is generally less selective than are drug-receptor associations, competition between drugs for binding sites is relatively common. Such interactions may reach clinical significance, however, only when the drugs are highly bound, are administered in large doses, and have a narrow margin of safety or a small V_d.

Tissue binding

As previously mentioned, drugs capable of associating with plasma proteins are also likely to bind to tissue protein constituents. Such binding does not impede the movement of drugs out of the bloodstream, but it does slow the rate of elimination. Various tissues have different affinities for drugs. By virtue of its aggregate size, muscle tissue is a significant reservoir for many drugs. Fat is also quantitatively important, especially for highly lipid-soluble compounds. Although uptake into fat is slow due to limited blood supply, adipose tissue constitutes 10% to more than 50% of total body weight, and most of an administered dose of a lipophilic drug may accumulate in fat over the course of several hours. Some tissues display unusual affinities for particular drugs; for example, the antimalarial agents chloroquine and quinacrine are heavily concentrated in the liver. Guanethidine and other quaternary ammonium compounds adhere to negatively charged residues in mucous secretions of the gastrointestinal tract.

The attachment of drugs to drug receptors warrants special comment. Important in the pharmacologic sense, the contribution of drug-receptor interactions to the total amount of binding is usually quite small. When distribution throughout the body and the various types of sequestration are considered, the percentage of drug administered that actually reaches its receptor to evoke a response is quantitatively very small.

Storage

The association between drugs and tissue elements is sometimes so stable that it is better to think of them as stored rather than transiently bound. When drugs are stored, they are not readily available for release and generally do not prolong the duration of action. Some of the most common examples of storage involve mineralized tissues and fat. Bone-seeking ions such as F^- and lead, and Ca^{++} chelators such as the tetracyclines, may be deposited with bone salts during mineralization or become associated with existing hydroxyapatite crystals. Essentially in an insoluble state, these substances are difficult or impossible to remove completely. Bone and tooth mineralization may benefit from appropriate concentrations of F^-, but most drug-induced alterations are detrimental. In the case of radioactive metals (e.g., strontium 90), storage in bone can lead to the development of leukemia, osteogenic sarcoma, and other forms of neoplasia. Zoledronic acid is exceptional in that storage in bone does lead to an extended duration of action. Given once a year for the treatment of postmenopausal osteoporosis, zoledronic acid is taken up by new bone formed during remodeling and is sequestered. Later, as osteoclasts restart bone turnover in the same area, zoledronic acid is released to inhibit further activity.

Redistribution

Strongly lipophilic drugs, especially when administered intravenously in bolus form, characteristically go through several phases of distribution: an initial transfer into vessel-rich organs (brain, heart, kidneys, liver, and lungs) followed by progressive redistribution to less highly vascularized tissues (muscle, skin, and eventually fat). When the target organ of a drug happens to have a high blood flow per unit mass, redistribution can result in the abrupt termination of drug effect. Thiopental has been extensively studied in this regard (Fig. 2-10). The onset of anesthesia with thiopental is almost instantaneous; however, consciousness is lost only temporarily, and the patient normally awakens in approximately

15 minutes. The quick onset and brief duration of thiopental reflect the rapidity by which the agent equilibrates between the blood and the CNS. Soon after a peak brain titer is reached (in 30 to 90 seconds), the concentration begins to decrease as thiopental continues to be absorbed by the relatively large mass of muscle. Consciousness returns at about the same time muscle reaches equilibrium with the blood. Thereafter, the brain and muscle concentrations parallel the plasma decay curve as the drug slowly passes into adipose tissue. With a metabolic half-time of approximately 10 hours, thiopental would be a relatively long-acting drug if not for redistribution. When repetitive injections saturate the fat reservoir, thiopental assumes the characteristics of a long-duration anesthetic.

Saliva

The transfer of drugs into saliva can be thought of as a form of redistribution because the drugs regain access to the systemic circulation after the saliva is swallowed. Although not involved in drug elimination, the entry of agents into the saliva is of pharmacologic interest in two other respects. First, drugs gaining access to the oral environment from the systemic circulation can affect microorganisms or tissue surfaces within the mouth. Although these influences are usually undesirable, a drug developed for a local effect, such as caries prevention, could conceivably be administered systemically to achieve a sustained therapeutic concentration in the saliva, while obviating the necessity of intraoral application. Drugs such as fluoride and antiplaque agents are examples of orally applied medications. Several unique factors are important in determining the clinical efficacy of medications on oral surfaces. One is substantivity of the preparation. Substantivity is the ability of a drug to remain for an extended time, due to the preparation itself or ability to form a retentive reservoir on hard or soft tissue. Salivary flow rate is important in determining the distribution of the medication. The second pharmacologic interest in saliva stems from the fact that salivary drug determinations can provide a noninvasive measure of the free plasma concentration of drugs. Because the free drug concentration in plasma is normally the primary determinant of patient response, the benefit of salivary drug quantitation to therapeutics is potentially great. Clinical studies have documented that saliva can be used to determine plasma levels of drugs, based on estimates of ratios of plasma to saliva drug concentrations. An example is shown in Table 2-3, in which the saliva concentrations reflect those of the plasma during the time period leading up to the peak concentration in the plasma. However, some drugs are not detected in saliva, even though with newer sensitive analysis methods it is possible to determine the concentration of many drugs in saliva. Moreover, the time and manner of sampling of saliva have to be controlled because salivary flows rates, which can alter drug concentrations, vary depending on several conditions. Given the fact that saliva has several advantages including its ease of collection, its noninvasive collection, and ease of storage, interest remains in using it for diagnostic purposes.

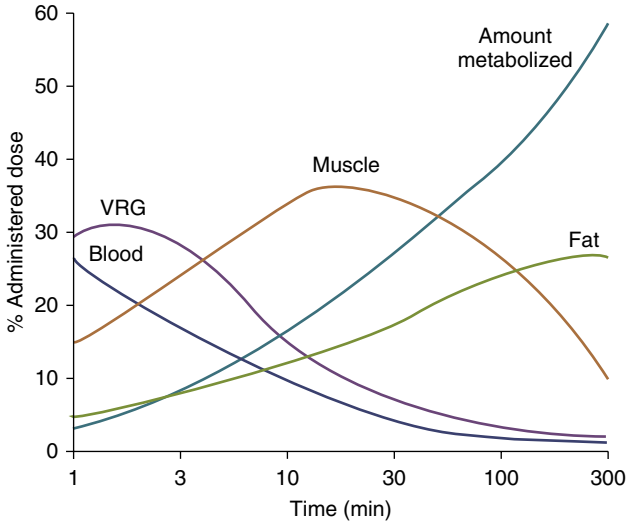


FIG 2-10 Redistribution of thiopental. *VRG,* Vessel-rich group tissues, including the brain, heart, lungs, kidneys, and liver. (Redrawn from Saidman LJ: Uptake, distribution and elimination of barbiturates. In Eger E II, editor: *Anesthetic uptake and action*, Baltimore, 1974, Williams & Wilkins.)

Drugs may enter the oral fluids from several sources: (1) passive diffusion across the alveolar and ductal cells of salivary glands, (2) active transport into saliva, (3) passive diffusion across the oral epithelium, and (4) bulk flow of fluid from the gingival crevice. Of these avenues, the first is the most important, and the fourth is the least important (except for drugs that cannot gain entry by any of the other routes). Drugs fit into different categories based on their levels in saliva. As shown in Table 2-3, the ratio of saliva/plasma concentrations varies among drugs taken from different classes. For the drugs shown in Table 2-3, there are good correlations between saliva and plasma concentration. Agents that are relatively lipid soluble (e.g., diazepam) or very small in size (e.g., ethanol) normally encounter little difficulty in equilibrating with saliva.

Active transport is a wild card with respect to predicting drug entry into saliva based on physicochemical characteristics. Digoxin is actively secreted into saliva by P-glycoprotein, effectively doubling the expected saliva/plasma ratio of 1/1 for a neutral drug with good lipid solubility. Coadministration of P-glycoprotein inhibitors significantly reduces the saliva/plasma ratio, as do polymorphisms that alter P-glycoprotein activity.

TABLE 2-3 Saliva/Plasma Values for Seven Representative Drugs

Drug	AUC (Saliva/Plasma)	C_{max} (Saliva/Plasma)	T_{max} (Saliva/Plasma)	Correlation Coefficient
Sitagliptin	0.16	0.19	4.00	0.99
Tolterodine	0.21	0.31	1.53	0.99
Hydrochlorothiazide	0.41	0.79	1.12	0.83
Metformin	0.11	0.12	2.23	0.87
Cloxacillin	1.76	2.61	1.00	0.99
Azithromycin	5.61	16.89	1.03	0.99
Rosuvastatin	0.08	0.17	1.05	0.89

The data in columns 2 to 4 are ratios (drugs present in saliva/drugs present in the plasma). *AUC*, Area under the curve (see later discussion of AUC); C_{max}, peak concentration of drug; T_{max}, time to peak concentration of drug. The correlation coefficients are the degree of linear relationship between drug concentration in saliva and drug concentration in plasma up to T_{max} for plasma.
Data taken from Idkaidek N, Arafat T: Saliva versus plasma pharmacokinetics: theory and application of a salivary excretion classification system, *Mol Pharmaceutics* 9:2358-2363, 2012.

METABOLISM

Metabolism is a major pathway for the termination of pharmacologic effects of drugs, and it is often a prerequisite for the excretion of lipid-soluble chemicals. Historically, the term **detoxification** was used in reference to drug metabolism. Typically, compounds are rendered **pharmacologically inactive** by metabolic attack; however, this is not always the case. Numerous drugs yield metabolites with full or partial activity, and some provide derivatives with novel or highly toxic drug effects. An increasing number of agents require chemical activation to be of therapeutic benefit (e.g., cyclophosphamide, mercaptopurine, methyldopa, and sulindac). The other typical effect of drug metabolism is the conversion of the parent drug to polar, relatively **lipid-insoluble compounds** that are susceptible to renal or biliary excretion or both.

Drug metabolism can be categorized according to the types of reactions involved and where they occur. Non-synthetic reactions include the various transformations of molecular structure: oxidation, reduction, and hydrolysis. These events are also called **phase I reactions** because they often represent the initial stage of biotransformation. A common outcome of phase I reactions is the addition or uncovering of one or more functional groups: —COOH, —NH_2, —O, —OH, or —SH. Synthetic, or **phase II, reactions** consist of the conjugation of drugs or their metabolites with functional groups provided by endogenous cofactors. Drugs may be metabolized by virtually any organ of the body, but quantitatively the most important enzyme systems for the biotransformation of exogenous substances are located in the liver.

Hepatic Microsomal Metabolism

Each hepatocyte contains an extensive network of **smooth endoplasmic reticulum** that catalyzes the metabolism of various endogenous chemicals (e.g., bilirubin, thyroxine, and steroids). Studies of fragmented reticular elements isolated along with other membrane structures in the form of **microsomes** have shown that numerous drugs are also chemically altered by enzymes located within this subcellular organelle. The greatest number of reactions involve oxidation; however, reduction, hydrolysis, and conjugation with glucuronic acid also occur.

Oxidation

The oxidation of drugs results in compounds that tend to be more polar, relatively more hydrophilic, and less likely to penetrate cells and bind to tissue elements. Microsomal oxidations are catalyzed by a set of mixed-function oxidases, so named because one atom of an oxygen dimer is incorporated into the drug, while the other is converted to water through the addition of two hydrogen atoms. Of particular significance to microsomal oxidation is the enzyme that actually binds the drug during metabolism: **cytochrome P450 (CYP).** This hemoprotein—actually a group of closely related isoenzymes—was designated P450 because of its absorption peak at 450 Å when combined in the reduced state with carbon monoxide. Multiple distinct CYP families have been identified in humans; the major enzymes involved in drug metabolism are shown in Figure 2-11.

In aggregate, the CYP superfamily constitutes up to 20% of the total protein content of liver microsomes. It acts as the terminal acceptor of electrons in a transport chain that also includes the reduced coenzyme nicotinamide adenine dinucleotide phosphate (NADPH) and the flavoprotein NADPH–cytochrome P450 oxidoreductase (Fig. 2-12). A unique ability of the CYP enzymes is their collective capacity to react with a diverse array of chemicals. The only identified requirement for microsomal oxidation is that the drug sufficiently penetrates the cell membranes to reach the hemoprotein. Table 2-4 lists the major CYP enzymes in humans along with some drugs that are metabolized by them and drugs that can inhibit or induce their activities.

The general pathway for oxidation of drugs by the hepatic microsomal enzyme system is depicted in Figure 2-13. The drug initially attaches to an oxidized (Fe^{+++}) CYP enzyme. This complex accepts an electron from the flavoprotein-catalyzed oxidation of NADPH. A ternary structure is produced next by the inclusion of molecular oxygen; the addition of a second electron and subsequently two protons causes the complex to break down, yielding the CYP enzyme, a water molecule, and the oxidized drug.

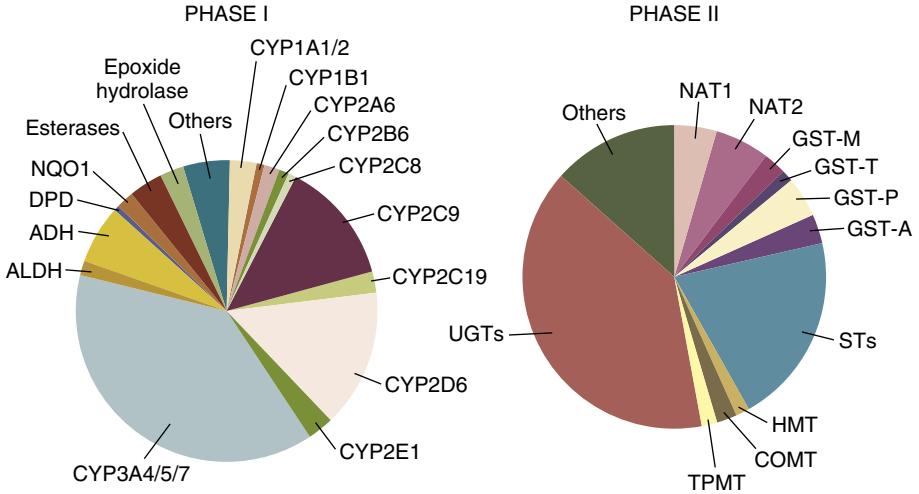


FIG 2-11 Major enzymes involved in drug metabolism. The percentage of phase I and phase II metabolism of drugs contributed by each enzyme is represented by the relative size of each section of the corresponding chart. *ADH,* Alcohol dehydrogenase; *ALDH,* aldehyde dehydrogenase; *CYP,* cytochrome P450; *DPD,* dihydropyrimidine dehydrogenase; *NQO1,* NAD(P)H:quinone oxidoreductase (or DT diaphorase); *COMT,* catechol-*O*-methyl transferase; *GST,* glutathione-*S*-transferase; *HMT,* histamine methyltransferase; *NAT,* N-acetyltransferase; *STs,* sulfotransferases; *TPMT,* thiopurine methyltransferase; *UGTs,* uridine diphosphate glucuronosyltransferases. (Adapted from Evans WE, Relling MV: Pharmacogenomics: translating functional genomics into rational therapeutics, *Science* 286:487-491, 1999.)