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Principles of Pharmacology

The Pathophysiologic Basis of Drug Therapy

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Ehrin J. Armstrong
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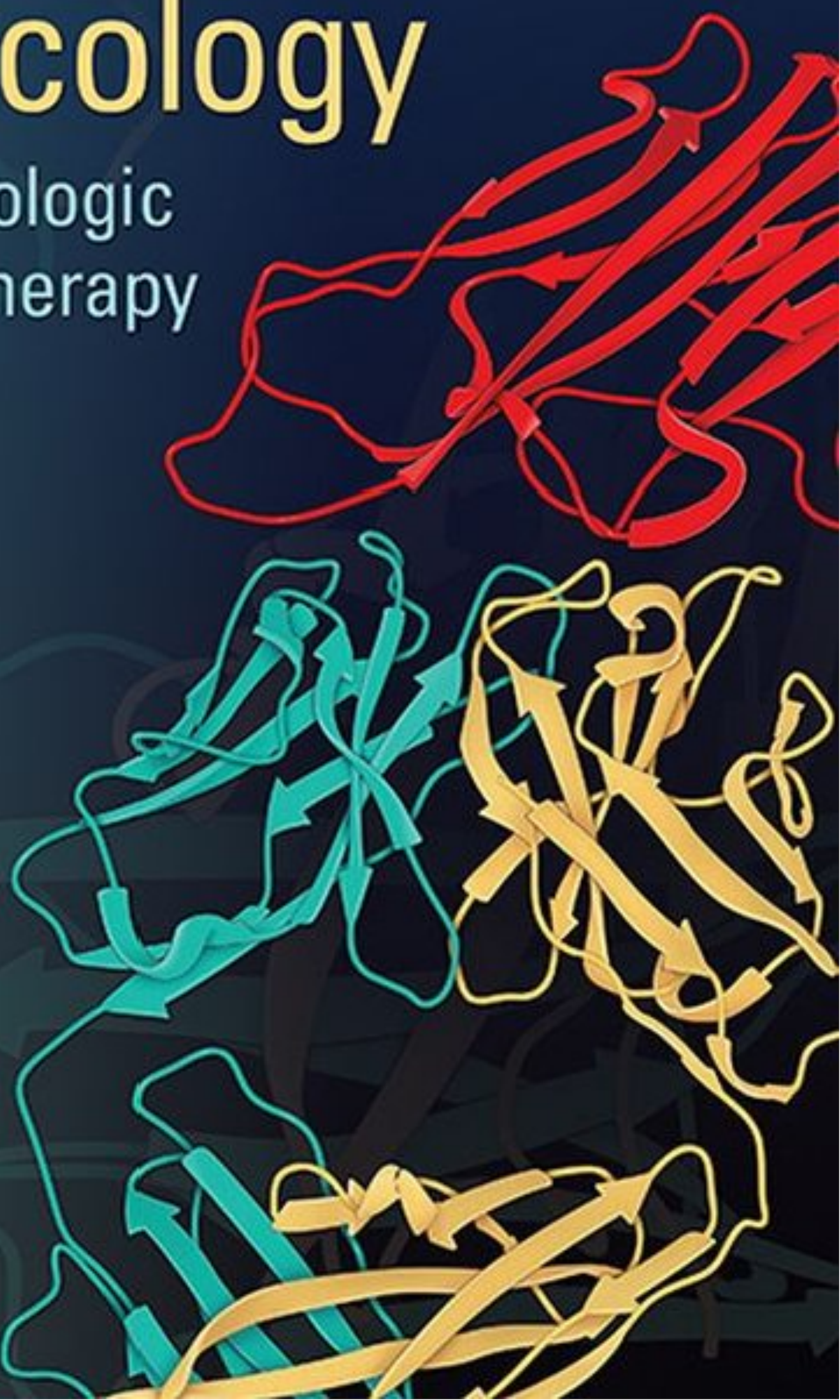

FOURTH EDITION

Wolters Kluwer

PRINCIPLES of PHARMACOLOGY

THE PATHOPHYSIOLOGIC BASIS OF DRUG THERAPY

Fourth Edition

PRINCIPLES of PHARMACOLOGY

THE PATHOPHYSIOLOGIC BASIS OF DRUG THERAPY

Fourth Edition

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To our students and the patients they will serve

Contents

Preface

The editors are grateful for many helpful suggestions from readers of the first, second, and third editions of *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy*. The fourth edition features many changes to reflect the rapidly evolving nature of pharmacology and drug development. We believe that these updates will continue to contribute to the learning and teaching of pharmacology both nationally and internationally:

- Comprehensive updates of *full-color figures* throughout the textbook—about 450 in all. Every figure has been updated and colorized, and over 50 figures are new or substantially modified to highlight advances in our understanding of physiologic, pathophysiologic, and pharmacologic mechanisms. As in the first three editions, our collaboration with a single illustrator creates a uniform "look and feel" among the figures that facilitates understanding and helps the reader make connections across broad areas of pharmacology.
- Comprehensive updates and additions in the *fundamentals of pharmacology*. Along with extensive updates in the chapters on drug–receptor interactions, pharmacodynamics, pharmacokinetics, drug metabolism, drug toxicity, and pharmacogenomics, a new chapter on *drug transporters* has been added. The first section of the textbook now provides a comprehensive framework for the fundamental principles of pharmacology that serve as the foundation for material in all subsequent chapters.
- Comprehensive updates of all 37 *drug summary tables*. These tables, which have been particularly popular with readers, group drugs and drug classes according to mechanism of action and list clinical applications, serious and common adverse effects, contraindications, and therapeutic considerations for each drug discussed in the chapter.
- Comprehensive *updates of all chapters*, including new drugs approved through 2014–2015. We have focused especially on newly discovered and revised mechanisms that sharpen our understanding of the physiology, pathophysiology, and pharmacology of the relevant system. Sections throughout the book contain substantial amounts of new and updated material, especially the chapters on drug–receptor interactions; drug toxicity; pharmacogenomics; adrenergic pharmacology; local anesthetic pharmacology; the pharmacology of serotonergic and central adrenergic neurotransmission; the pharmacology of analgesia; the pharmacology of cholesterol and lipoprotein metabolism; the pharmacology of volume regulation; the pharmacology of vascular tone; the pharmacology of hemostasis and thrombosis; the pharmacology of the thyroid gland; the pharmacology of the endocrine pancreas and glucose homeostasis; the pharmacology of bone mineral homeostasis; the pharmacology of bacterial DNA replication, transcription, and translation; the pharmacology of bacterial and mycobacterial cell wall synthesis; the pharmacology of viral infections; the pharmacology of cancer; the pharmacology of eicosanoids; the pharmacology of immunosuppression; the fundamentals of drug development and regulation; and protein therapeutics.

As with the third edition, we have recruited a panel of new, expert chapter authors who have added tremendous strength and depth to the existing panel of authors, and the editorial team has reviewed each chapter in detail to achieve uniformity of style, presentation, and currency across the entire text.

Finally, we would like to acknowledge the immeasurable contributions of the late Armen H. Tashjian, Jr., MD, to the conception, design, and implementation of this text. Armen was our friend, mentor, and close colleague, and his indomitable spirit lives on in this fourth edition of *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy*.

David E. Golan, MD, PhD
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Preface

to the First Edition

This book represents a new approach to the teaching of a first or second year medical school pharmacology course. The book, titled *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy*, departs from standard pharmacology textbooks in several ways. *Principles of Pharmacology* provides an understanding of drug action in the framework of human physiology, biochemistry, and pathophysiology. Each section of the book presents the pharmacology of a particular physiologic or biochemical system, such as the cardiovascular system or the inflammation cascade. Chapters within each section present the pharmacology of a particular aspect of that system, such as vascular tone or eicosanoids. Each chapter presents a clinical vignette, illustrating the relevance of the system under consideration; then discusses the biochemistry, physiology, and pathophysiology of the system; and, finally, presents the drugs and drug classes that activate or inhibit the system by interacting with specific molecular and cellular targets. In this scheme, the therapeutic and adverse actions of drugs are understood in the framework of the drug's mechanism of action. The physiology, biochemistry, and pathophysiology are illustrated using clear and concise figures, and the pharmacology is depicted by displaying the targets in the system on which various drugs and drug classes act. Material from the clinical vignette is referenced at appropriate points in the discussion of the system. Contemporary directions in molecular and human pharmacology are introduced in chapters on modern methods of drug discovery and drug delivery and in a chapter on pharmacogenomics.

This approach has several advantages. We anticipate that students will use the text not only to learn pharmacology but also to review essential aspects of physiology, biochemistry, and pathophysiology. Students will learn pharmacology in a conceptual framework that fosters mechanism-based learning rather than rote memorization, and that allows for ready incorporation of new drugs and drug classes into the student's fund of knowledge. Finally, students will learn pharmacology in a format that integrates the actions of drugs from the level of an individual molecular target to the level of the human patient.

The writing and editing of this textbook have employed a close collaboration among Harvard Medical School students and faculty in all aspects of book production, from student–faculty co-authorship of individual chapters to student–faculty editing of the final manuscript. In all, 43 HMS students and 39 HMS faculty have collaborated on the writing of the book's 52 chapters. This development plan has blended the enthusiasm and perspective of student authors with the experience and expertise of faculty authors to provide a comprehensive and consistent presentation of modern, mechanism-based pharmacology.

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The editors are grateful for the support of students and faculty from around the world who have provided encouragement and helpful suggestions.

Stuart Ferguson continued his exemplary work as an executive assistant by managing all aspects of project coordination, including submission of chapter manuscripts, multiple layers of editorial revisions, coordination of f gure generation and revision, and delivery of the f nal manuscript. We are extraordinarily grateful for his unwavering dedication to this project.

Rob Duckwall did a superb job to update the full-color f gures. Rob's standardization and coloration of the f gures in this textbook reflect his creativity and expertise as a leading medical illustrator. His artwork is a major asset and highlight of this textbook.

Quentin Baca electronically rendered the striking image on the cover of this textbook. We are most grateful for his creativity and expertise.

The editors would like to thank the publication, editorial, and production staff at Wolters Kluwer for their expert management and production of this handsome volume.

David Golan would like to thank the many faculty, student, and administrative colleagues whose support and understanding were critical for the successful completion of this project. Members of the Golan laboratory and faculty and staff in the Department of Biological Chemistry and Molecular Pharmacology at Harvard Medical School and in the Hematology Division at Brigham and Women's Hospital and the Dana-Farber Cancer Institute were gracious and supportive throughout. Deans Jeffrey Flier and John Czajkowski were especially supportive and encouraging. Laura, Liza, and Sarah provided valuable insights at many critical stages of this project and were constant sources of support and love.

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April Armstrong would like to thank Drs. David Golan and Laura Green for their constant support over the years. She thanks her dedicated coauthors Eryn Royer, Elizabeth Brezinski, and Chelsea Ma for their hard work. She also thanks Drs. David Norris, David West, and Fu-Tong Liu for fostering her career. She is grateful for the love of her family—Amy, Yanni, and Susan.

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Fundamental Principles of Pharmacology

1

Drug–Receptor Interactions

Francis J. Alenghat and David E. Golan

INTRODUCTION

Why is it that one drug affects cardiac function and another alters the transport of specific ions in the kidney? Why do antibiotics effectively kill bacteria but rarely harm patients? These questions can be answered by first examining the interaction between a drug and its specific molecular target and then considering the role of that action in a broader physiologic context. This chapter focuses on the molecular details of drug–receptor interactions, emphasizing the variety of receptors and their molecular mechanisms. This discussion provides a conceptual basis for the action of the many drugs and drug classes discussed in this book. It also serves as a background for Chapter 2, Pharmacodynamics, which discusses the quantitative relationships between drug–receptor interactions and pharmacologic effect.

Although drugs can theoretically bind to almost any three-dimensional target, most drugs achieve their desired (therapeutic) effects by interacting selectively with target molecules that play important physiologic or pathophysiologic roles. In many cases, selectivity of drug binding to receptors also determines the undesired (adverse) effects of a drug. In general, drugs are molecules that interact with specific molecular components of an organism to cause biochemical and physiologic changes within that organism. Drug receptors are macromolecules that, upon binding to a drug, mediate those biochemical and physiologic changes.

CONFORMATION AND CHEMISTRY OF DRUGS AND RECEPTORS

An understanding of why a drug binds to a particular receptor can be found in the structure and chemical properties of the two molecules. This section discusses the basic determinants of receptor structure and the chemistry of drug–receptor binding. The discussion here focuses primarily on the interactions of drugs that are small molecules with target receptors that are mainly macromolecules (especially proteins), but many of these principles also apply to the interactions of antibody- or other protein-based therapeutics with their molecular targets (see Chapter 54, Protein Therapeutics).

Because many human and microbial drug receptors are proteins, it is useful to review the four major levels of protein structure (Fig. 1-1). At the most basic level, proteins consist of long chains of amino acids, the sequences of which are determined by the sequences of the DNA that code for the proteins. A protein's amino acid sequence is referred to as its primary structure. Once a long chain of amino acids has been synthesized on a ribosome, many of the amino acids

Intent on enjoying his newly found retirement, Mr. B has made a point of playing tennis as often as possible during the past year. For the past 3 months, however, he has noted increasing fatigue. Moreover, he is now unable to finish a meal, despite his typically voracious appetite. Worried and wondering what these symptoms mean, Mr. B schedules an appointment with his doctor. On physical examination, the physician notes that Mr. B has an enlarged spleen, extending approximately 10 cm below the left costal margin; the physical exam is otherwise within normal limits. Blood tests show an increased total white blood cell count (70,000 cells/mm^3) with an absolute increase in neutrophils, band forms, metamyelocytes, and myelocytes, but no blast cells (undifferentiated precursor cells). Cytogenetic analysis of metaphase cells demonstrates that 90% of Mr. B's myeloid cells possess the Philadelphia chromosome (indicating a translocation between chromosomes 9 and 22), confirming the diagnosis of chronic myeloid leukemia. The physician initiates therapy with imatinib, a highly selective inhibitor of the BCR-Abl tyrosine kinase fusion protein that is encoded by the Philadelphia chromosome. Over the next month, the cells containing the Philadelphia chromosome disappear completely from Mr. B's blood, and he begins to feel well enough to compete in a seniors tennis tournament. Mr. B continues to take imatinib every day, and he has a completely normal blood count and no fatigue. He is not sure what the future will bring, but he is glad to have been given the chance to enjoy a healthy retirement.

Questions

1. How does imatinib interrupt the activity of the BCR-Abl tyrosine kinase fusion protein?
2. Unlike imatinib, most of the older therapies for chronic myeloid leukemia (such as interferon-α) had significant "flu-like" adverse effects. Why did these therapies cause significant adverse effects in most patients, whereas (as in this case) imatinib causes adverse effects in very few patients?
3. Why is imatinib a selective therapy for chronic myeloid leukemia? Is this selectivity related to the lack of adverse effects associated with imatinib therapy?
4. How does the BCR-Abl protein affect intracellular signaling pathways?

begin to interact with nearby amino acids in the polypeptide chain. These interactions, which are typically mediated by hydrogen bonding, give rise to the secondary structure of a protein by forming well-defined conformations such as the α helix, β pleated sheet, and β barrel. As a result of their highly organized shape, these structures often pack tightly with one another, further defining the overall shape of the protein. Tertiary structure results from the interaction of amino acids more distant from one another along a single amino acid chain. These interactions include hydrogen bond and ionic bond formation as well as the covalent linkage of sulfur atoms to form intramolecular disulfide bridges. Finally, polypeptides may oligomerize to form more complex structures. The conformation that results from the interaction of separate polypeptides is referred to as the quaternary structure.

Different portions of a protein's structure generally have different affinities for water, and this feature has an additional effect on the protein's shape. Because both the extracellular and intracellular environments are composed primarily of water, hydrophobic protein segments are often drawn to the inside of the protein or shielded from water by insertion into lipid bilayer membranes. Conversely, hydrophilic protein segments are often located on a protein's exterior surface. After all of this twisting and turning is completed, each protein has a unique shape that determines its function, location in the body, relationship to cellular membranes, and binding interactions with drugs and other macromolecules.

The site on the receptor at which the drug binds is called its binding site. Each binding site has unique chemical characteristics that are determined by the specific properties of the amino acids that make up the site. The three-dimensional structure, shape, and reactivity of the site, and the inherent structure, shape, and reactivity of the drug, determine the orientation of the drug with respect to the receptor and govern how tightly these molecules bind to one another. Drug–receptor binding is the result of multiple chemical interactions between the two molecules, some of which are fairly weak (such as van der Waals forces) and some of which are extremely strong (such as covalent bonding). The sum total of these interactions provides the specificity of the overall drug–receptor interaction. The favorability of a drug–receptor interaction is referred to as the affinity of the drug for its binding site on the receptor. This concept is discussed in more detail in Chapter 2. The chemistry of the local environment in which these interactions occur—such as the hydrophobicity, hydrophilicity, and pK_a of amino acids near the binding site—may also affect the affinity of the drug–receptor interaction. The primary forces that contribute to drug–receptor affinity are described below and in Table 1-1.

van der Waals forces, resulting from the polarity induced in a molecule by the shifting of its electron density in response to the close proximity of another molecule, provide a weak attractive force for drugs and their receptors. This induced polarity is a ubiquitous component of all molecular interactions. Hydrogen bonds have substantial strength and are often important for drug–receptor association. This type of bond is mediated by the interaction between positively polarized hydrogen atoms (which are covalently attached to more electronegative atoms such as nitrogen or oxygen) and negatively polarized atoms (such as oxygen, nitrogen, or sulfur that are covalently attached to less electronegative atoms such as carbon or hydrogen). Ionic interactions,

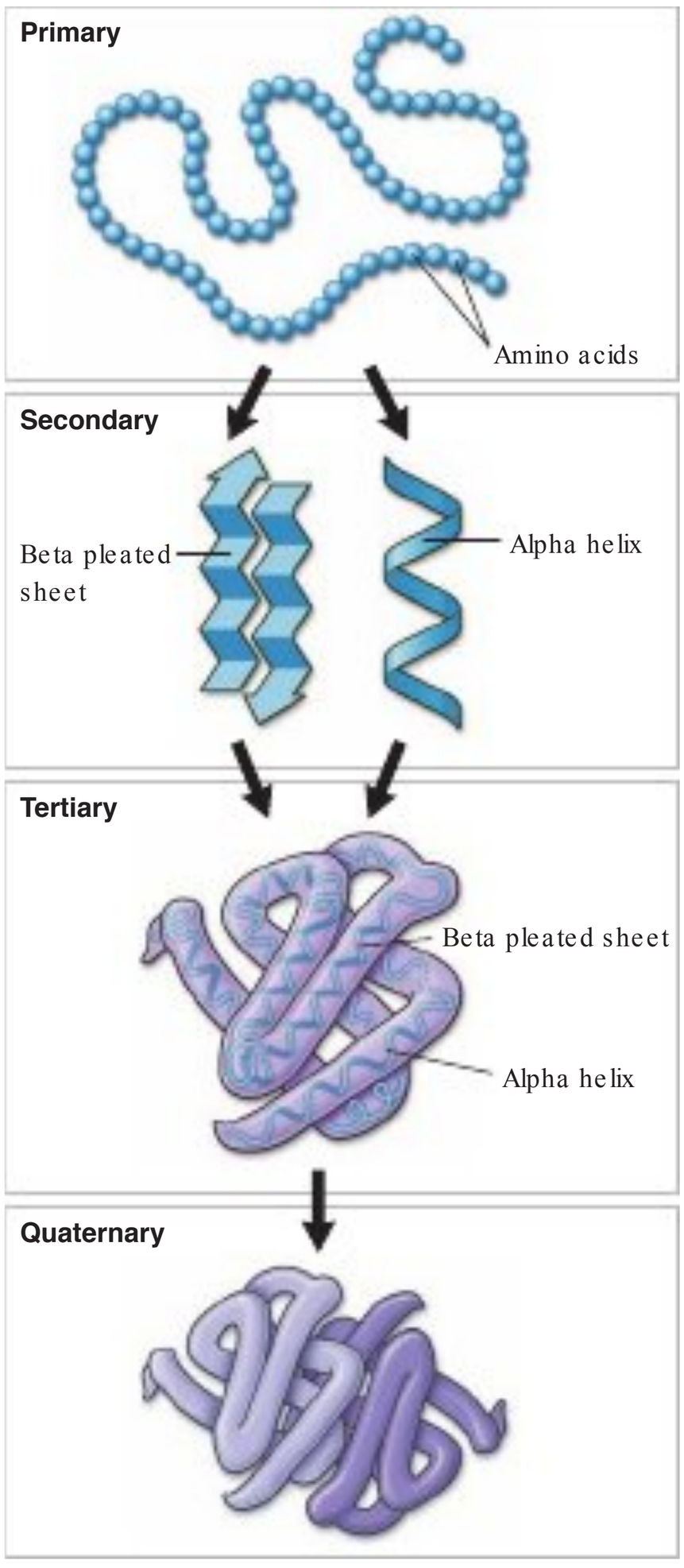

FIGURE 1-1. Levels of protein structure. Protein structure can be divided into four levels of complexity, referred to as primary, secondary, tertiary, and quaternary structure. Primary structure is determined by the sequence of amino acids that make up the polypeptide chain. Secondary structure is determined by the interaction of positively polarized hydrogen atoms with negatively polarized atoms (such as oxygen) on the same polypeptide chain. These interactions result in a number of characteristic secondary patterns of protein conformation, including the α helix and β pleated sheet. Tertiary structure is determined by the interactions of amino acids that are relatively far apart on the protein backbone. These interactions, which include ionic bonds and covalent disulfide linkages (among others), give proteins their characteristic three-dimensional structure. Quaternary structure is determined by the binding interactions among two or more independent protein subunits.

which occur between atoms with opposite charges, are stronger than hydrogen bonds but less strong than covalent bonds. Covalent bonding results from the sharing of a pair of electrons between two atoms on different molecules. Covalent interactions are so strong that, in most cases, they are essentially irreversible. Table 1-1 indicates the mechanism of interaction and relative strength of each of these types of bonds. As noted above, the environment in which drugs and receptors interact also affects the favorability of binding. The hydrophobic effect refers to the mechanism by which the unique properties of the ubiquitous solvent water cause the interaction of a hydrophobic molecule with a hydrophobic binding site to be enhanced.

Rarely is drug–receptor binding caused by a single type of interaction; rather, it is a combination of these binding interactions that provides drugs and receptors with the forces necessary to form a stable drug–receptor complex. In general, multiple weak forces comprise the majority of drug–receptor interactions. For example, imatinib forms many van der Waals interactions and hydrogen bonds with the ATP-binding site of the BCR-Abl tyrosine kinase. The sum total of these relatively weak forces creates a strong (high affinity) interaction between this drug and its receptor (Fig. 1-2). Ionic and hydrophobic interactions exert force at a greater distance than van der Waals interactions and hydrogen bonds; for this reason, the former interactions are often critical to initiate the association of a drug and receptor.

Although relatively rare, covalent interactions between a drug and its receptor are a special case. The formation of a covalent bond is often essentially irreversible, and in such cases, the drug and receptor form an inactive complex. To regain activity, the cell must synthesize a new receptor molecule to replace the inactivated protein; and the drug molecule, which is also part of the inactive complex, is generally not available to inhibit other receptor molecules. Drugs that modify their target receptors (often enzymes) through this mechanism are sometimes called suicide substrates. Aspirin is an example of such a drug; it irreversibly acetylates cyclooxygenases to reduce the production of prostaglandins (anti-inflammatory effect) and thromboxanes (antiplatelet effect) (see Chapter 43, Pharmacology of Eicosanoids).

The molecular structure of a drug dictates the physical and chemical properties that contribute to its specific binding to the receptor. Important factors include hydrophobicity, ionization state (pK_a), conformation, and stereochemistry of the drug molecule. All of these factors combine to determine the complementarity of the drug to the binding site. Receptor binding pockets are highly specific, and small changes in the drug can have a large effect on the affinity of the drug–receptor interaction. For example, the stereochemistry of the drug has a great impact on the strength of the binding interaction. Warfarin is synthesized and administered as a racemic mixture (a mixture containing 50% of the right-handed molecule and 50% of the left-handed molecule); however, the S enantiomer is four times more potent than the R because of a stronger interaction of the S form with its binding site on vitamin K epoxide reductase. Stereochemistry can also affect toxicity in cases where one enantiomer of a drug causes the desired therapeutic effect and the other enantiomer causes an undesired toxic effect, perhaps due to an interaction with a second receptor or to metabolism to a toxic species. Although it is sometimes difficult for pharmaceutical companies to synthesize and purify individual enantiomers on a large scale, a number of currently marketed drugs are produced as individual enantiomers in cases where one enantiomer has higher efficacy and/or lower toxicity than its mirror image.

TABLE 1-1 Relative Strength of Bonds between Receptors and Drugs

BOND TYPE	MECHANISM	BOND STRENGTH
van der Waals	Shifting electron density in areas of a molecule, or in a molecule as a whole, results in the generation of transient positive or negative charges. These areas interact with transient areas of opposite charge on another molecule.	+
Hydrogen	Hydrogen atoms bound to nitrogen or oxygen become more positively polarized, allowing them to bond to more negatively polarized atoms such as oxygen, nitrogen, or sulfur.	++
Ionic	Atoms with an excess of electrons (imparting an overall negative charge on the atom) are attracted to atoms with a deficiency of electrons (imparting an overall positive charge on the atom).	+++
Covalent	Two bonding atoms share electrons.	++++

Impact of Drug Binding on the Receptor

How does drug binding produce a biochemical and/or physiologic change in the organism? In the case of receptors with enzymatic activity, the binding site of the drug is often the active site at which an enzymatic transformation is catalyzed, and the catalytic activity of the enzyme is inhibited by drugs that prevent substrate binding to the site or that covalently modify the site. In cases where the binding site is not the active site of the enzyme, drugs can cause a change by preventing the binding of endogenous ligands to their receptor binding pockets. In many drug–receptor interactions, however, the binding of a drug to its receptor results in a change in the conformation of the receptor. Altering the shape of the receptor can affect its function, including enhancing the affinity of the drug for the receptor. Such an interaction is often referred to as induced fit, because the receptor's conformation changes so as to improve the quality of the binding interaction.

The principle of induced fit suggests that drug–receptor binding can have profound effects on the conformation of the receptor. By inducing conformational changes in the receptor, many drugs not only improve the quality of the binding interaction but also alter the action of the receptor. The change in shape induced by the drug is sometimes identical to that caused by the binding of an endogenous ligand. For example, exogenously administered insulin analogues all stimulate the insulin receptor to the same extent, despite their slightly different amino acid sequences. In other cases, drug binding alters the shape of the receptor so as to make it more or less functional than normal. For example, imatinib binding to the BCR-Abl tyrosine kinase causes the protein to assume an enzymatically inactive conformation, thus inhibiting the kinase activity of the receptor.

Another way to describe the induced fit principle is to consider that many receptors exist in multiple conformational states—such as inactive (or closed), active (or open), and desensitized (or inactivated)—and that the binding of a

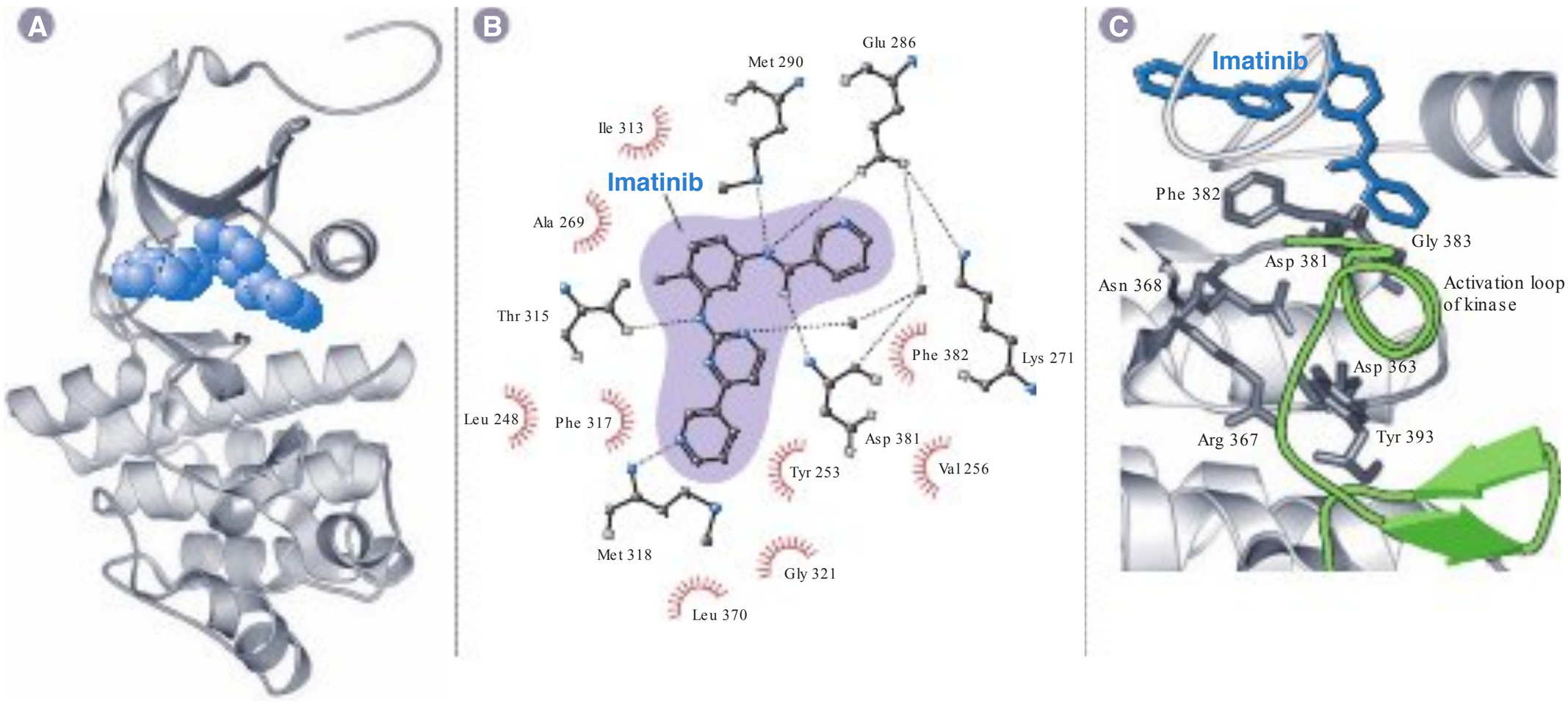

FIGURE 1-2. Structural basis of specific enzyme inhibition: imatinib interaction with the BCR-Abl kinase. A. The kinase portion of the BCR-Abl tyrosine kinase is shown in a ribbon format (gray). An analogue of imatinib, a specific inhibitor of the BCR-Abl tyrosine kinase, is shown as a space-filling model (blue). B. Detailed diagram of the intermolecular interactions between the drug (shaded in purple) and amino acid residues in the BCR-Abl protein. Hydrogen bonds are indicated by dashed lines, while van der Waals interactions (indicated by halos around the amino acid name and its position in the protein sequence) are shown for nine amino acids with hydrophobic side chains. C. The interaction of the drug (blue) with the BCR-Abl protein (gray) inhibits phosphorylation of a critical activation loop (green-highlighted ribbon format), thus preventing catalytic activity.

drug to the receptor stabilizes one or more of these conformations. Quantitative models that incorporate these concepts of drug–receptor interactions are discussed in Chapter 2.

Membrane Effects on Drug–Receptor Interactions

The structure of the receptor also determines where the protein is located in relationship to cellular boundaries such as the plasma membrane. Proteins that have large hydrophobic domains are able to reside in the plasma membrane because of the membrane's high lipid content. Many receptors that span the plasma membrane have lipophilic domains that are located in the membrane and hydrophilic domains that reside in the intracellular and extracellular spaces. Other drug receptors, including a number of transcription regulators (also called transcription factors), have only hydrophilic domains and reside in the cytoplasm, nucleus, or both.

Just as the structure of the receptor determines its location in relationship to the plasma membrane, *the structure of a drug affects its ability to gain access to the receptor*. For example, many drugs that are highly water-soluble are unable to pass through the plasma membrane and bind to target molecules in the cytoplasm. Certain hydrophilic drugs are able to pass through transmembrane channels (or use other transport mechanisms) and gain ready access to cytoplasmic receptors. Drugs that are highly lipophilic, such as many steroid hormones, are often able to pass through the hydrophobic lipid environment of the plasma membrane without special channels or transporters and thereby gain access to intracellular targets.

Drug-induced alterations in receptor shape can allow drugs bound to cell surface receptors to affect functions inside cells. Many cell surface receptors have extracellular domains that are linked to intracellular effector molecules by receptor domains that span the plasma membrane and extend into the cytoplasm. In some cases, changing the shape of the extracellular domain can alter the conformation of the membrane-spanning and/or intracellular domains of the receptor, resulting in a change in receptor function. In other cases, drugs can cross-link the extracellular domains of two receptor molecules, forming a dimeric receptor complex that activates effector molecules inside the cell.

All of these factors—drug and receptor structure, the chemical forces influencing drug–receptor interaction, drug solubility in water and in the plasma membrane, and the function of the receptor in its cellular environment—confer substantial specificity on the interactions between drugs and their target receptors. This book discusses numerous examples of drugs that can gain access and bind to receptors, induce conformational changes in the receptors, and thereby produce biochemical and physiologic effects. Specificity of drug–receptor binding suggests that, armed with the knowledge of the structure of a receptor, one could theoretically design a drug that interrupts or enhances receptor activity. This process, known as rational drug design, could potentially increase the efficacy and reduce the toxicity of drugs by optimizing their structure so that they bind more selectively to their targets. Rational drug design was first used to develop highly selective agents such as the antiviral protease inhibitor ritonavir and the antineoplastic tyrosine kinase inhibitor imatinib. Indeed, further rounds of rational drug design have led to the development of second-generation protease inhibitors and antineoplastics with high affinity for the mutated drug targets that can evolve in patients who develop resistance to first-generation drugs. The rational drug design approach is discussed in greater detail in Chapter 51, Drug Discovery and Preclinical Development.

MOLECULAR AND CELLULAR DETERMINANTS OF DRUG SELECTIVITY

The ideal drug would interact only with a molecular target that causes the desired therapeutic effect but not with molecular targets that cause unwanted adverse effects. Although no such drug has yet been discovered (i.e., all drugs currently in clinical use have the potential to cause adverse effects as well as therapeutic effects; see Chapter 6, Drug Toxicity), pharmacologists can take advantage of several determinants of drug selectivity in an attempt to reach this goal. Selectivity of drug action can be conferred by at least two classes of mechanisms, including (1) the cell-type specificity of receptor subtypes and (2) the cell-type specificity of receptor–effector coupling.

Although many potential receptors for drugs are widely distributed among diverse cell types, some receptors are more limited in their distribution. Systemic administration of drugs that interact with such localized receptors can result in a highly selective therapeutic effect. For example, drugs that target ubiquitous processes such as DNA synthesis are likely to cause significant toxic side effects; this is the case with many currently available chemotherapeutics for the treatment of cancer. Other drugs that target cell-type restricted processes such as acid generation in the stomach may have fewer adverse effects. Imatinib, for example, is an extremely selective drug because the BCR-Abl protein is not expressed in normal (noncancerous) cells. In general, *the more restricted the cell-type distribution of the receptor targeted by a particular drug, the more selective the drug is likely to be*.

Similarly, even though many different cell types may express the same molecular target for a drug, the effect of that drug may differ in the various cell types because of differential receptor–effector coupling mechanisms or differential requirements for the drug target in the various cell types. For example, although voltage-gated calcium channels are ubiquitously expressed in the heart, cardiac pacemaker cells are relatively more sensitive to the effects of calcium channel blocking agents than are cardiac ventricular muscle cells. This differential effect is attributable to the fact that action potential propagation depends mainly on the action of calcium channels in cardiac pacemaker cells, whereas sodium channels are more important than calcium channels in the action potentials of ventricular muscle cells. In general, *the more the receptor–effector coupling mechanisms differ among the various cell types that express a particular molecular target for a drug, the more selective the drug is likely to be*.

MAJOR TYPES OF DRUG RECEPTORS

Given the great diversity of drug molecules, it might seem likely that the interactions between drugs and their molecular targets would be equally diverse. This is only partly true. In fact, *most of the currently understood drug–receptor interactions can be classified into six major groups*. These groups comprise the interactions between drugs and (1) transmembrane

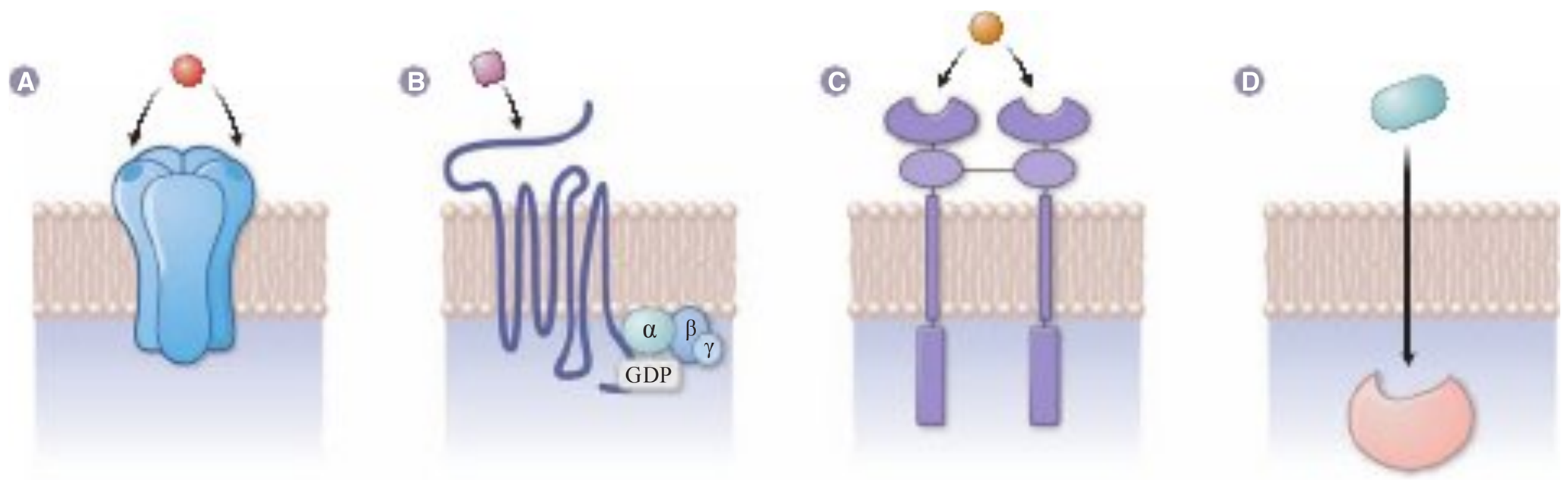

FIGURE 1-3. Major types of interactions between drugs and receptors. Most drug–receptor interactions can be divided into six groups, four of which are shown here. A. Drugs can bind to ion channels spanning the plasma membrane, causing an alteration in the channel's conductance. B. Heptahelical receptors spanning the plasma membrane are functionally coupled to intracellular G proteins. Drugs can influence the actions of these receptors by binding to the extracellular surface or transmembrane region of the receptor. C. Drugs can bind to the extracellular domain of a transmembrane receptor and cause a change in signaling within the cell by activating or inhibiting an enzymatic intracellular domain (rectangular box) of the same receptor molecule. D. Drugs can diffuse through the plasma membrane and bind to cytoplasmic or nuclear receptors. This is often the pathway used by lipophilic drugs (e.g., drugs that bind to steroid hormone receptors). Additionally, drugs can bind to enzymes and other targets in the extracellular space and to cell surface adhesion receptors without the need to cross the plasma membrane (not shown).

ion channels; (2) transmembrane receptors coupled to intracellular G proteins; (3) transmembrane receptors with linked enzymatic domains; (4) intracellular receptors, including enzymes, signal transduction molecules, transcription factors, structural proteins, and nucleic acids; (5) extracellular targets; and (6) cell surface adhesion receptors (Fig. 1-3). Table 1-2 provides a summary of each major interaction type.

Knowing whether and to what extent a drug activates or inhibits its target provides valuable information about the interaction. Although pharmacodynamics (the effects of drugs on the human body) is covered in detail in the next chapter, it is useful to state brief y the major pharmacodynamic relationships between drugs and their targets before examining the molecular mechanisms of drug–receptor interactions. Agonists *are molecules that, upon binding to their targets, cause a change in the activity of those targets.* Full agonists bind to and activate their targets to the maximal extent possible. For example, acetylcholine binds to the nicotinic acetylcholine receptor and induces a conformational change in the receptor-associated ion channel from a nonconducting to a fully conducting state. Partial agonists produce a submaximal response upon binding to their targets. Inverse agonists cause constitutively active targets to become inactive. Antagonists *inhibit the ability of their targets to be activated (or inactivated) by physiologic or pharmacologic agonists.* Drugs that directly block the binding site of a physiologic agonist are called competitive antagonists; drugs that bind to other sites on the target molecule, and thereby prevent the conformational change required for receptor activation (or inactivation), may be either noncompetitive or uncompetitive antagonists (see Chapter 2). As the mechanism of each drug–receptor interaction is outlined in the next several sections, it will be useful to consider at a structural level how these different pharmacodynamic effects could be produced.

Transmembrane Ion Channels

Many cellular functions require the passage of ions and other hydrophilic molecules across the plasma membrane.

TABLE 1-2 Six Major Types of Drug–Receptor Interactions

RECEPTOR TYPE	SITE OF DRUG–RECEPTOR INTERACTION	SITE OF RESULTANT ACTION	EXAMPLES
Transmembrane ion channel	Extracellular, intrachannel, or intracellular	Cytoplasm	Amlodipine, diazepam, lidocaine, omeprazole
Transmembrane linked to intracellular G protein	Extracellular or intramembrane	Cytoplasm	Albuterol, loratadine, losartan, metoprolol
Transmembrane with linked enzymatic domain	Extracellular or intracellular	Cytoplasm	Erlotinib, insulin, nesiritide, sunitinib
Intracellular	Cytoplasm or nucleus	Cytoplasm or nucleus	Atorvastatin, doxycycline, levothyroxine, paclitaxel
Extracellular target	Extracellular	Extracellular	Dabigatran, donepezil, etanercept, lisinopril
Adhesion	Extracellular	Extracellular	Eptif batide, natalizumab

Specialized transmembrane channels regulate these processes. The functions of ion channels are diverse, including fundamental roles in neurotransmission, cardiac conduction, muscle contraction, and secretion. Because of this, drugs targeting ion channels can have a substantial impact on major body functions.

Three major mechanisms are used to regulate the activity of transmembrane ion channels. In some channels, the conductance is controlled by ligand binding to the channel. In other channels, the conductance is regulated by changes in voltage across the plasma membrane. In still other channels, the conductance is controlled by ligand binding to plasma membrane receptors that are linked to the channel in some way. The first group of channels is referred to as ligand-gated, the second as voltage-gated, and the third as second messenger-regulated. Table 1-3 summarizes the mechanism of activation and function of each channel type.

Channels are generally highly selective for the ions they conduct. For example, action potential propagation in neurons of the central and peripheral nervous systems occurs as a result of the synchronous stimulation of voltage-gated ion channels that permit the selective passage of Na^+ ions into the cell. When the membrane potential in such a neuron becomes sufficiently positive, the voltage-gated Na^+ channels open, allowing a large influx of extracellular sodium ions that further depolarizes the cell. The role of ion-selective channels in action potential generation and propagation is discussed in Chapter 8, Principles of Cellular Excitability and Electrochemical Transmission.

Most ion channels share some structural similarity, regardless of their ion selectivity, the magnitude of their conductance, or their mechanism of activation (gating) or inactivation. Ion channels are pore-forming macromolecules consisting of one or more protein subunits that pass through the plasma membrane. The ligand-binding domain can be extracellular, within the channel, or intracellular, whereas the domain that interacts with other receptors or modulators is most often intracellular. The structures of several ion channels have been determined to atomic resolution; the nicotinic acetylcholine (ACh) receptor provides an example of the structure of an important ligand-gated ion channel. This receptor consists of five subunits, each of which crosses the plasma membrane (Fig. 1-4). Two of the subunits have been designated α; each contains a single extracellular binding site for ACh. In the free (nonliganded) state of the receptor, the channel is occluded by amino acid side chains and does not allow the passage of ions. Binding of two molecules of acetylcholine to the receptor induces a conformational change that opens the channel and allows ion conductance.

Although the nicotinic ACh receptor appears to assume only two states, open or closed, many ion channels assume other states as well. For example, some ion channels are able to become refractory or inactivated. In this state, the channel's permeability cannot be altered for a certain period of time, known as the channel's refractory period. The voltage-gated sodium channel undergoes a cycle of activation, channel opening, channel closing, and channel inactivation. During the inactivation (refractory) period, the channel

TABLE 1-3 Three Major Types of Transmembrane Ion Channels

CHANNEL TYPE	MECHANISM OF ACTIVATION	FUNCTION
Ligand-gated	Binding of ligand to channel	Altered ion conductance
Voltage-gated	Change in transmembrane voltage gradient	Altered ion conductance
Second messenger-regulated	Binding of ligand to transmembrane receptor with G protein-coupled cytosolic domain, leading to second messenger generation	Second messenger regulates ion conductance of channel

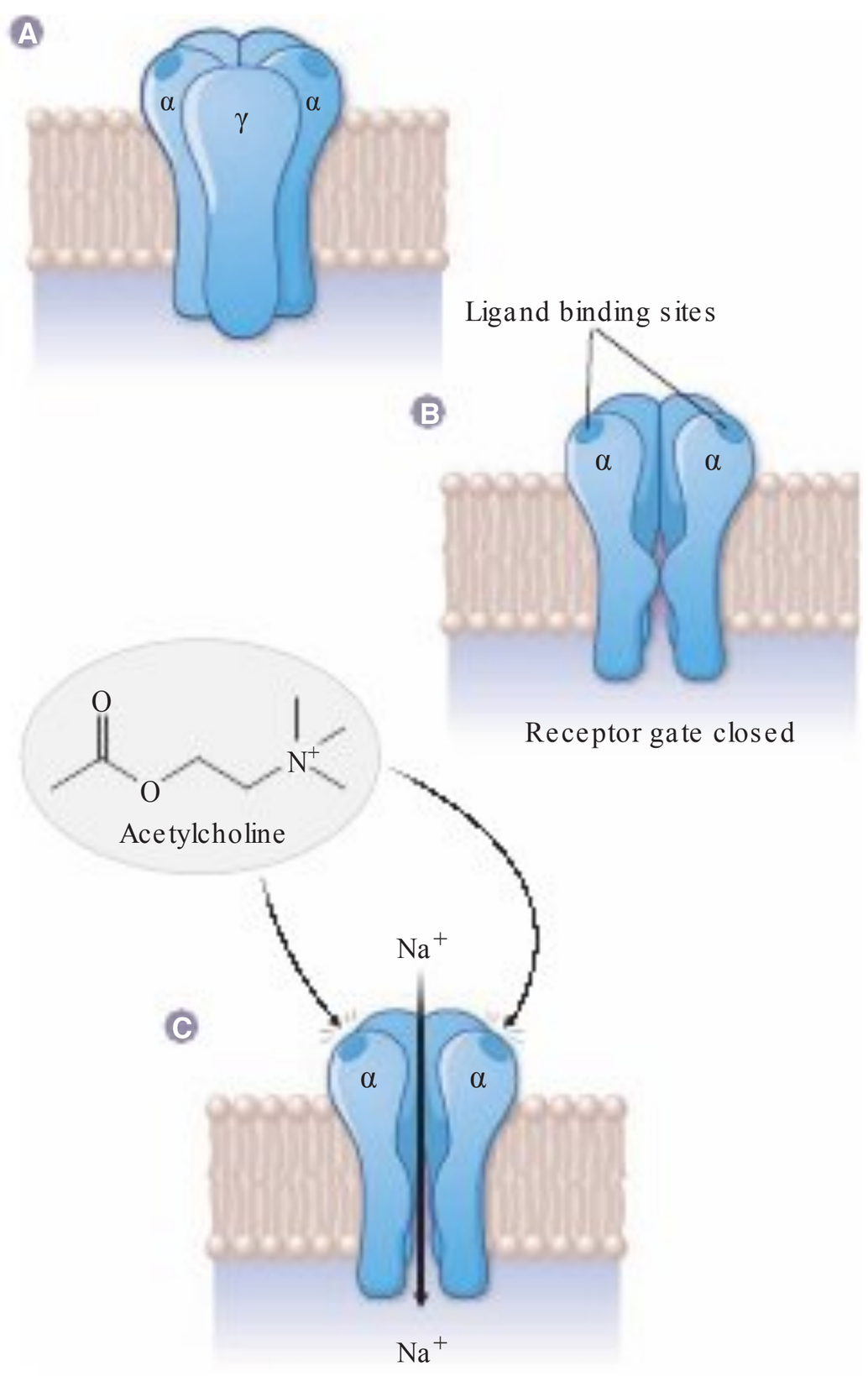

FIGURE 1-4. Ligand-gated nicotinic acetylcholine receptor. A. The plasma membrane acetylcholine (ACh) receptor is composed of five subunits—two α subunits, a β subunit, a γ subunit, and a δ subunit. B. The γ subunit has been removed to show an internal schematic view of the receptor, demonstrating that it forms a transmembrane channel. In the absence of ACh, the receptor gate is closed, and cations (most importantly, sodium ions [Na^+]) are unable to traverse the channel. C. When ACh is bound to both α subunits, the channel opens, and sodium can pass down its concentration gradient into the cell.

cannot be reactivated for a number of milliseconds, even if the membrane potential returns to a voltage that normally stimulates the channel to open. Some drugs bind with different affinities to different states of the same ion channel. This state-dependent binding is important in the mechanism of action of some local anesthetic and antiarrhythmic drugs, as discussed in Chapters 12 (Local Anesthetic Pharmacology) and 24 (Pharmacology of Cardiac Rhythm), respectively.

Two important classes of drugs that act by altering the conductance of ion channels are the local anesthetics and the benzodiazepines. Local anesthetics block the conductance of sodium ions through voltage-gated sodium channels in neurons that transmit pain information from the periphery to the central nervous system, thereby preventing action potential propagation and, hence, pain perception (nociception). Benzodiazepines also act on the nervous system, but by a different mechanism. These drugs inhibit neurotransmission in the central nervous system by potentiating the ability of the neurotransmitter gamma-aminobutyric acid (GABA) to increase the conductance of chloride ions across neuronal membranes, thereby driving the membrane potential further away from its threshold for activation.

Transmembrane G Protein-Coupled Receptors

G protein-coupled receptors are the most abundant class of receptors in the human body. These receptors are exposed at the extracellular surface of the plasma membrane, traverse the membrane, and possess intracellular regions that activate a unique class of signaling molecules called G proteins. (G proteins are so named because they bind the guanine nucleotides GTP and GDP.) G protein-coupled signaling mechanisms are involved in many important processes, including vision, olfaction, and neurotransmission.

G protein-coupled receptors have seven transmembrane regions within a single polypeptide chain. Each transmembrane region consists of a single α helix, and the α helices are arranged in a characteristic structural motif that is similar in all members of this receptor class. The extracellular domain of this class of proteins usually contains the ligand-binding region, although some G protein-coupled receptors bind ligands within the transmembrane domain of the receptor. G proteins have α and βγ subunits that are noncovalently linked in the resting state. Stimulation of a G protein-coupled receptor causes its cytoplasmic domain to bind and activate a nearby G protein, whereupon the α subunit of the G protein exchanges GDP for GTP. The α-GTP subunit then dissociates from the βγ subunit, and the α or βγ subunit diffuses along the inner leaflet of the plasma membrane to interact with a number of different effectors. These effectors include adenylyl cyclase, phospholipase C, various ion channels, and other classes of proteins. Signals mediated by G proteins are usually terminated by the hydrolysis of GTP to GDP, which is catalyzed by the inherent GTPase activity of the α subunit (Fig. 1-5).

One major role of the G proteins is to activate the production of second messengers; that is, signaling molecules that convey the input provided by the first messenger—usually an endogenous ligand or an exogenous drug—to cytoplasmic effectors (Fig. 1-6). The activation of cyclases such as adenylyl cyclase, which catalyzes the production of the second messenger cyclic adenosine-3′,5′-monophosphate (cAMP), and guanylyl cyclase, which catalyzes the production of cyclic guanosine-3′,5′-monophosphate (cGMP), constitutes the most common pathway linked to G proteins. In addition, G proteins can activate the enzyme phospholipase C (PLC), which, among other functions, plays a key role in regulating the concentration of intracellular

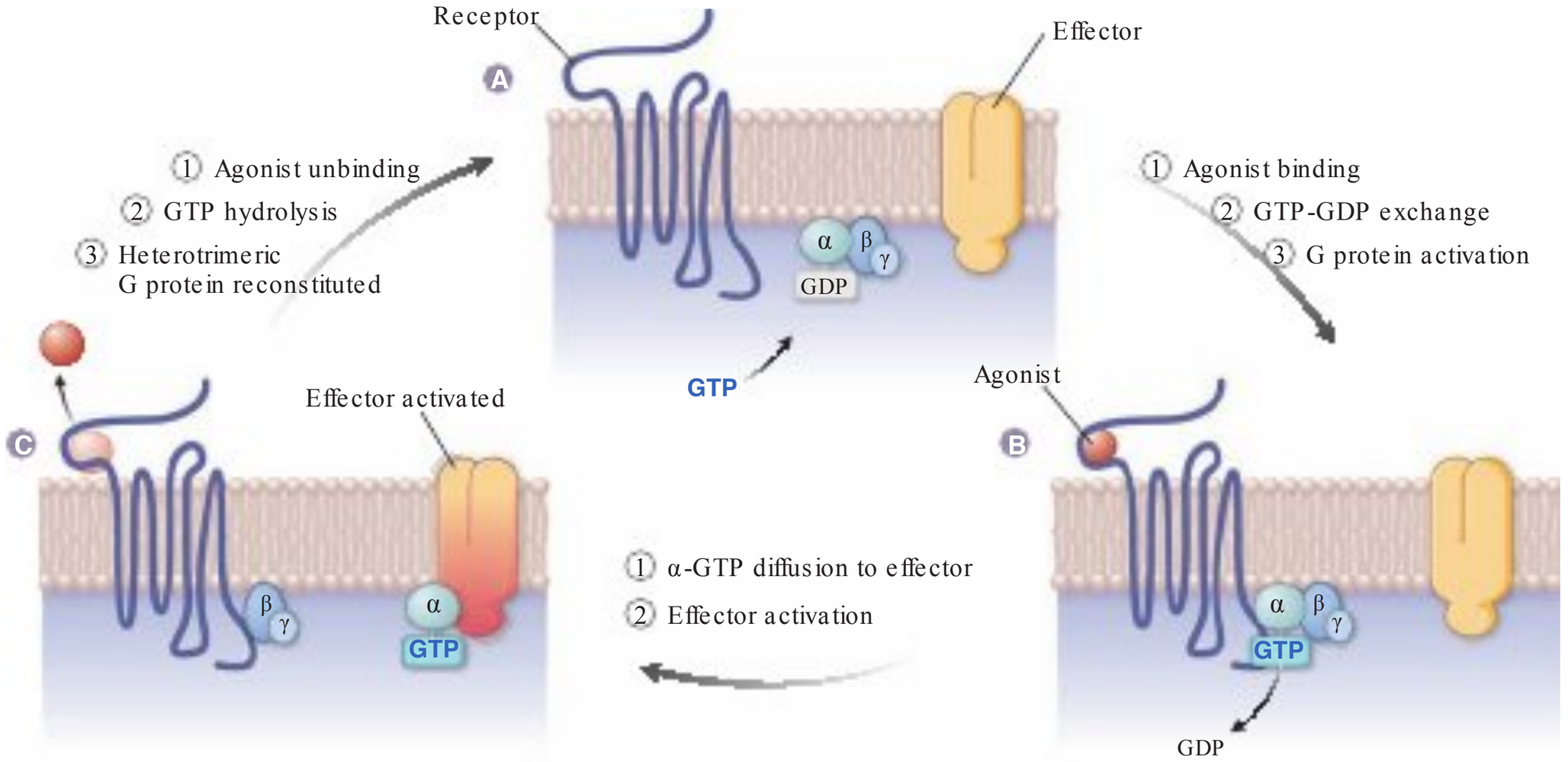

FIGURE 1-5. Receptor-mediated activation of a G protein and the resultant effector interaction. A. In the resting state, the α and βγ subunits of a G protein are associated with one another, and GDP is bound to the α subunit. B. Binding of an extracellular ligand (agonist) to a G protein-coupled receptor causes the exchange of GTP for GDP on the α subunit. C. The βγ subunit dissociates from the α subunit, which diffuses to interact with effector proteins. Interaction of the GTP-associated α subunit with an effector activates the effector. In some cases (not shown), the βγ subunit can also activate effector proteins. Depending on the receptor subtype and the specific Gα isoform, Gα can also inhibit the activity of an effector molecule. The α subunit possesses intrinsic GTPase activity, which leads to hydrolysis of GTP to GDP. This leads to reassociation of the α subunit with the βγ subunit, and the cycle can begin again.

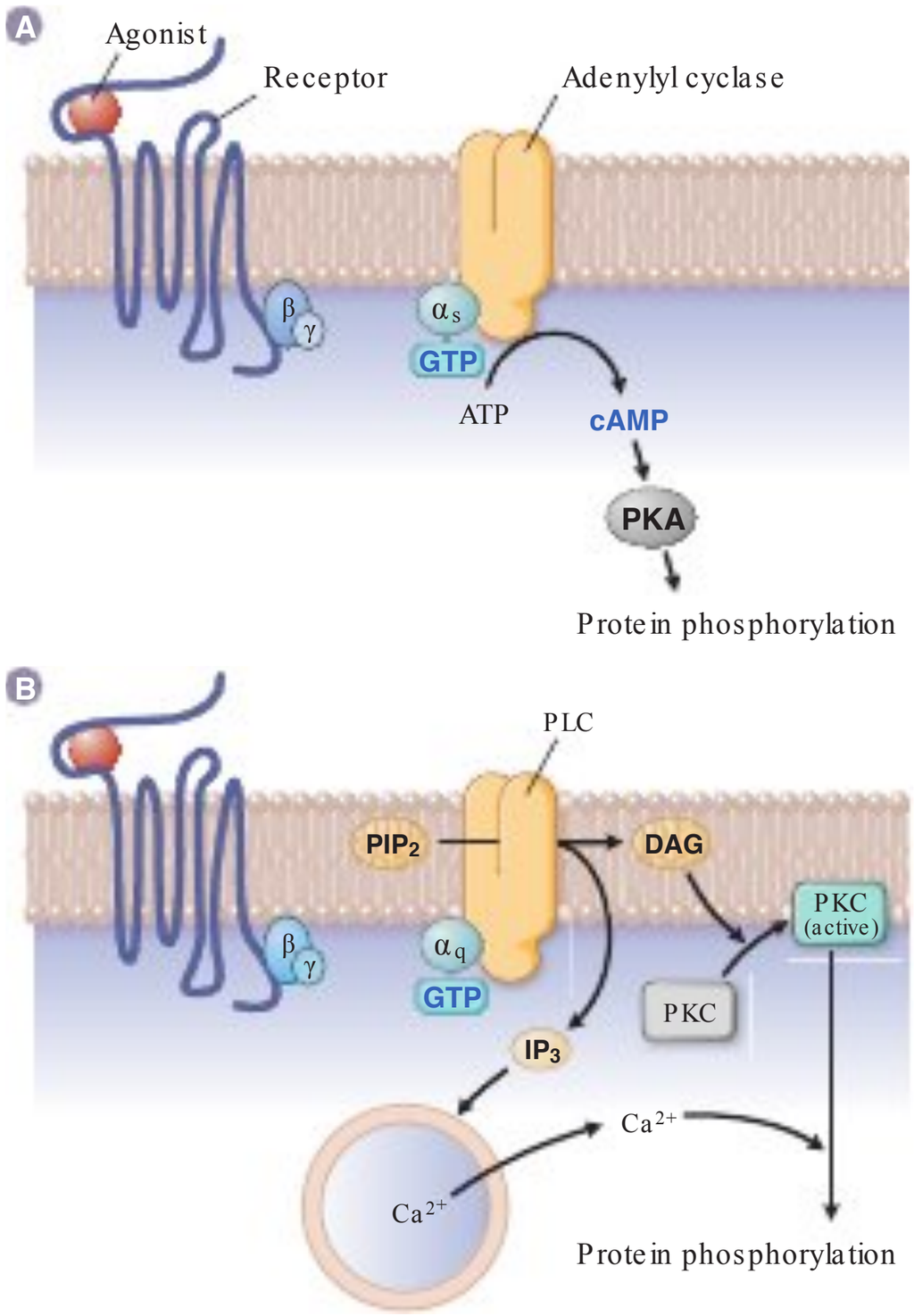

FIGURE 1-6. Activation of adenylyl cyclase (AC) and phospholipase C (PLC) by G proteins. G proteins can interact with several different types of effector molecules. The subtype of Gα protein that is activated often determines which effector the G protein will activate. Two of the most common Gα subunits are $G\alpha_s$ and $G\alpha_q$, which stimulate adenylyl cyclase and phospholipase C, respectively. A. When stimulated by $G\alpha_s$, adenylyl cyclase converts ATP to cyclic AMP (cAMP). cAMP then activates protein kinase A (PKA), which phosphorylates a number of specific intracellular proteins. B. When stimulated by $G\alpha_q$, phospholipase C (PLC) cleaves the membrane phospholipid phosphatidylinositol-4,5-bisphosphate (PIP_2) into diacylglycerol (DAG) and inositol-1,4,5-trisphosphate (IP_3). DAG diffuses in the membrane to activate protein kinase C (PKC), which then phosphorylates specific cellular proteins. IP_3 stimulates release of Ca^{2+} from the endoplasmic reticulum into the cytosol. Calcium release also stimulates protein phosphorylation events that lead to changes in protein activation. Although not shown, the βγ subunits of G proteins can also affect certain cellular signal transduction cascades.

calcium. Upon activation by a G protein, PLC cleaves the membrane phospholipid phosphatidylinositol-4,5-bisphosphate (PIP_2) to the second messengers diacylglycerol (DAG) and inositol-1,4,5-trisphosphate (IP_3). IP_3 triggers the release of Ca^{2+} from intracellular stores, thereby dramatically increasing the cytosolic Ca^{2+} concentration and activating downstream molecular and cellular events. DAG activates protein kinase C, which then mediates other molecular and cellular events including smooth muscle contraction and transmembrane ion transport. All of these events are dynamically regulated, so that the different steps in the pathways are activated and inactivated with characteristic kinetics.

A large number of Gα protein isoforms have been identified, each with unique effects on its targets. Based on the primary sequence of the Gα subunit, these isoforms can be grouped into five major families—G-stimulatory (G_s), G-inhibitory (G_i), G_o, G_q, and $G_{12/13}$. Examples of the effects of these isoforms are shown in Table 1-4. The differential functioning of these G proteins, some of which may couple in different ways to the same receptor in different cell types, is likely to be important for the potential selectivity of future drugs. The βγ subunits of G proteins can also act as second messenger molecules, although their actions are not as completely characterized.

One important class in the G protein-coupled receptor family is the β-adrenergic receptor group. The most thoroughly studied of these receptors have been designated β_1, β_2, and β_3. As discussed in more detail in Chapter 11, Adrenergic Pharmacology, β_1 receptors play a role in controlling heart rate; β_2 receptors are involved in the relaxation of smooth muscle; and β_3 receptors play a role in the mobilization of energy by fat cells. Each of these receptors is stimulated by the binding of endogenous catecholamines, such as epinephrine and norepinephrine, to the extracellular domain of the receptor. Epinephrine binding induces a conformational change in the receptor and thereby activates G proteins associated with the cytoplasmic domain of the receptor. The activated (GTP-bound) form of the G protein activates adenylyl cyclase, resulting in increased intracellular cAMP levels and downstream cellular effects. Table 1-5 indicates

TABLE 1-4 The Major G Protein Families and Examples of Their Actions

G PROTEIN	ACTIONS
G-stimulatory (G_s)	Activates Ca^{2+} channels, activates adenylyl cyclase
G-inhibitory (G_i)	Activates K^+ channels, inhibits adenylyl cyclase
G_o	Inhibits Ca^{2+} channels
G_q	Activates phospholipase C
$G_{12/13}$	Diverse ion transporter interactions

TABLE 1-5 Tissue Localization and Action of β-Adrenergic Receptors

RECEPTOR	TISSUE LOCALIZATION	ACTION
β_1	Sinoatrial (SA) node of heart	Increases heart rate
	Cardiac muscle	Increases contractility
	Adipose tissue	Increases lipolysis
β_2	Bronchial smooth muscle	Dilates bronchioles
	Gastrointestinal smooth muscle	Constricts sphincters and relaxes gut wall
	Uterus	Relaxes uterine wall
	Bladder	Relaxes bladder
	Liver	Increases gluconeogenesis and glycolysis
	Pancreas	Increases insulin release
β_3	Adipose tissue	Increases lipolysis

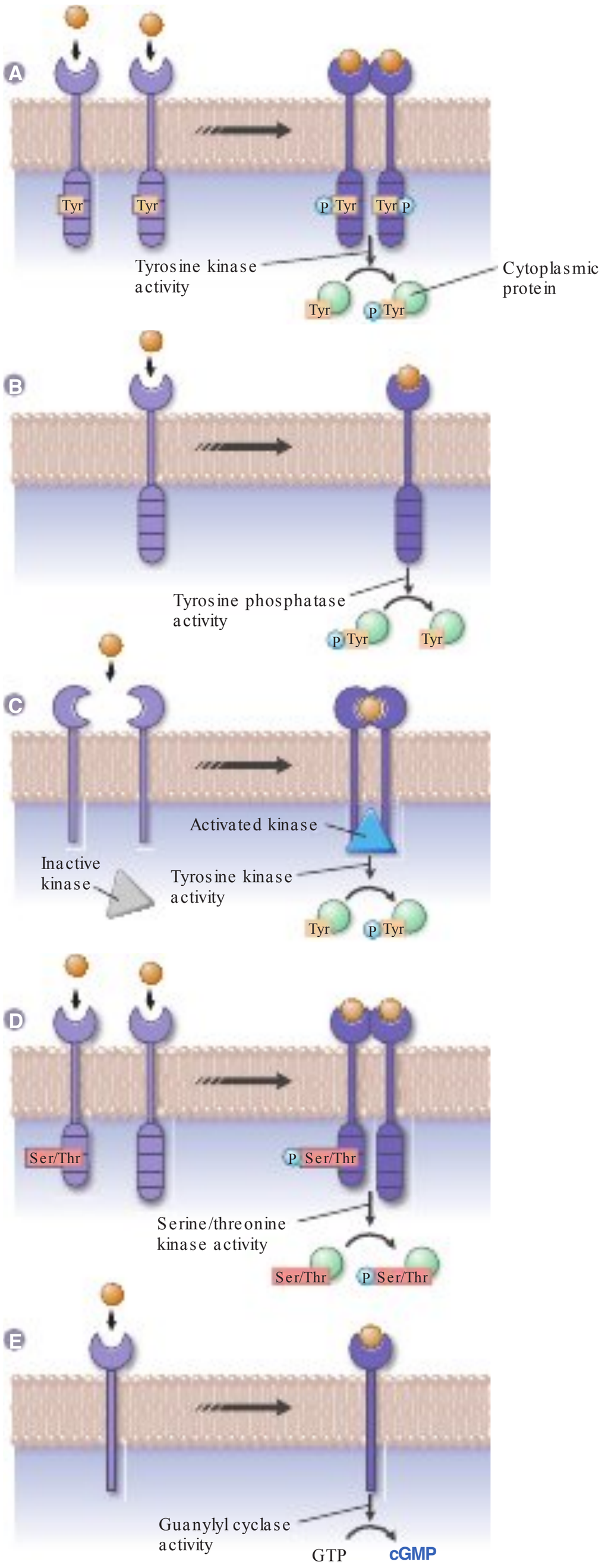

FIGURE 1-7. Major types of transmembrane receptors with linked enzymatic domains. There are five major categories of transmembrane receptors with linked enzymatic domains. A. The largest group is composed of receptor tyrosine kinases. After ligand-induced activation, these receptors dimerize and transphosphorylate tyrosine residues in the receptor and, often, on target cytosolic proteins. Examples of receptor tyrosine kinases include the insulin receptor and many growth factor receptors. B. Some receptors can act as tyrosine phosphatases. These receptors dephosphorylate tyrosine residues either on other transmembrane receptors or on cytosolic proteins. Many cells of the immune system have receptor tyrosine phosphatases. C. Some tyrosine kinase-associated receptors lack a definitive enzymatic domain, but binding of ligand to the receptor triggers activation of receptor-associated protein 1 (termed nonreceptor tyrosine kinases) that then phosphorylate tyrosine residues on certain cytosolic proteins. D. Receptor serine/threonine kinases phosphorylate serine and threonine residues on certain target cytosolic proteins. Members of the TGF-β superfamily of receptors are in this category. E. Receptor guanylyl cyclases contain a cytosolic domain that catalyzes the formation of cGMP from GTP. The receptor for B-type natriuretic peptide is one of the receptor guanylyl cyclases that has been well characterized.

some of the diverse tissue localizations and actions of the β-adrenergic receptors.

Transmembrane Receptors with Linked Enzymatic Domains

The third major class of cellular drug targets consists of transmembrane receptors that transduce an extracellular ligand-binding interaction into an intracellular action through the activation of a linked enzymatic domain. The enzymatic domain may be part of the receptor itself or part of a cytosolic protein that is recruited to the receptor in response to receptor activation. Such receptors play roles in a diverse set of physiologic processes, including cell metabolism, growth, and differentiation. Receptors that have a linked enzymatic domain can be grouped into five major classes based on their cytoplasmic mechanism of action (Fig. 1-7). All of these receptors are single–membrane-spanning proteins, in contrast to the seven–membrane-spanning motif present in G protein-coupled receptors. Many receptors with enzymatic cytosolic domains form dimers or multisubunit complexes to transduce their signals.

Many receptors with linked enzymatic domains modify proteins by adding or removing phosphate groups to or from specific amino acid residues. *Phosphorylation is a ubiquitous mechanism of protein signaling.* The large negative charge of phosphate groups can dramatically alter the three-dimensional structure of a protein and thereby change that protein's activity. In addition, phosphorylation is easily reversible, thus allowing this signaling mechanism to act specifically in time and space.

Receptor Tyrosine Kinases

The largest group of transmembrane receptors with enzymatic cytosolic domains is the receptor tyrosine kinase family. These receptors transduce signals from many hormones and growth factors by phosphorylating tyrosine residues on the cytoplasmic tail of the receptor. This leads to recruitment and subsequent tyrosine phosphorylation of cytosolic signaling molecules. When aberrantly expressed or overexpressed, growth factor-responsive receptor tyrosine kinases (such as epidermal growth factor receptor [EGFR], HER2/neu, and vascular endothelial growth factor receptor [VEGFR]) are

associated with a wide array of cancers; these receptor tyrosine kinases are the targets of several monoclonal antibody and small-molecule inhibitor drugs (see Chapter 40, Pharmacology of Cancer: Signal Transduction).

The insulin receptor is a well-characterized receptor tyrosine kinase. This receptor consists of two extracellular α subunits that are covalently linked to two membrane-spanning β subunits. Binding of insulin to the α subunits results in a change in conformation of the adjacent β subunits, causing the β subunits to move closer to one another on the intracellular side of the membrane. The proximity of the two β subunits promotes a transphosphorylation reaction, in which one β subunit phosphorylates the other (autophosphorylation). The phosphorylated tyrosine residues then act to recruit other cytosolic proteins, known as insulin receptor substrate (IRS) proteins. Type 2 diabetes mellitus may, in some cases, be associated with defects in post-insulin receptor signaling; thus, understanding the insulin receptor signaling pathways is relevant for the potential design of rational therapeutics. The mechanism of insulin receptor signaling is discussed in more detail in Chapter 31, Pharmacology of the Endocrine Pancreas and Glucose Homeostasis.

Receptor Tyrosine Phosphatases

Just as receptor tyrosine kinases phosphorylate the tyrosine residues of cytoplasmic proteins, receptor tyrosine phosphatases remove phosphate groups from specif c tyrosine residues. In some cases, this may be an example of receptor convergence (discussed later), where the differential effects of two receptor types can negate one another. However, receptor tyrosine phosphatases possess novel signaling mechanisms as well. Many receptor tyrosine phosphatases are found in immune cells, where they regulate cell activation. These receptors are discussed further in Chapter 46, Pharmacology of Immunosuppression.

Tyrosine Kinase-Associated Receptors

Tyrosine kinase-associated receptors constitute a diverse family of proteins that, although lacking inherent catalytic activity, recruit active cytosolic signaling proteins in a ligand-dependent manner. These cytosolic proteins are also called (somewhat confusingly) nonreceptor tyrosine kinases. Ligand activation of cell surface tyrosine kinase-associated receptors causes the receptors to cluster together. This clustering event recruits cytoplasmic proteins that are then activated to phosphorylate other proteins on tyrosine residues. Thus, the downstream effect is much like that of receptor tyrosine kinases, except that tyrosine kinase-associated receptors rely on a nonreceptor kinase to phosphorylate target proteins. Important examples of tyrosine kinase-associated receptors include cytokine receptors and a number of other receptors in the immune system. These receptors are discussed in detail in Chapter 46.

Receptor Serine/Threonine Kinases

Some transmembrane receptors are capable of catalyzing the phosphorylation of serine or threonine residues on cytoplasmic protein substrates. Ligands for such receptors are typically members of the transforming growth factor β (TGF-β) superfamily. Many receptor serine/threonine kinases are important mediators of cell growth and differentiation that have been implicated in cancer progression and metastasis. While there are many approved drugs that target *cytosolic* serine/threonine kinases (see Intracellular Receptors below), drugs selective for *receptor* serine/threonine kinases are mainly in development.

Receptor Guanylyl Cyclases

As illustrated in Figure 1-6, the stimulation of G protein-coupled receptors may cause activation and release of Gα subunits, which, in turn, alter the activity of adenylyl and guanylyl cyclases. In contrast, receptor guanylyl cyclases have no intermediate G protein. Instead, ligand binding stimulates intrinsic receptor guanylyl cyclase activity, in which GTP is converted to cGMP. This is the smallest family of transmembrane receptors. B-type natriuretic peptide, a hormone secreted by the ventricles in response to volume overload, acts via a receptor guanylyl cyclase. Nesiritide, a recombinant version of the native peptide ligand, is approved for the treatment of decompensated heart failure (although it does not reliably improve outcomes), as discussed in Chapter 21, Pharmacology of Volume Regulation.

Intracellular Receptors

The plasma membrane provides a unique barrier for drugs that have intracellular receptors. Many such drugs are small or lipophilic and are thus able to cross the membrane by diffusion. Others require specialized protein transporters for facilitated diffusion or active transport into the cell.

Intracellular Enzymes and Signal Transduction Molecules

Enzymes are common intracellular drug targets. Many drugs that target intracellular enzymes exert their effect by altering the enzyme's production of critical signaling or metabolic molecules. Vitamin K epoxide reductase, a cytosolic enzyme involved in the post-translational modif cation of glutamate residues in certain coagulation factors, is the target of the anticoagulant drug warfarin. HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis, is the target of atorvastatin and the other lipid-lowering statins. Many inhibitors of cytosolic signal transduction molecules are approved or in development. For example, inhibitors of the serine/threonine kinase mTOR (such as everolimus) are used to prevent rejection of transplanted organs, to treat certain cancers, and to prevent restenosis in drug-eluting coronary stents.

Many other intracellular kinases play important roles in cellular growth and differentiation, and it is not surprising that "gain-of-function" mutations in these proteins can lead to uncontrolled cell growth and cancer. Recall from the introductory case that chronic myeloid leukemia is associated with the Philadelphia chromosome, which results from a reciprocal translocation between the long arms of chromosomes 9 and 22. The mutant chromosome codes for a constitutively active tyrosine kinase referred to as the BCR-Abl protein. (BCR and Abl are short for "break-point cluster region" and "Abelson," respectively, the two chromosomal regions that undergo translocation with high frequency in this form of leukemia.) The constitutive activity of this kinase results in phosphorylation of a number of cytosolic proteins, leading to dysregulated myeloid cell growth and chronic myeloid leukemia. Imatinib is a selective therapy for chronic myeloid leukemia because it selectively targets the BCR-Abl protein; the drug inhibits BCR-Abl activity by neutralizing its ability to phosphorylate substrates. Imatinib was the f rst example of a drug targeted selectively to tyrosine kinases,

and its success has led to the development of a number of drugs that act by similar mechanisms. Such drugs include second-generation drugs such as dasatinib and nilotinib that are used to treat CML patients with imatinib-resistant BCR-Abl isoforms, as well as the inhibitors of growth factor-responsive receptor tyrosine kinases discussed above. Indeed, the kinase targets of antineoplastic drugs are diverse. For instance, sorafenib targets both receptor tyrosine kinases and intracellular serine/threonine kinases, and vemurafenib is a recently approved late-stage melanoma treatment that targets a specific mutant of the serine/threonine kinase B-RAF. As a final example, idelalisib is a recently approved phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) inhibitor used to treat certain leukemias and lymphomas (see Chapter 40).

Transcription Factors

The transcription regulatory factors are important intracellular receptors that are targeted by lipophilic drugs. All proteins in the body are encoded by DNA. The transcription of DNA into RNA and the translation of RNA into protein are controlled by a diverse set of molecules. Transcription of many genes is regulated, in part, by the interaction between lipid-soluble signaling molecules and transcription regulatory factors. Because of the fundamental role played by control of transcription in many biological processes, transcription regulators (also called transcription factors) are the targets of some important drugs. Steroid hormones are a class of lipophilic drugs that diffuse readily through the plasma membrane and act by binding to transcription factors in the cytoplasm or nucleus (Fig. 1-8).

Just as the shape of a transcription factor governs the drugs to which it binds, the shape also determines where on the genome the transcription factor attaches and which coactivator or corepressor molecules bind to it. By activating or inhibiting transcription, thereby altering the intracellular or extracellular concentrations of specific gene products, drugs that target transcription factors can have profound effects on cellular function. The cellular responses to such drugs, and the effects that result from these cellular responses in tissues and organ systems, provide links between the molecular drug–receptor interaction and the effects of the drug on the organism as a whole. Because gene transcription is a relatively slow and long-lasting process (minutes to hours), drugs that target transcription factors often require a longer period of time for the onset of action to take place, and have longer lasting effects, than do drugs that alter more transient processes such as ion conductance (seconds to minutes).

Structural Proteins

Structural proteins are another important class of intracellular drug targets. For example, the antimitotic vinca alkaloids bind to tubulin monomers and prevent the polymerization of this molecule into microtubules. Inhibition of microtubule formation arrests the affected cells in metaphase, making the vinca alkaloids useful antineoplastic drugs.

Nucleic Acids

Nucleic acids are a fourth subset of intracellular drug targets. Some small-molecule drugs bind directly to RNA or ribosomes; these include important antibiotics (such as doxycycline and azithromycin) that block translation in target microorganisms. DNA- and RNA-binding chemotherapeutic agents (such as doxorubicin) are mainstays of treatment for many cancers. Drugs composed of nucleic acids can also target nucleic acids. Antisense therapeutics (such as the recently approved drug mipomersen) bind target mRNA to block transcription of specific proteins. With continued development of such antisense approaches and of related RNA interference (RNAi) therapeutics, such targeting could someday enable physicians to routinely modify the expression levels of specific gene transcripts. To date, technical challenges in delivering such therapeutics to their targets have limited their utility to specialized applications.

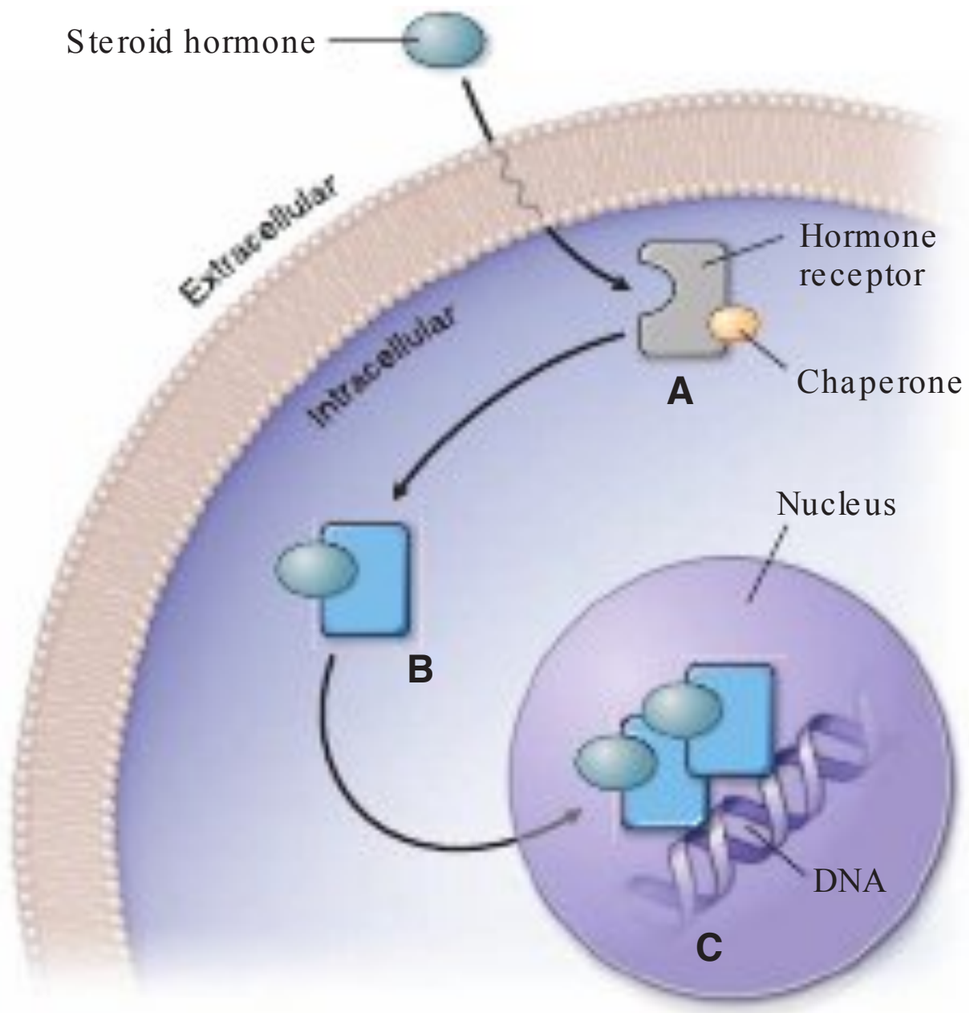

FIGURE 1-8. Lipophilic molecule binding to an intracellular transcription factor. A. Small lipophilic molecules can diffuse through the plasma membrane and bind to intracellular transcription factors. In this example, steroid hormone binding to a cytosolic hormone receptor is shown, although some receptors of this class may be located in the nucleus before ligand binding. B. Ligand binding triggers a conformational change in the receptor (and often, as shown here, dissociation of a chaperone repressor protein) that leads to transport of the ligand–receptor complex into the nucleus. In the nucleus, the ligand–receptor complex typically dimerizes. In the example shown, the active form of the receptor is a homodimer (two identical receptors binding to one another), but heterodimers (such as the thyroid hormone receptor and the retinoid Xreceptor) may also form. C. The dimerized ligand–receptor complex binds to DNA and may then recruit coactivators or corepressors (not shown). These complexes alter the rate of gene transcription, leading to a change (either up or down) in cellular protein expression.

Extracellular Targets

Many important drug receptors are enzymes with active sites located outside the plasma membrane. The extracellular environment consists of a milieu of proteins and signaling molecules. Many of these proteins serve a structural role, and others are used to communicate information between cells. Enzymes that modify the molecules mediating these important signals can influence physiologic processes such as vasoconstriction and neurotransmission. One example of this class of receptors is the angiotensin converting enzyme (ACE), which converts angiotensin I to the potent vasoconstrictor angiotensin II. ACE inhibitors are drugs that inhibit

this enzymatic conversion and thereby lower blood pressure (among other effects; see Chapter 21). Another example is acetylcholinesterase, which degrades acetylcholine after this neurotransmitter is released from cholinergic neurons. Acetylcholinesterase inhibitors enhance neurotransmission at cholinergic synapses by preventing neurotransmitter degradation at these sites (see Chapter 10, Cholinergic Pharmacology).

Some extracellular targets are not enzymes. For example, several proteins, including monoclonal antibodies, are used to target soluble cytokines and block them from interacting with their endogenous receptors. One set of such drugs is the anti-TNF-α agents, including etanercept, infliximab, adalimumab, and others, which are commonly used to treat autoimmune diseases such as rheumatoid arthritis (see Chapter 46).

Cell Surface Adhesion Receptors

Cells often interact directly with other cells to perform specific functions or to communicate information. The formation of tissues and the migration of immune cells to a site of inflammation are examples of physiologic processes that require cell–cell adhesive interactions. A region of contact between two cells is termed an adhesion, and cell–cell adhesive interactions are mediated by pairs of adhesion receptors on the surfaces of the individual cells. In many cases, several such receptor–counter-receptor pairs combine to secure a firm adhesion, and intracellular regulators control the activity of the adhesion receptors by changing their affinity or by controlling their expression and localization on the cell surface. Adhesion receptors also mediate adhesion of cells to the extracellular matrix. Several adhesion receptors involved in the inflammatory response are attractive targets for selective inhibitors. Inhibitors of a specific class of adhesion receptors, known as integrins, have entered the clinic in recent years, and these drugs are used in the treatment of a range of conditions including thrombosis (abciximab, eptifibatide), inflammatory bowel disease (vedolizumab), and multiple sclerosis (natalizumab) (see Chapter 23, Pharmacology of Hemostasis and Thrombosis, and Chapter 46).

PROCESSING OF SIGNALS RESULTING FROM DRUG–RECEPTOR INTERACTIONS

Many cells in the body are continuously inundated with multiple inputs, some stimulatory and some inhibitory. How do cells integrate these signals to produce a coherent response? G proteins and other second messengers appear to provide important points of integration. As noted above, relatively few second messengers have been identified, and it is unlikely that many more remain to be discovered. Thus, second messengers are an attractive candidate mechanism for providing cells with a set of common points upon which numerous outside stimuli could converge to generate a coordinated cellular effect (Fig. 1-9).

Ion concentrations provide another point of integration for cellular effects because the cellular concentration of a particular ion is the result of the integrated activity of *multiple* ionic currents that both increase and decrease the concentration of the ion within the cell. For example, the contractile state of a smooth muscle cell is a function of the intracellular calcium ion concentration, which is determined by several different Ca^{2+} conductances. These conductances include calcium ion leaks into the cell and calcium currents into and out of the cytoplasm through specialized channels in the plasma membrane and smooth endoplasmic reticulum.

Because the magnitude of cellular response is often considerably greater than the magnitude of the stimulus that caused the response, cells appear to have the ability to amplify the effects of receptor binding. G proteins provide an excellent example of signal amplification. Ligand binding to a G protein-coupled receptor activates a single G protein molecule. This G protein molecule can then bind to and activate many effector molecules, such as adenylyl cyclase, which can then generate an even greater number of second messenger molecules (in this example, cAMP). Another example of signal amplification is "trigger Ca^{2+}" or calcium-induced calcium release, in which a small influx

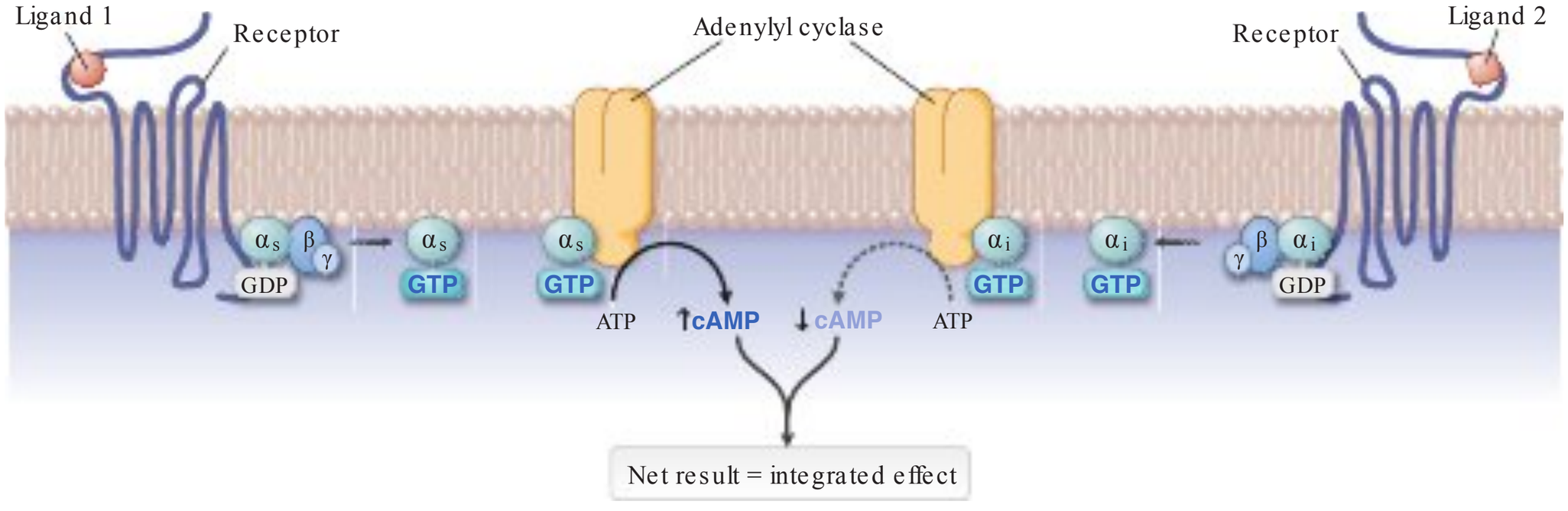

FIGURE 1-9. Signaling convergence of two receptors. A limited number of mechanisms are used to transduce intracellular signal cascades. In some cases, this allows for convergence, where two different receptors have opposite effects that tend to negate one another in the cell. In a simple example, two different G protein-coupled receptors could be stimulated by different ligands. The receptor shown on the left is coupled to $G\alpha_s$, a G protein that stimulates adenylyl cyclase to catalyze the formation of cAMP. The receptor shown on the right is coupled to $G\alpha_i$, a G protein that inhibits adenylyl cyclase. When both of these receptors are activated simultaneously, they can attenuate or even neutralize each other, as shown. Sometimes, signaling through a pathway may alternate as the two receptors are sequentially activated.

of Ca^{2+} through voltage-gated Ca^{2+} channels in the plasma membrane "triggers" the release of larger amounts of Ca^{2+} from intracellular stores into the cytoplasm.

CELLULAR REGULATION OF DRUG–RECEPTOR INTERACTIONS

Drug-induced activation or inhibition of a receptor often has a lasting impact on the receptor's subsequent responsiveness to drug binding. Mechanisms that mediate such effects are important because they prevent overstimulation that could lead to cellular damage or adversely affect the organism as a whole. Many drugs show diminishing effects over time; this phenomenon is called tachyphylaxis. In pharmacologic terms, the receptor and the cell become desensitized to the action of the drug. Mechanisms of desensitization can be divided into two types: homologous, in which the effects of agonists at only one type of receptor are diminished, and heterologous, in which the effects of agonists at two or more types of receptors are coordinately diminished. Heterologous desensitization is thought to be caused by drug-induced alteration in a common point of convergence in the signaling pathways activated by the involved receptors, such as a shared effector molecule.

Many receptors exhibit desensitization. For example, the cellular response to repeated stimulation of β-adrenergic receptors by epinephrine diminishes steadily over time (Fig. 1-10). β-Adrenergic receptor desensitization is mediated by epinephrine-induced phosphorylation of the cytoplasmic tail of the receptor. This phosphorylation promotes the binding of β-arrestin to the receptor; in turn, β-arrestin inhibits the receptor's ability to stimulate the G protein G_s. With lower levels of activated G_s present, adenylyl cyclase produces less cAMP. In this manner, repeated cycles of ligand–receptor binding result in smaller and smaller cellular effects. Other molecular mechanisms have even more profound effects, completely turning off the receptor to stimulation by ligand. The latter phenomenon, referred to as inactivation, may also result from phosphorylation of the receptor; in this case, the phosphorylation completely blocks the signaling activity of the receptor or causes removal of the receptor from the cell surface.

Another mechanism that can affect the cellular response caused by drug–receptor binding is called *refractoriness*. Receptors that assume a refractory state following activation require a period of time to pass before they can be stimulated again. As noted above, voltage-gated sodium channels, which mediate the firing of neuronal action potentials, are subject to refractory periods. After channel opening induced by membrane depolarization, the voltage-gated sodium channel spontaneously closes and cannot be reopened for some period of time (called the refractory period). This inherent property of the channel determines the maximum rate at which neurons can be stimulated and transmit information.

The effect of drug–receptor binding can also be influenced by drug-induced changes in the number of receptors on or in a cell. One example of a molecular mechanism by which receptor number can be altered is called down-regulation. In this phenomenon, prolonged receptor stimulation by ligand induces the cell to endocytose and sequester receptors in endocytic vesicles. This sequestration prevents the receptors from coming into contact with ligands, resulting in cellular desensitization. When the stimulus that caused the receptor sequestration subsides, the receptors can be recycled to the cell surface and thereby rendered functional again (Fig. 1-10). Cells also have the ability to alter the rates of synthesis or degradation of receptors and thereby to regulate the number of receptors available for drug binding. Receptor sequestration and alterations in receptor synthesis and degradation occur on a longer time scale than does phosphorylation and have longer lasting effects as well. Table 1-6 provides a summary of the mechanisms by which the effects of drug–receptor interactions can be regulated.

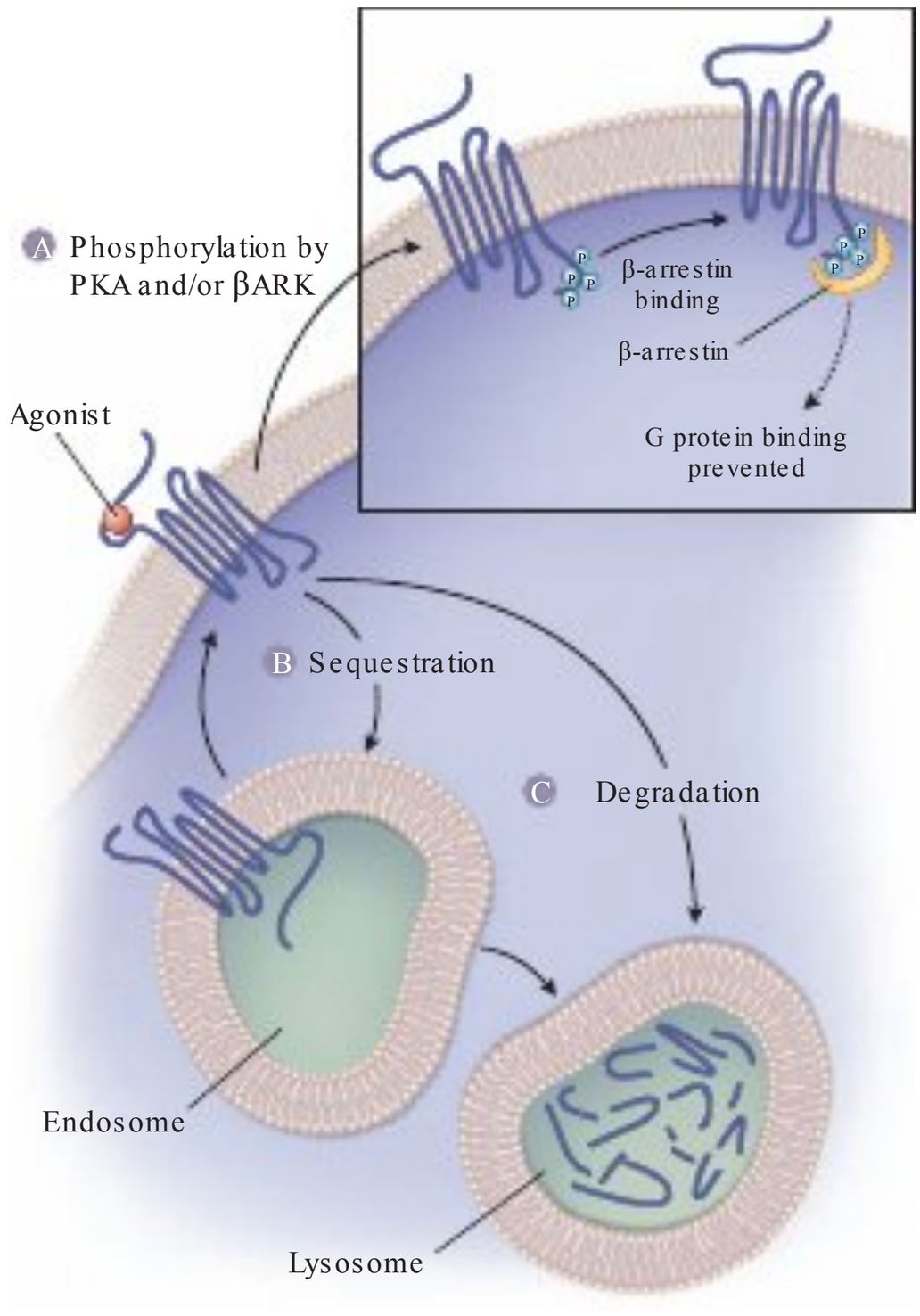

FIGURE 1-10. **β**-Adrenergic receptor regulation. Agonist-bound β-adrenergic receptors activate G proteins, which then stimulate adenylyl cyclase activity (not shown). A. Repeated or persistent stimulation of the receptor by agonist results in phosphorylation of amino acids at the C-terminus of the receptor by protein kinase A (PKA) and/or β-adrenergic receptor kinase (βARK). β-Arrestin then binds to the phosphorylated domain of the receptor and blocks G_s binding, thereby decreasing adenylyl cyclase (effector) activity. B. Binding of β-arrestin also leads to receptor sequestration into endosomal compartments via clathrin-mediated endocytosis (not shown), effectively neutralizing β-adrenergic receptor signaling activity. The receptor can then be recycled and reinserted into the plasma membrane. C. Prolonged receptor occupation by an agonist can lead to receptor down-regulation and eventual receptor degradation. Cells can also reduce the number of receptors by inhibiting the transcription or translation of the gene coding for the receptor (not shown).

TABLE 1-6 Mechanisms of Receptor Regulation

MECHANISM	DEFINITION
Tachyphylaxis	Repeated administration of the same dose of a drug results in a diminishing effect of the drug over time
Desensitization	Decreased ability of a receptor to respond to stimulation by a drug or ligand
Homologous	Decreased response at a single type of receptor
Heterologous	Decreased response at two or more types of receptor
Inactivation	Loss of ability of a receptor to respond to stimulation by a drug or ligand
Refractory	After a receptor is stimulated, a period of time is required before the next drug–receptor interaction can produce an effect
Down-regulation	Repeated or persistent drug–receptor interaction results in removal of the receptor from sites where subsequent drug–receptor interactions could take place

DRUGS THAT DO NOT FIT THE DRUG–RECEPTOR MODEL

Although most drugs interact with one of the basic receptor types outlined above, others act by nonreceptor-mediated mechanisms. Two examples are the osmotic diuretics and the antacids.

Diuretics control fluid balance in the body by altering the relative rates of water and ion absorption and secretion in the kidney. Many of these drugs act on ion channels. One class of diuretics, however, alters water and ion balance not by binding to ion channels or G protein-coupled receptors but by changing the osmolarity in the nephron directly. The sugar mannitol, which is used mainly to treat increased intracranial pressure, is secreted into the lumen of the nephron and increases the osmolarity of the urine to such a degree that water is drawn from the peritubular blood into the lumen. This fluid shift serves to increase the volume of urine while decreasing the blood volume.

Another class of drugs that does not f t the drug–receptor model is the antacids, which are used to treat gastroesophageal reflux disease and peptic ulcer disease. Unlike antiulcer agents that bind to receptors involved in the physiologic generation of gastric acid, antacids act nonspecif cally by absorbing or chemically neutralizing stomach acid. Examples of these agents include bases such as $NaHCO_3$ and $Mg(OH)_2$.

CONCLUSION AND FUTURE DIRECTIONS

Although the molecular details of drug–receptor interactions vary widely among drugs of different classes and receptors of different types, the fundamental mechanisms of action described in this chapter serve as paradigms for the principles of pharmacodynamics. The ability to classify drugs based on their receptors and mechanisms of action makes it possible to simplify the study of pharmacology, because the molecular mechanism of action of a drug can usually be linked to its cellular, tissue, organ, and system levels of action. In turn, it becomes easier to understand how a given drug mediates its therapeutic effects and its unwanted or adverse effects in a particular patient. The major aim of modern drug development is to identify drugs that are highly selective by tailoring drug molecules to unique targets responsible for disease. As knowledge of drug development and the genetic and pathophysiologic basis of disease progresses, physicians and scientists will learn to combine the *molecular* specif city of a drug with the *genetic* and *pathophysiologic* specif city of the drug target to provide more and more selective therapies.

Acknowledgment

We thank Josef B. Simon, Christopher W. Cairo, and Zachary S. Morris for their valuable contributions to this chapter in the First, Second, and Third Editions of *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy*.

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2

Pharmacodynamics

Quentin J. Baca and David E. Golan

INTRODUCTION

Pharmacodynamics is the term used to describe the effects of a drug on the body. These effects are typically described in quantitative terms. The previous chapter considered the molecular interactions by which pharmacologic agents exert their effects. The integration of these molecular actions into an effect on the organism as a whole is the subject addressed in this chapter. It is important to describe the effects of a drug quantitatively in order to determine appropriate dose ranges for patients, as well as to compare the potency, efficacy, and safety of one drug to that of another.

DRUG–RECEPTOR BINDING

The study of pharmacodynamics is based on the concept of drug–receptor binding. When either a drug or an endogenous ligand (such as a hormone or neurotransmitter) binds to its receptor, a response may result from that binding interaction. When a sufficient number of receptors are bound (or "occupied") on or in a cell, the cumulative effect of receptor "occupancy" may become apparent in that cell. At some point, all of the receptors may be occupied, and a maximal response may be observed (an exception is the case of spare receptors; see below). When the response occurs in many cells, the effect can be seen at the level of the organ or even the patient. But this all starts with the binding of drug or ligand to a receptor (for the purpose of discussion, "drug" and "ligand" will be used interchangeably for the remainder of this chapter). A model that accurately describes the binding of drug to receptor would therefore be useful in predicting the effect of the drug at the molecular, cellular, tissue (organ), and organism (patient) levels. This section describes one such model.

Consider the simplest case, in which the receptor is either free (unoccupied) or reversibly bound to drug (occupied). We can describe this case as follows:

$$L + R \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} LR \qquad \text{Equation 2-1}$$

where L is ligand (drug), R is free receptor, and LR is bound drug–receptor complex. At equilibrium, the fraction of receptors in each state is dependent on the dissociation constant, K_d, where $K_d = k_{off}/k_{on}$. K_d is an intrinsic property of any given drug–receptor pair. Although K_d varies with temperature, the temperature of the human body is relatively constant, and it can therefore be assumed that K_d is a constant for each drug–receptor combination.

According to the law of mass action, the relationship between free and bound receptor can be described as follows:

$$K_d = \frac{[L][R]}{[LR]}, \text{ rearranged to } [LR] = \frac{[L][R]}{K_d} \qquad \text{Equation 2-2}$$

where $[L]$ is free ligand concentration, $[R]$ is free receptor concentration, and $[LR]$ is ligand–receptor complex concentration. Because K_d is a constant, some important properties of the drug–receptor interaction can be deduced from this equation. First, as ligand concentration is increased, the concentration of bound receptors increases. Second, and not so obvious, is that as free receptor concentration is increased (as may happen, for example, in disease states or upon repeated exposure to a drug), bound receptor concentration also increases. Therefore, *an increase in the effect of a drug can result from an increase in the concentration of either the ligand or the receptor*.

The remainder of the discussion in this chapter, however, assumes that the total concentration of receptors is a

Admiral X is a 66-year-old retired submarine captain with a 70 pack–year smoking history (two packs a day for 35 years) and a family history of coronary artery disease. He takes daily atorvastatin to reduce his cholesterol level and aspirin to reduce his risk of coronary artery occlusion.

One day, while working in his wood shop, Admiral X begins to feel tightness in his chest. The feeling rapidly becomes painful, and the pain radiates down his left arm. He calls 911, and an ambulance transports him to the local emergency department. After evaluation, it is determined that Admiral X is having an anterior myocardial infarction. Because Admiral X cannot be transferred to a hospital with a cardiac catheterization laboratory within 120 minutes of first medical contact, and he has no relative contraindications to thrombolytic therapy (such as uncontrolled hypertension, history of stroke, or recent surgery), the physician initiates therapy with both a thrombolytic agent, tissue-type plasminogen activator (tPA), and an anticoagulant, heparin. Because of their low therapeutic indices, improper dosing of both of these drugs can have dire consequences (hemorrhage and death). Therefore, Admiral X is closely monitored, and the pharmacologic effect of the heparin is measured periodically by testing the partial thromboplastin time (PTT). Admiral X's symptoms resolve over the next several hours, although he remains in the hospital for monitoring. He is discharged after 4 days in the hospital; his discharge medications include atorvastatin, aspirin, atenolol, lisinopril, and clopidogrel for secondary prevention of myocardial infarction.

Questions

1. How does the molecular interaction of a drug with its receptor determine the potency and efficacy of the drug?
2. Why does the fact that a drug has a low therapeutic index mean that the physician must use greater care in its administration?
3. What properties of certain drugs, such as aspirin, allow them to be taken without monitoring of plasma drug levels, whereas other drugs, such as heparin, require such monitoring?

constant, so that $[LR] + [R] = [R_o]$. This allows Equation 2-2 to be arranged as follows:

$$[R_o] = [R] + [LR] = [R] + \frac{[L][R]}{K_d}$$

$$= [R]\left(1 + \frac{[L]}{K_d}\right) \qquad \text{Equation 2-3}$$

Solving for $[R]$ and substituting Equation 2-3 into Equation 2-2 yields:

$$[LR] = \frac{[R_o]\,[L]}{[L] + K_d}, \text{ rearranged to}$$

$$\frac{[LR]}{[R_o]} = \frac{[L]}{[L] + K_d} \qquad \text{Equation 2-4}$$

Note that the left side of this equation, $[LR]/[R_o]$, represents the fraction of all available receptors that are bound to ligand.

Figure 2-1 shows two plots of Equation 2-4 for the binding of two hypothetical drugs to the same receptor. These plots are known as drug–receptor binding curves. Figure 2-1A shows a linear plot, and Figure 2-1B shows the same plot on a semilogarithmic scale. Because drug responses occur over a wide range of doses (concentrations), the semilog plot is often used to display drug–receptor binding data. The two drug–receptor interactions are characterized by different values of K_d. In this case, $K_{dA} < K_{dB}$.

Notice from Figure 2-1 that maximal drug–receptor binding occurs when $[LR]$ is equal to $[R_o]$, or $[LR]/[R_o] = 1$. Also notice that, according to Equation 2-4, when $[L] = K_d$, then $[LR]/[R_o] = K_d/2K_d = ½$. Thus, *$K_d$ can be defined as the concentration of ligand at which 50% of the available receptors are occupied*.

DOSE–RESPONSE RELATIONSHIPS

The pharmacodynamics of a drug can be quantified by the relationship between the dose (concentration) of the drug and the organism's (patient's) response to that drug. One might intuitively expect the dose–response relationship to be related closely to the drug–receptor binding relationship, and this turns out to be the case for many drug–receptor combinations. Thus, a useful assumption at this stage of discussion is that *the response to a drug is proportional to the concentration of receptors that are bound (occupied) by the drug*. This assumption can be quantified by the following relationship:

$$\frac{\text{response}}{\text{max response}} = \frac{[DR]}{[R_o]} = \frac{[D]}{[D] + K_d} \qquad \text{Equation 2-5}$$

where $[D]$ is the concentration of free drug, $[DR]$ is the concentration of drug–receptor complexes, $[R_o]$ is the concentration of total receptors, and K_d is the equilibrium dissociation constant for the drug–receptor interaction. (Note that the right side of Equation 2-5 is equivalent to Equation 2-4, with $[D]$ substituted for $[L]$.) The generalizability of this assumption is examined below.

There are two major types of dose–response relationships—graded and quantal. The difference between the two types is that graded dose–response relationships describe the effect of various doses of a drug on an individual, whereas quantal relationships show the effect of various doses of a drug on a population of individuals.

Graded Dose–Response Relationships

Figure 2-2 shows graded dose–response curves for two hypothetical drugs that elicit the same biological response.

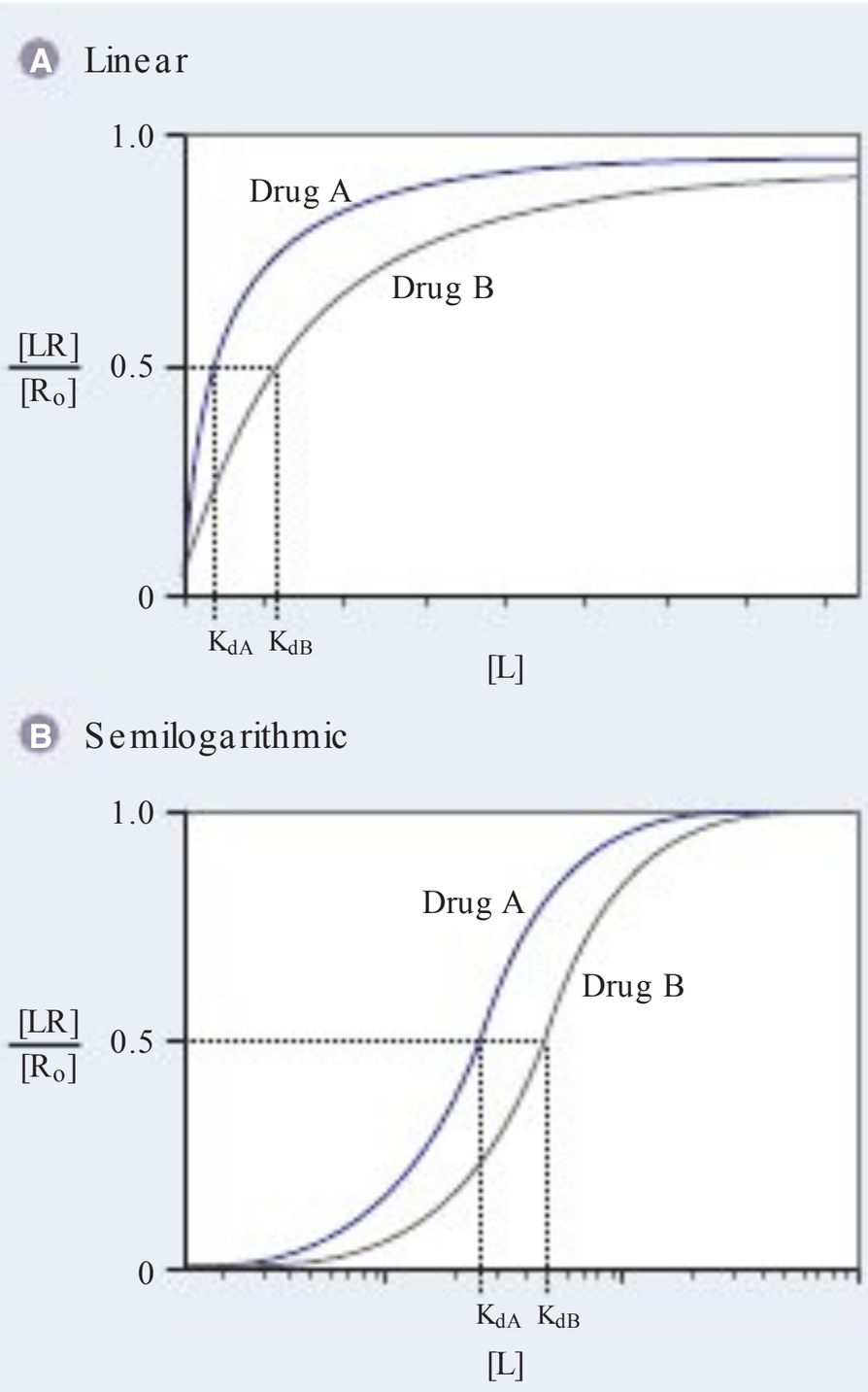

FIGURE 2-1. Ligand–receptor binding curves. A. Linear graphs of drug–receptor binding for two drugs with different values of K_d. B. Semilogarithmic graphs of the same drug–receptor binding. K_d is the equilibrium dissociation constant for a given drug–receptor interaction—a lower K_d indicates a tighter drug–receptor interaction (higher affinity). Because of this relationship, Drug A, which has the lower K_d, will bind a higher proportion of total receptors than Drug B at any given drug concentration. Notice that K_d corresponds to the ligand concentration [L] at which 50% of the receptors are bound (occupied) by ligand. [L] is the concentration of free (unbound) ligand (drug), [LR] is the concentration of ligand–receptor complexes, and $[R_o]$ is the total concentration of occupied and unoccupied receptors. Thus, $[LR]/[R_o]$ is the fractional occupancy of receptors, or the fraction of total receptors that are occupied (bound) by ligand.

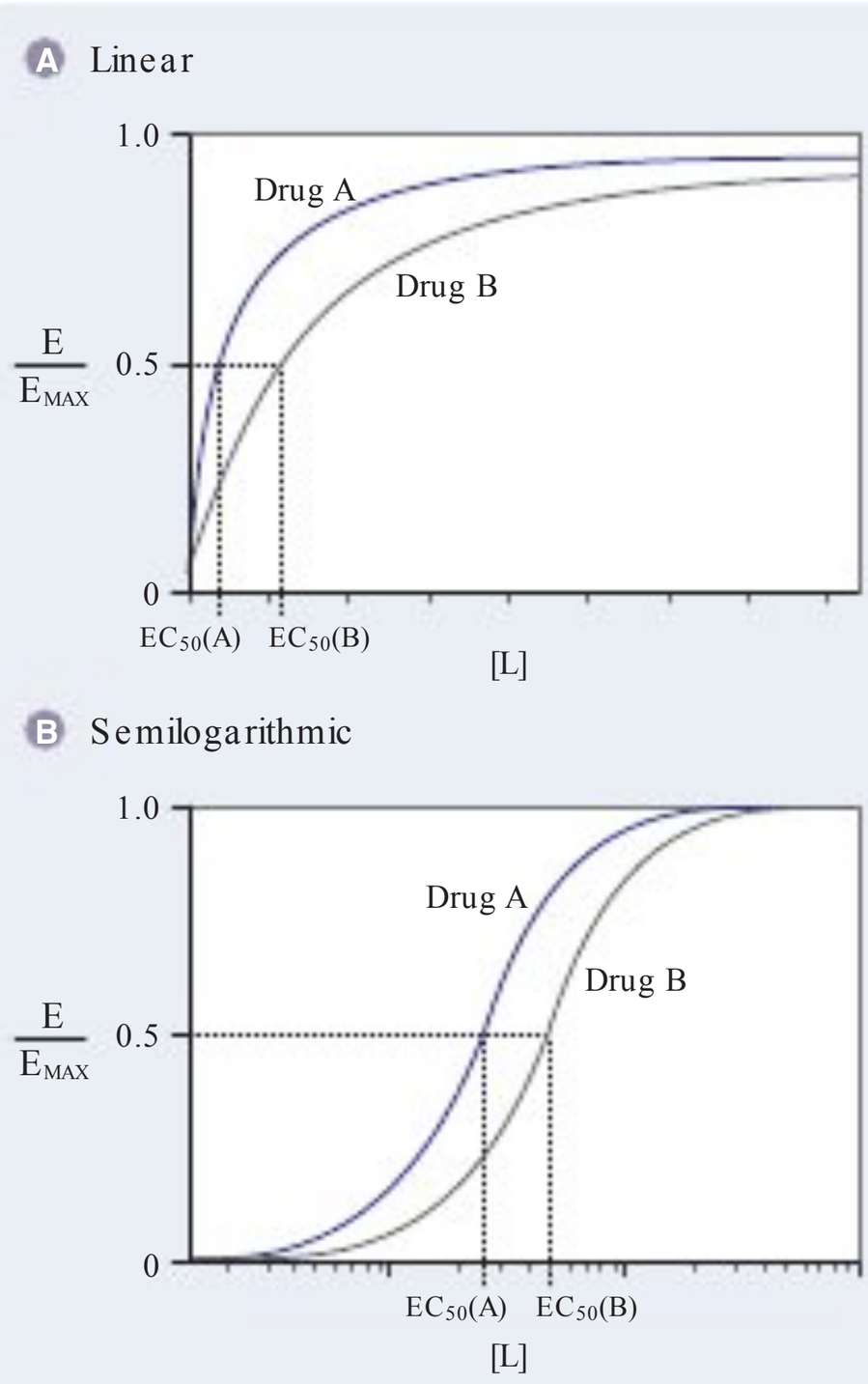

FIGURE 2-2. Graded dose–response curves. Graded dose–response curves demonstrate the effect of a drug as a function of its concentration. A. Linear graphs of graded dose–response curves for two drugs. B. Semilogarithmic graphs of the same dose–response curves. Note the close resemblance to Figure 2-1: the fraction of occupied receptors $[LR]/[R_o]$ has been replaced by the fractional effect E/E_{max}, where E is a quantifiable response to a drug (e.g., an increase in blood pressure). EC_{50} is the potency of the drug, or the concentration at which the drug elicits 50% of its maximal effect. In the figure, Drug A is more potent than Drug B because it elicits a half-maximal effect at a lower concentration than Drug B. Drugs A and B exhibit the same efficacy (the maximal response to the drug). Note that potency and efficacy are not intrinsically related—a drug can be extremely potent but have little efficacy, and vice versa. [L] is drug concentration, E is effect, E_{max} is efficacy, and EC_{50} is potency.

The curves are presented on both linear and semilogarithmic scales. The curves are similar in shape to those in Figure 2-1, consistent with the assumption that response is proportional to receptor occupancy.

Two important parameters—potency and efficacy—can be deduced from the graded dose–response curve. The potency (EC_{50}) of a drug is *the concentration at which the drug elicits 50% of its maximal response*. The efficacy (E_{max}) is *the maximal response produced by the drug*. In accordance with the assumption stated above, efficacy can be thought of as the state at which receptor-mediated signaling is maximal and, therefore, additional drug will produce no additional response. This usually occurs when all the receptors are occupied by the drug. Some drugs, however, are capable of eliciting a maximal response when less than 100% of the drug's receptors are occupied; the remaining receptors can be called spare receptors. This concept is discussed further in the text that follows. Note again that the graded dose–response curve of Figure 2-2 bears a close resemblance to the drug–receptor binding curve of Figure 2-1, with EC_{50} replacing K_d and E_{max} replacing R_o.

Quantal Dose–Response Relationships

The quantal dose–response relationship plots the fraction of the population that responds to a given dose of drug as a function of the drug dose. Quantal dose–response relationships describe the concentrations of a drug that produce a given effect in a population. Figure 2-3 shows an example of quantal dose–response curves. Because of differences in biological response among individuals, the effects of a drug are seen over a range of doses. The responses are defined as either present or not present (i.e., *quantal*, not *graded*). Endpoints such as "sleep/no sleep" or "alive at

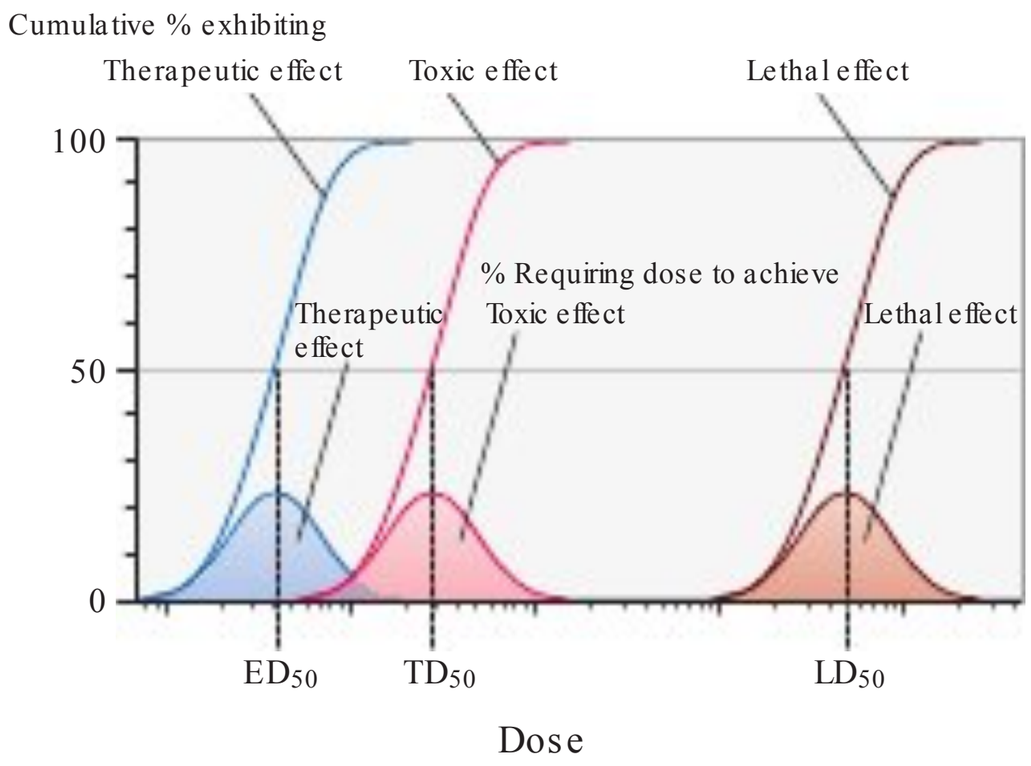

FIGURE 2-3. Quantal dose–response curves. Quantal dose–response curves demonstrate the average effect of a drug, as a function of its concentration, in a population of individuals. Individuals are typically observed for the presence or absence of a response (e.g., sleep or no sleep), and this result is then used to plot the percentage of individuals who respond to each dose of drug. Quantal dose–response relationships are useful for predicting the effects of a drug when it is administered to a population of individuals and for determining population-based toxic doses and lethal doses. These doses are called the ED_{50} (dose at which 50% of subjects exhibit a therapeutic response to a drug), TD_{50} (dose at which 50% of subjects experience a toxic response), and LD_{50} (dose at which 50% of subjects die). Note that ED_{50} is the dose at which 50% of subjects respond to a drug, whereas EC_{50} (as described in the previous figure) is the dose at which a drug elicits a half-maximal effect in an individual subject.

12 months/not alive at 12 months" are examples of quantal responses; in contrast, graded dose–response relationships are generated using scalar responses such as change in blood pressure or heart rate. The goal is to generalize a result to a population rather than to examine the graded effect of different drug doses on a single individual. Types of responses that can be examined using the quantal dose–response relationship include effectiveness (therapeutic effect), toxicity (adverse effect), and lethality (lethal effect). The doses that produce these responses in 50% of a population are known as the median effective dose (ED_{50}), median toxic dose (TD_{50}), and median lethal dose (LD_{50}), respectively.

DRUG–RECEPTOR INTERACTIONS

Many receptors for drugs can be modeled as having two conformational states that are in reversible equilibrium with one another. These two states are called the active state and the inactive state. Many drugs function as ligands for such receptors and affect the probability that the receptor exists preferentially in one conformation or the other. The pharmacologic properties of drugs are often based on their effects on the state of their cognate receptors. A drug that, upon binding to its receptor, favors the active receptor conformation is called an agonist; a drug that prevents agonist-induced activation of the receptor is referred to as an antagonist. Some drugs do not fit neatly into this simple definition of agonist and antagonist; these include partial agonists and inverse agonists. The following sections describe these pharmacologic classifications in more detail.

Agonists

An agonist is a molecule that binds to a receptor and stabilizes the receptor in a particular conformation (usually, the active conformation). When bound by an agonist, a typical receptor is more likely to be in its active conformation than its inactive conformation. Depending on the receptor, agonists may be drugs or endogenous ligands. A useful model for understanding the relationship between agonist binding and receptor activation is shown in Equation 2-6:

$$\begin{array}{ccc} D + R & \rightleftarrows & D + R^* \\ \not\Updownarrow & & \not\Updownarrow \\ DR & \rightleftarrows & DR^* \end{array} \qquad \text{Equation 2-6}$$

where D and R are unbound (free) drug and receptor concentrations, respectively, DR is the concentration of the agonist–receptor complex, and R^* indicates the active conformation of the receptor. For most receptors and agonists, R^* and DR are unstable species that exist only briefly and are quantitatively insignificant compared to R and DR^*. Therefore, in most cases, Equation 2-6 simplifies to

$$D + R \rightleftarrows DR^* \qquad \text{Equation 2-7}$$

Note that Equation 2-7 is identical to Equation 2-1, which was used for the analysis of drug–receptor binding. This suggests that, for most receptors, agonist binding is proportional to receptor activation. Some receptors, however, do have limited stability in the R^* and/or DR conformations; in these cases, Equation 2-6 must be revisited (see below).

Equation 2-6 can also be used to illustrate quantitatively the concepts of potency and efficacy. Recall that potency is the agonist concentration required to elicit a half-maximal effect, and efficacy is the maximal effect of the agonist. Assuming that a receptor is not active unless bound to a drug (i.e., R^* is insignificant compared to DR^*), Equation 2-8 provides a quantitative description of potency and efficacy:

$$D + R \underset{k_{off}}{\overset{k_{on}}{\rightleftarrows}} DR \underset{k_{\beta}}{\overset{k_{\alpha}}{\rightleftarrows}} DR^* \qquad \text{Equation 2-8}$$

Potency **Efficacy**

Here, k_α is the rate constant for receptor activation, and k_β is the rate constant for receptor deactivation. This equation demonstrates the relationship between potency ($K_d = k_{off}/k_{on}$) and agonist binding ($D + R \rightleftarrows DR$), as well as the relationship between efficacy (k_α/k_β) and the conformational change required for activation of the receptor ($DR \rightleftarrows DR^*$). These relationships are intuitive when we consider that more potent drugs are those that have a higher affinity for their receptors (lower K_d), and more efficacious drugs are those that cause a higher fraction of receptors to be activated.

Antagonists

An antagonist is a molecule that inhibits the action of an agonist but has no effect in the absence of the agonist. Figure 2-4 shows one approach to classifying the various types of antagonists. Antagonists can be divided into receptor and nonreceptor antagonists. A receptor antagonist binds to either the active site (agonist binding site) or an allosteric site on a receptor. Binding of an antagonist to the active site prevents the binding of the agonist to the receptor, whereas binding

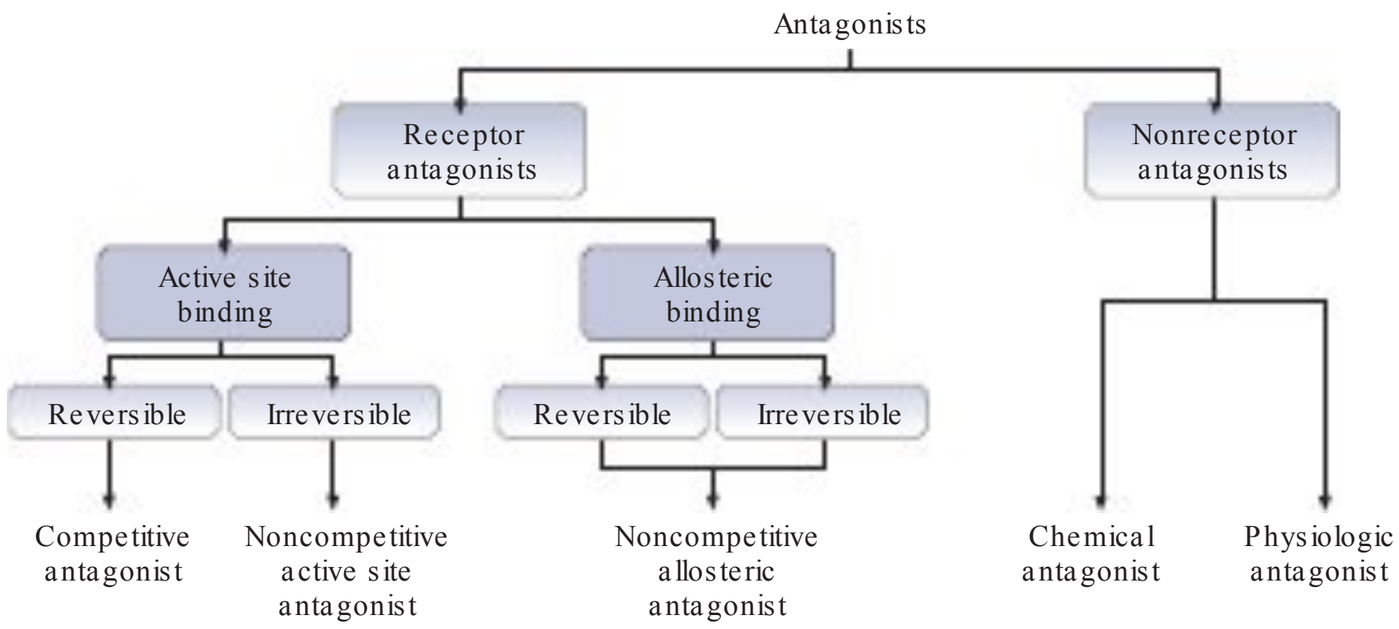

FIGURE 2-4. Antagonist classif cation. Antagonists can be categorized based on whether they bind to a site on the receptor for agonist (receptor antagonists) or interrupt agonist–receptor signaling by other means (nonreceptor antagonists). Receptor antagonists can bind either to the agonist (active) site or to an allosteric site on the receptor; in either case, they do not affect basal receptor activity (i.e., the activity of the receptor in the absence of agonist). Agonist (active) site receptor antagonists prevent the agonist from binding to the receptor. If the antagonist competes with the ligand for agonist site binding, it is termed a competitive antagonist; high concentrations of agonist are able to overcome competitive antagonism. Noncompetitive active site antagonists bind covalently or with very high aff nity to the agonist site, so that even high concentrations of agonist are unable to activate the receptor. Allosteric receptor antagonists bind to the receptor at a site other than the agonist site. They do not compete directly with agonist for receptor binding, but rather alter the K_d for agonist binding or inhibit the receptor from responding to agonist binding. High concentrations of agonist are generally unable to reverse the effect of an allosteric antagonist. Nonreceptor antagonists fall into two categories. Chemical antagonists sequester agonist and thus prevent the agonist from interacting with the receptor. Physiologic antagonists induce a physiologic response opposite to that of an agonist, but by a molecular mechanism that does not involve the receptor for agonist.

of an antagonist to an allosteric site either alters the K_d for agonist binding or prevents the conformational change required for receptor activation. Receptor antagonists can also be divided into reversible and irreversible antagonists; that is, antagonists that bind to their receptors reversibly and those that bind irreversibly. Figure 2-5 illustrates the general effects of these antagonist types on agonist binding; more detail is provided in the following sections.

A nonreceptor antagonist does not bind to the same receptor as an agonist, but it nonetheless inhibits the ability of an agonist to initiate a response. At the molecular level, this inhibition can occur by inhibiting the agonist directly (e.g., using antibodies), by inhibiting a downstream molecule in the activation pathway, or by activating a pathway that opposes the action of the agonist. Nonreceptor antagonists can be divided into chemical antagonists and physiologic antagonists. Chemical antagonists inactivate an agonist before it has the opportunity to act (e.g., by chemical neutralization); physiologic antagonists cause a physiologic effect opposite to that induced by the agonist.

Competitive Receptor Antagonists

A competitive antagonist *binds reversibly to the active site of a receptor.* Unlike an agonist, which also binds to the active site of the receptor, a competitive antagonist does not stabilize the conformation required for receptor activation. Therefore, the antagonist blocks an agonist from binding to its receptor, while maintaining the receptor in the inactive conformation. Equation 2-9 is a modif cation of Equation 2-7 that incorporates the effect of a competitive antagonist (*A*).

$$AR \rightleftharpoons A + D + R \rightleftharpoons DR^* \qquad \text{Equation 2-9}$$

In this equation, a fraction of the free receptor molecules (*R*) are unable to form a drug (agonist)–receptor complex (*DR**), because receptor binding to the antagonist results in the

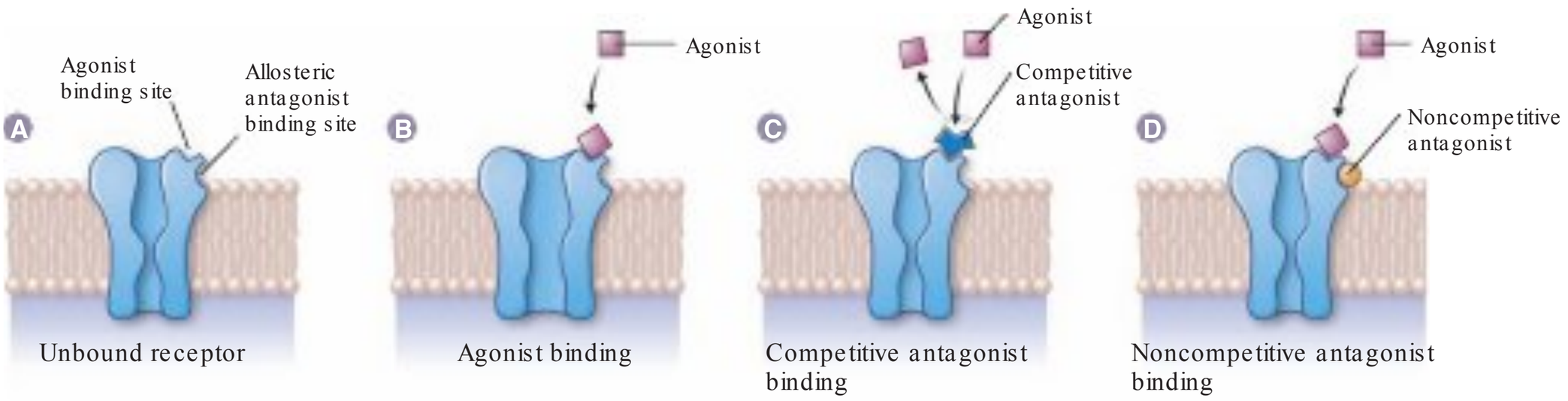

FIGURE 2-5. Types of receptor antagonists. A schematic illustrating the differences between agonist (active) site and allosteric antagonists. A. The unbound inactive receptor. B. The receptor activated by agonist. Note the conformational change induced in the receptor by agonist binding, for example, the opening of a transmembrane ion channel. C. Agonist site antagonists bind to the receptor's agonist site but do not activate the receptor; these agents block agonist binding to the receptor. D. Allosteric antagonists bind to an allosteric site (different from the agonist site) and thereby prevent receptor activation, even when the agonist is bound to the receptor.

formation of an antagonist–receptor complex (*AR*) instead. In effect, the formation of the *AR* complex sets up a second equilibrium reaction that competes with the equilibrium for agonist–receptor binding. Note that *AR* is incapable of undergoing a conformational change to the active (*R**) state of the receptor.

Quantitative analysis yields the following equation for agonist (*D*) binding to the receptor in the presence of a competitive antagonist (*A*):

$$\frac{[DR]}{[R_o]} = \frac{[D]}{[D] + K_d\left(1 + \frac{[A]}{K_A}\right)} \qquad \text{Equation 2-10}$$

Equation 2-10 is similar to Equation 2-4, except that the effective K_d has been increased by a factor of $(1 + [A]/K_A)$, where K_A is the dissociation constant for binding of the antagonist to the receptor (i.e., $K_A = [A][R]/[AR]$). Because an increase in K_d is equivalent to a decrease in potency, *the presence of a competitive antagonist (A) reduces the potency of an agonist (D) by a factor of* $(1 + [A]/K_A)$. Although the potency of an agonist decreases as the concentration of competitive antagonist increases, the efficacy of the agonist is unaffected. This occurs because the agonist concentration [*D*] can be increased to counteract ("outcompete") the antagonist, thereby "washing out" or reversing the effect of the antagonist. Figure 2-6A shows the effect of a competitive antagonist on the agonist dose–response relationship. Note that the competitive antagonist has the effect of shifting the agonist dose–response curve to the right, causing a decrease in agonist potency while maintaining agonist efficacy.

Atorvastatin, the drug used in the case at the beginning of this chapter to lower Admiral X's cholesterol, is an example of a competitive antagonist. Atorvastatin is a member of the HMG-CoA reductase inhibitor (statin) class of lipid-lowering drugs. HMG-CoA reductase is an enzyme that catalyzes the reduction of HMG-CoA, which is the rate-limiting step in cholesterol biosynthesis. The similarity between the chemical structures of statins and HMG-CoA allows the statin molecule to bind to the active site of HMG-CoA reductase and thereby to prevent HMG-CoA from binding. This inhibition is reversible because no covalent bonds are formed between the statin and the enzyme. Inhibition of HMG-CoA reductase decreases endogenous cholesterol synthesis and lowers the patient's cholesterol levels. For a more detailed discussion of the mechanism of action of atorvastatin and other HMG-CoA reductase inhibitors, see Chapter 20, Pharmacology of Cholesterol and Lipoprotein Metabolism.

Noncompetitive Receptor Antagonists

Noncompetitive antagonists can bind to either the active site or an allosteric site of a receptor (Fig. 2-4). A noncompetitive antagonist that binds to the active site of a receptor can bind either covalently or with very high affinity; in either case, the binding is effectively irreversible. Because an irreversibly bound active site antagonist cannot be "outcompeted," even at high agonist concentrations, such an antagonist exhibits noncompetitive antagonism.

A noncompetitive allosteric antagonist acts by preventing the receptor from being activated, even when the agonist is bound to the active site. An allosteric antagonist exhibits noncompetitive antagonism regardless of the reversibility of its binding, because such an antagonist acts not by competing

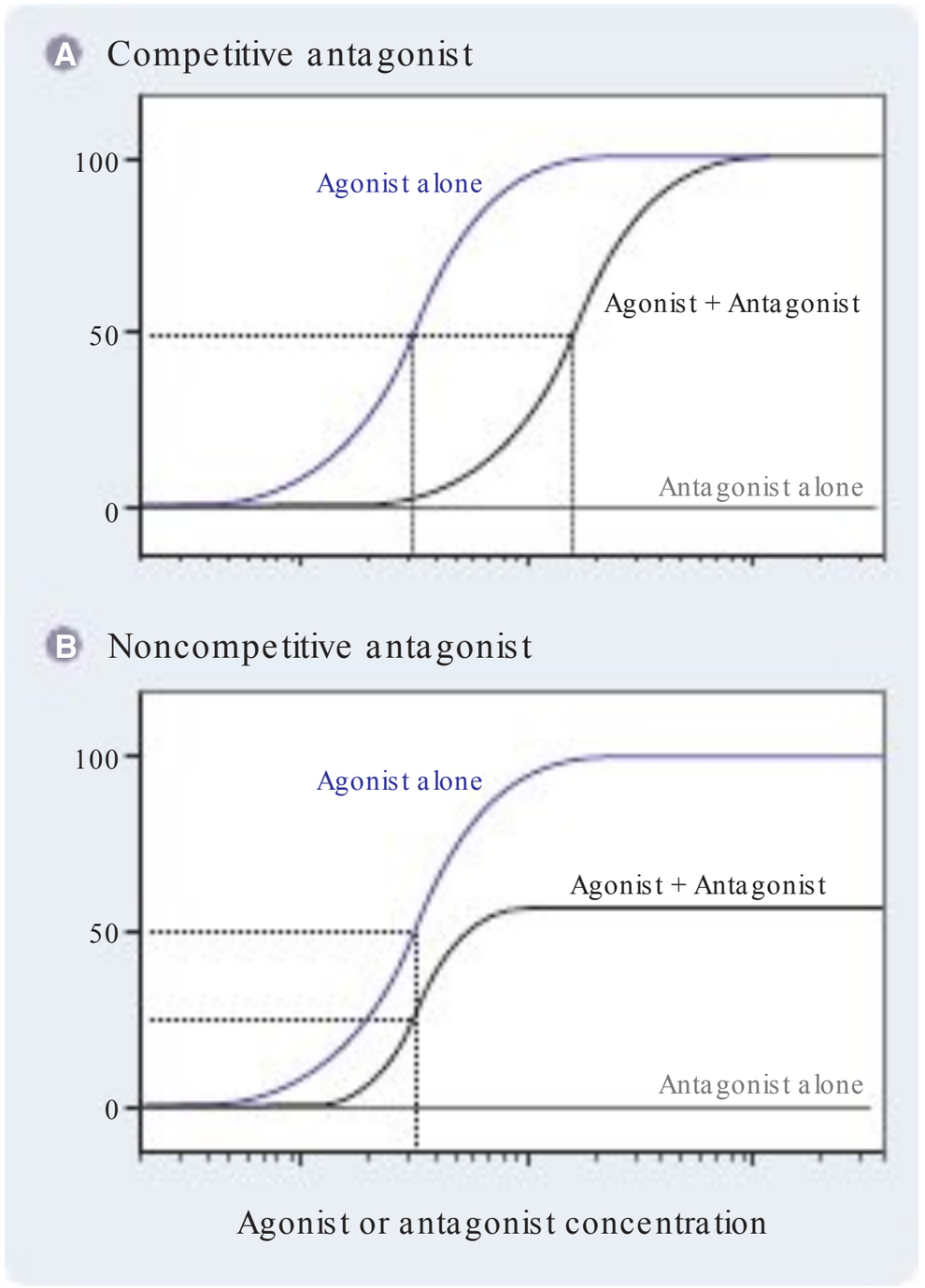

FIGURE 2-6. Antagonist effects on the agonist dose–response relationship. Competitive and noncompetitive antagonists have different effects on potency (the concentration of agonist that elicits a half-maximal response) and efficacy (the maximal response to an agonist). A. A competitive antagonist reduces the potency of an agonist, without affecting agonist efficacy. B. A noncompetitive antagonist reduces the efficacy of an agonist. As shown here, most allosteric noncompetitive antagonists do not affect agonist potency.

with the agonist for binding to the active site, but rather by preventing receptor activation. The reversibility of antagonist binding is nonetheless important, because the effect of an irreversible antagonist does not diminish when the free (unbound) drug is eliminated from the body, whereas the effect of a reversible antagonist can be "washed out" over time as it dissociates from the receptor (see Equation 2-9).

A receptor that is bound by a noncompetitive antagonist can no longer be activated by the binding of an agonist. Therefore, the maximal response (efficacy) of the agonist is reduced. A characteristic difference between competitive and noncompetitive antagonists is that *competitive antagonists reduce agonist potency*, *whereas noncompetitive antagonists reduce agonist efficacy*. This difference can be explained by considering that a competitive antagonist continuously competes for receptor binding, effectively reducing the receptor's affinity for an agonist without limiting the number of available receptors. In contrast, a noncompetitive antagonist removes functional receptors from the system, thereby limiting the number of available receptors. Figures 2-6A and 2-6B compare the effects of competitive and noncompetitive antagonists on the agonist dose–response relationship.

Aspirin is one example of a noncompetitive antagonist. This agent irreversibly acetylates cyclooxygenase, the enzyme

responsible for generating thromboxane A_2 in platelets. In the absence of thromboxane A_2 generation, platelet aggregation is inhibited. Because the inhibition is irreversible and platelets are not capable of synthesizing new cyclooxygenase molecules, the effects of a single dose of aspirin last for 7 to 10 days (the time required for the bone marrow to generate new platelets), even though the free drug is cleared from the body much more rapidly.

Nonreceptor Antagonists

Nonreceptor antagonists can be divided into chemical antagonists and physiologic antagonists. A chemical antagonist inactivates the agonist of interest by modifying or sequestering it, so that the agonist is no longer capable of binding to and activating the receptor. Protamine is an example of a chemical antagonist; this basic protein binds stoichiometrically to the acidic heparin class of anticoagulants and thereby inactivates these agents (see Chapter 23, Pharmacology of Hemostasis and Thrombosis). Because of this chemical antagonism, protamine can be used to terminate the effects of heparin rapidly.

A physiologic antagonist either blocks a receptor that mediates the physiologic response of the receptor for agonist or activates a receptor that mediates a response physiologically opposite to that of the receptor for agonist. For example, in the treatment of hyperthyroidism, **β**-adrenergic antagonists are used as physiologic antagonists to counteract the tachycardic effect of excess thyroid hormone. Excess thyroid hormone produces tachycardia, at least in part, via up-regulation of cardiac β-adrenoceptors, and blocking β-adrenergic stimulation relieves the tachycardia (see Chapter 11, Adrenergic Pharmacology, and Chapter 28, Pharmacology of the Thyroid Gland).

Partial Agonists

A partial agonist *is a molecule that binds to a receptor at its active site but produces only a partial response, even when all of the receptors are occupied (bound) by the agonist.* Figure 2-7A shows a family of dose–response curves for several full and partial agonists. Each agonist acts by binding to the same site on the muscarinic acetylcholine (ACh) receptor. Note that butyl trimethylammonium (TMA) is not only more potent than longer chain derivatives at stimulating muscle contraction but also more eff cacious than some of the derivatives (e.g., the heptyl and octyl forms) at producing a greater maximal response. For this reason, butyl TMA is a *full agonist* at the muscarinic ACh receptor, whereas the octyl derivative is a *partial agonist* at this receptor.

Because partial agonists and full agonists bind to the same site on a receptor, a partial agonist can reduce the response produced by a full agonist. In this way, the partial agonist can act as a competitive antagonist. For this reason, partial agonists are sometimes called *partial antagonists* or even *mixed agonist-antagonists*.

It is interesting to consider how an agonist could produce a less-than-maximal response if a receptor can exist in only the active or the inactive state. This is an area of current investigation, for which several hypotheses have been proposed. Recall that Equation 2-6 was simplif ed to Equation 2-7 based on the assumption that *R* and *DR** are much more stable than *R** and *DR*. But what would happen if a drug (call it a partial agonist) could stabilize *DR* as well

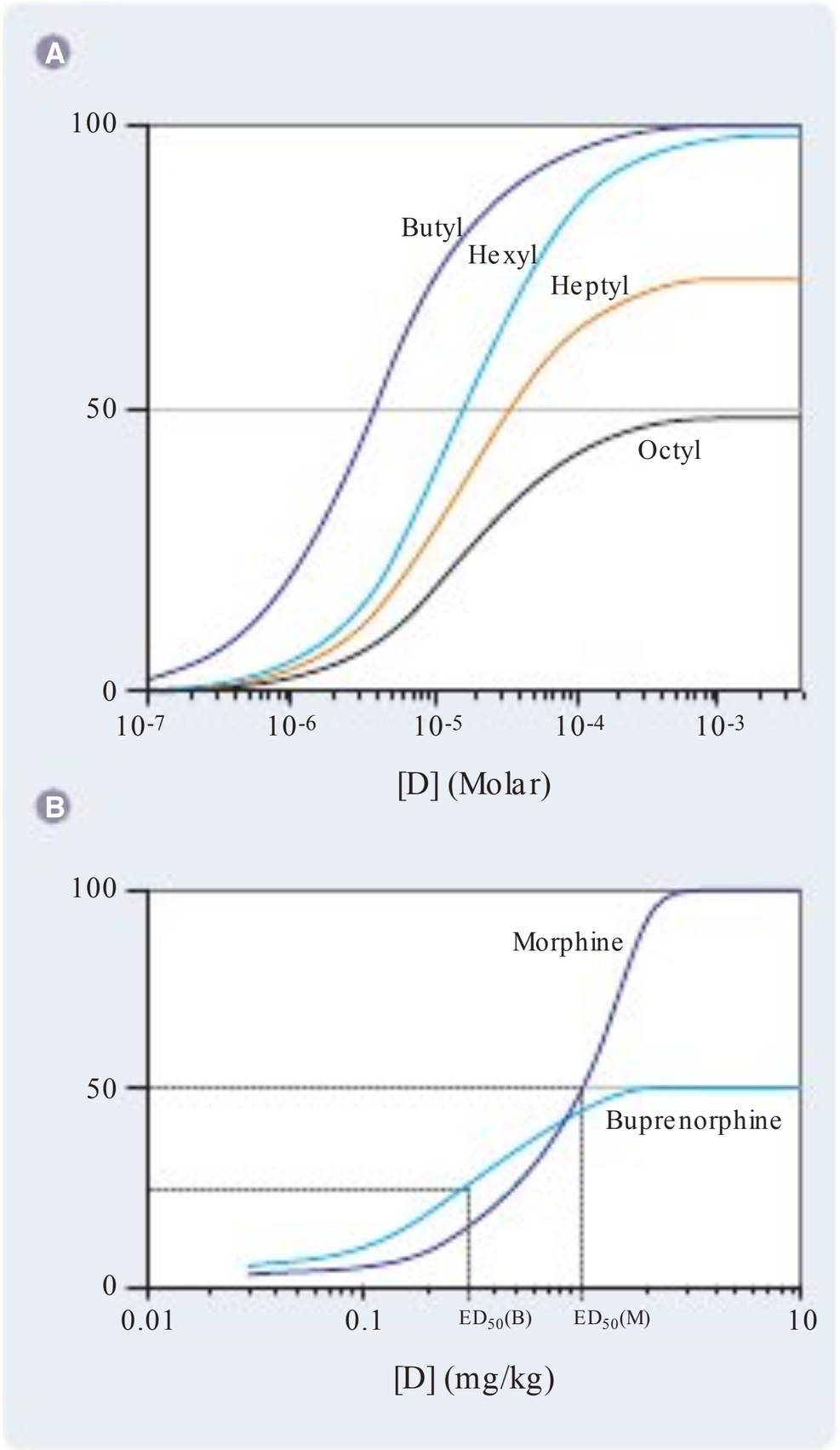

FIGURE 2-7. Full and partial agonist dose–response curves. There are many instances in which drugs that all act at the agonist site on the same receptor produce different maximal effects. A. Various alkyl derivatives of trimethylammonium all stimulate muscarinic acetylcholine (ACh) receptors to cause muscle contraction in the gut, but they produce different maximal responses, even when all receptors are occupied. In this example, the butyl and hexyl trimethylammonium derivatives are full agonists—although they have different potencies, they are both capable of eliciting a maximal response. Agonists that produce only a partial response, such as the heptyl and octyl derivatives, are called partial agonists. Note that the dose–response curves of these partial agonists plateau at values less than those of full agonists. ACh acts as a full agonist in this system (not shown). B. Partial agonists may be more or less potent than full agonists. In this case, buprenorphine (ED_{50} = 0.3 mg/kg) is more potent than morphine (ED_{50} = 1.0 mg/kg), although it cannot achieve the same maximal response as the full agonist. Buprenorphine is used clinically in the treatment of opioid addiction, where it is desirable to use a partial agonist that is less eff cacious than an addicting opioid such as heroin or morphine. Low concentrations of the partial agonist buprenorphine bind tightly to the opioid receptor and competitively inhibit the binding of the more eff cacious opioids. Very high doses of buprenorphine show a paradoxically diminished analgesic effect that may be due to lower aff nity interactions of the drug with non–mu-opioid receptors (not shown).