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Principles of Pharmacology

The Pathophysiologic Basis of Drug Therapy

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Ehrin J. Armstrong
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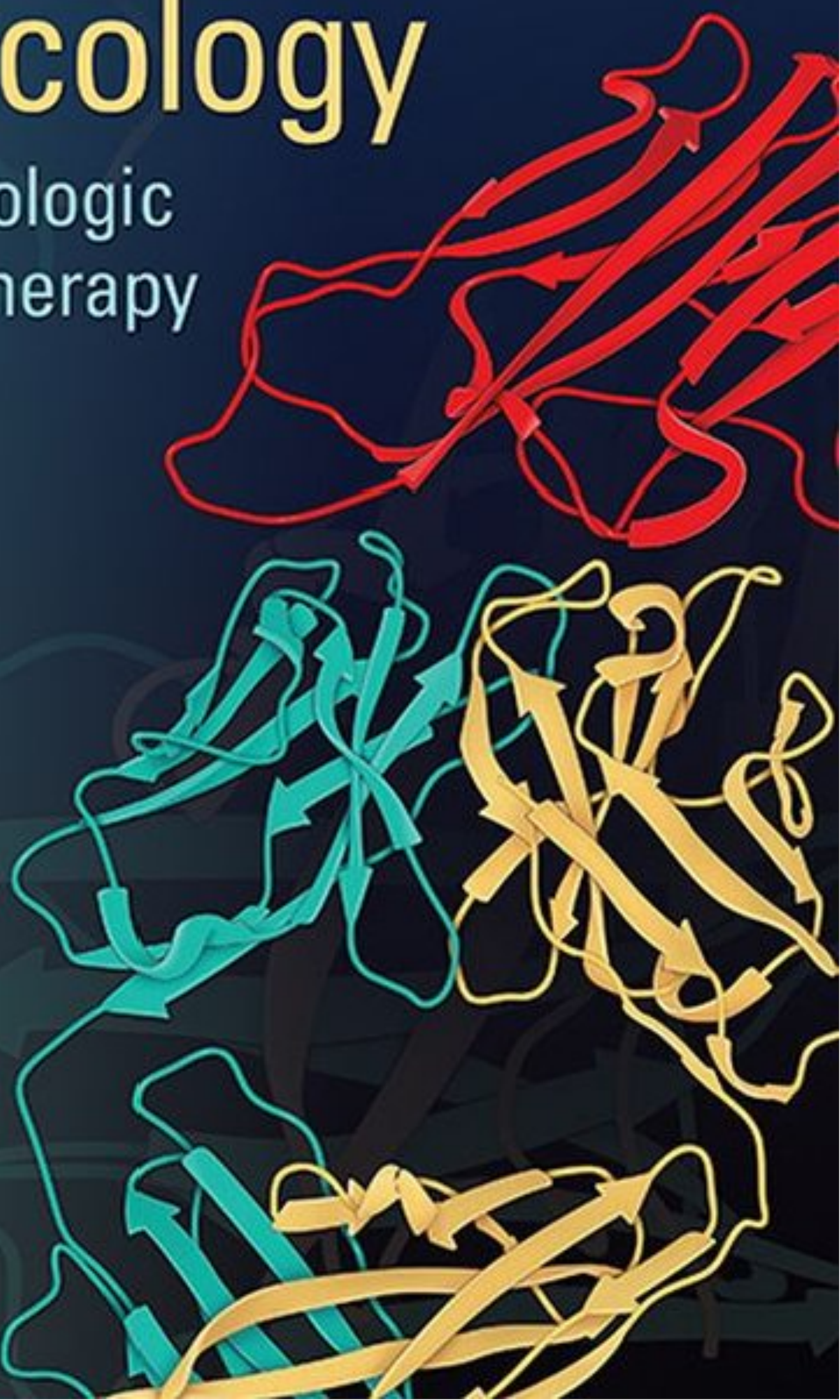

FOURTH EDITION

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,

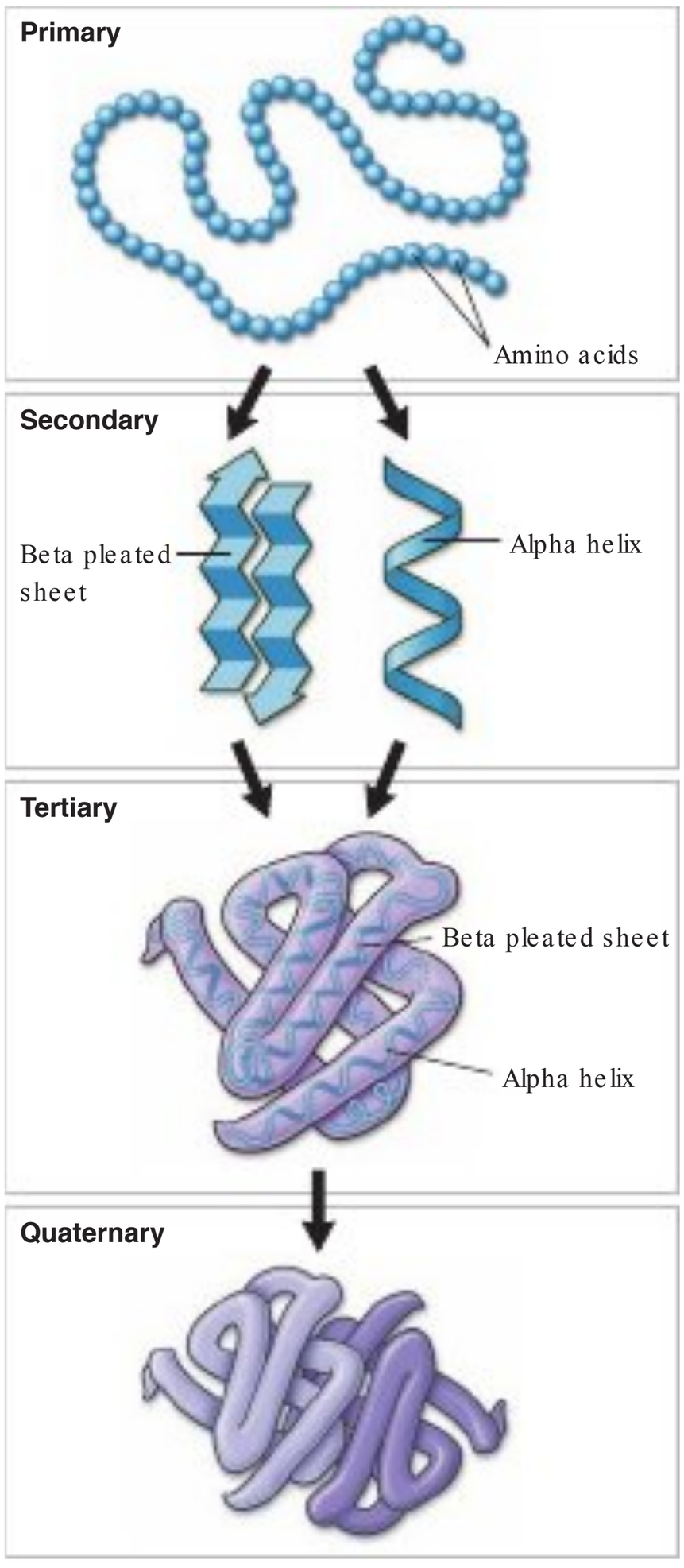

FIGURE 1-1. Levels of protein structure. Protein structure can be divided into four levels of complexity, referred to as primary, secondary, tertiary, and quaternary structure. Primary structure is determined by the sequence of amino acids that make up the polypeptide chain. Secondary structure is determined 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

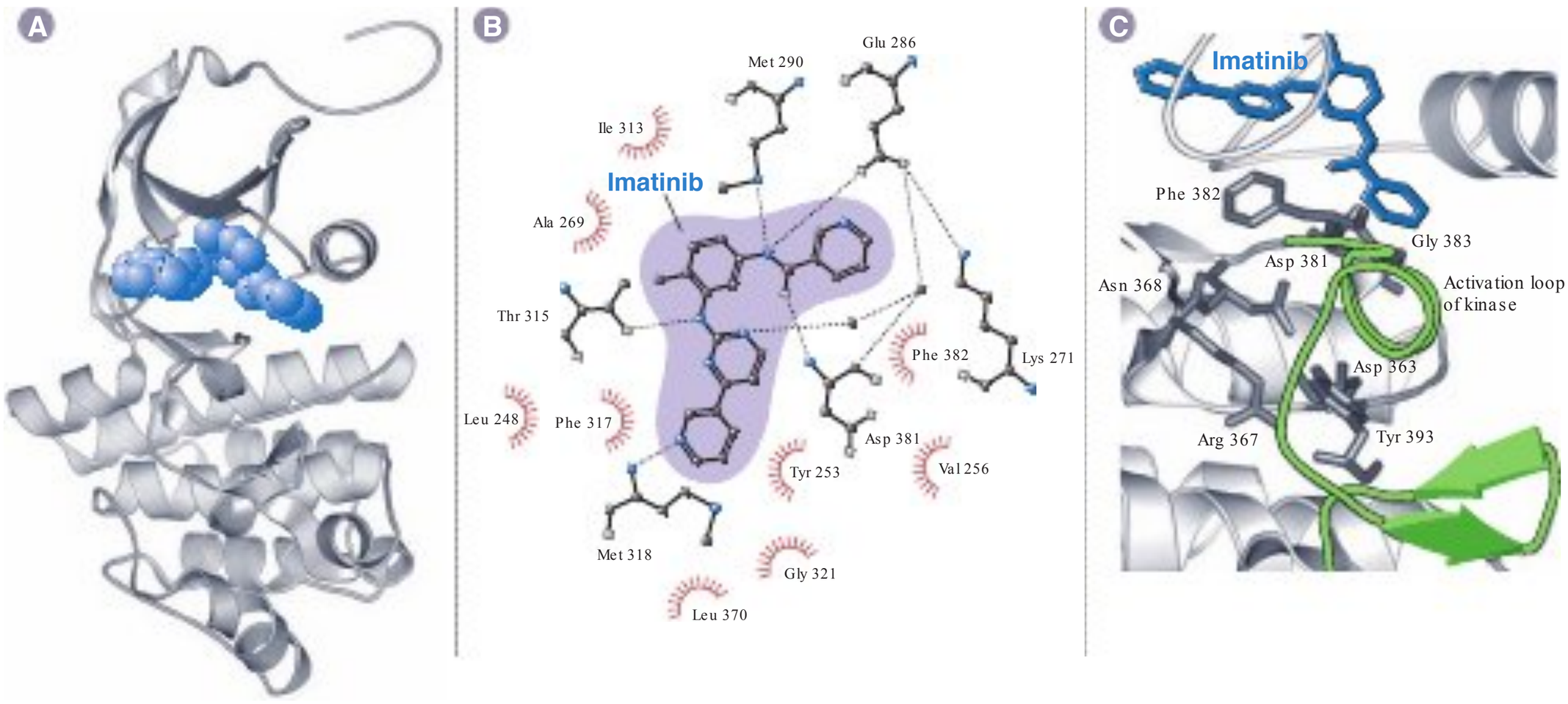

FIGURE 1-2. Structural basis of specific enzyme inhibition: imatinib interaction with the BCR-Abl kinase. A. The kinase portion of the BCR-Abl tyrosine kinase is shown in a ribbon format (gray). An analogue of imatinib, a specific inhibitor of the BCR-Abl tyrosine kinase, is shown as a space-filling 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

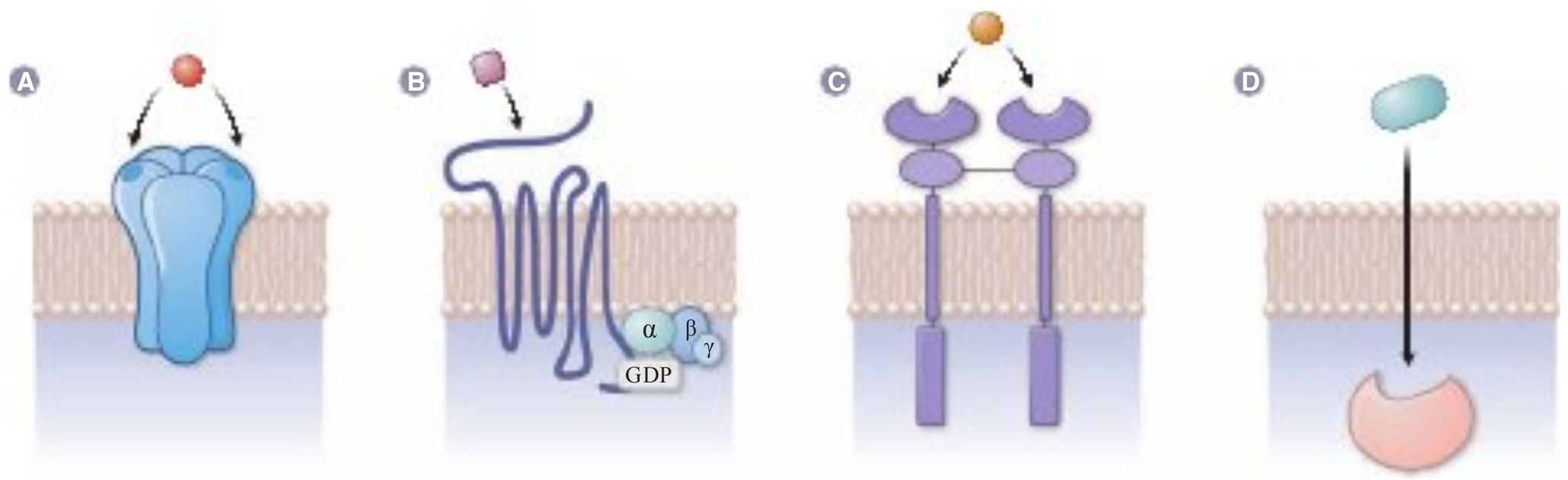

FIGURE 1-3. Major types of interactions between drugs and receptors. Most drug–receptor interactions can be divided into six groups, four of which are shown here. A. Drugs can bind to ion channels spanning the plasma membrane, causing an alteration in the channel's conductance. B. Heptahelical receptors 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

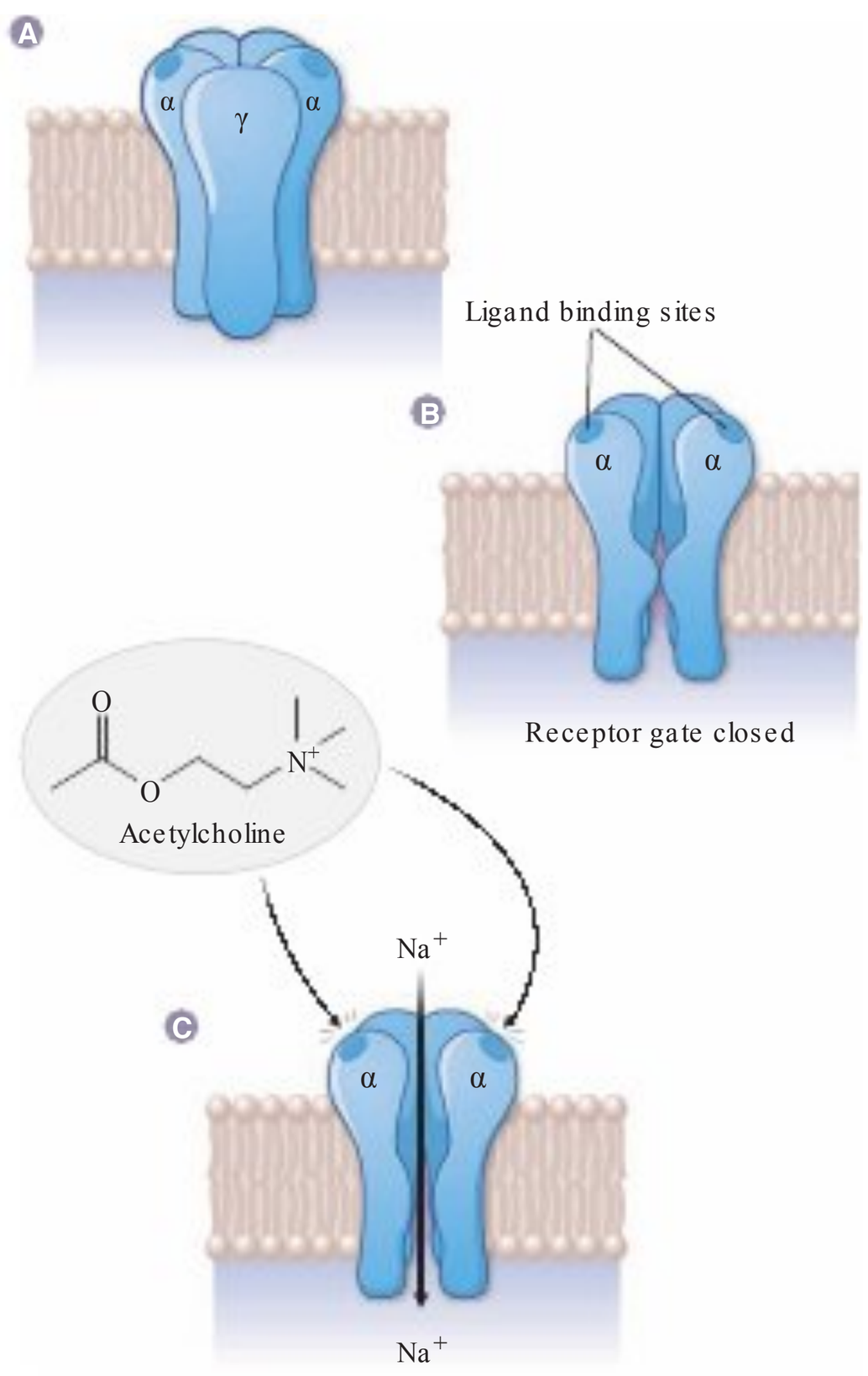

FIGURE 1-4. Ligand-gated nicotinic acetylcholine receptor. A. The plasma membrane acetylcholine (ACh) receptor is composed of five subunits—two α subunits, a β subunit, a γ subunit, and a δ subunit. B. The γ subunit has been removed to show an internal schematic view of the receptor, demonstrating that 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.