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Principles of Pharmacology

The Pathophysiologic Basis of Drug Therapy

David E. Golan
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FOURTH EDITION

 Wolters Kluwer



PRINCIPLES of PHARMACOLOGY
THE PATHOPHYSIOLOGIC BASIS OF DRUG THERAPY

Fourth Edition



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To our students and the patients they will serve

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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*.

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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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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 figure generation and revision, and delivery of the final manuscript. We are extraordinarily grateful for his unwavering dedication to this project.

Rob Duckwall did a superb job to update the full-color figures. Rob's standardization and coloration of the figures 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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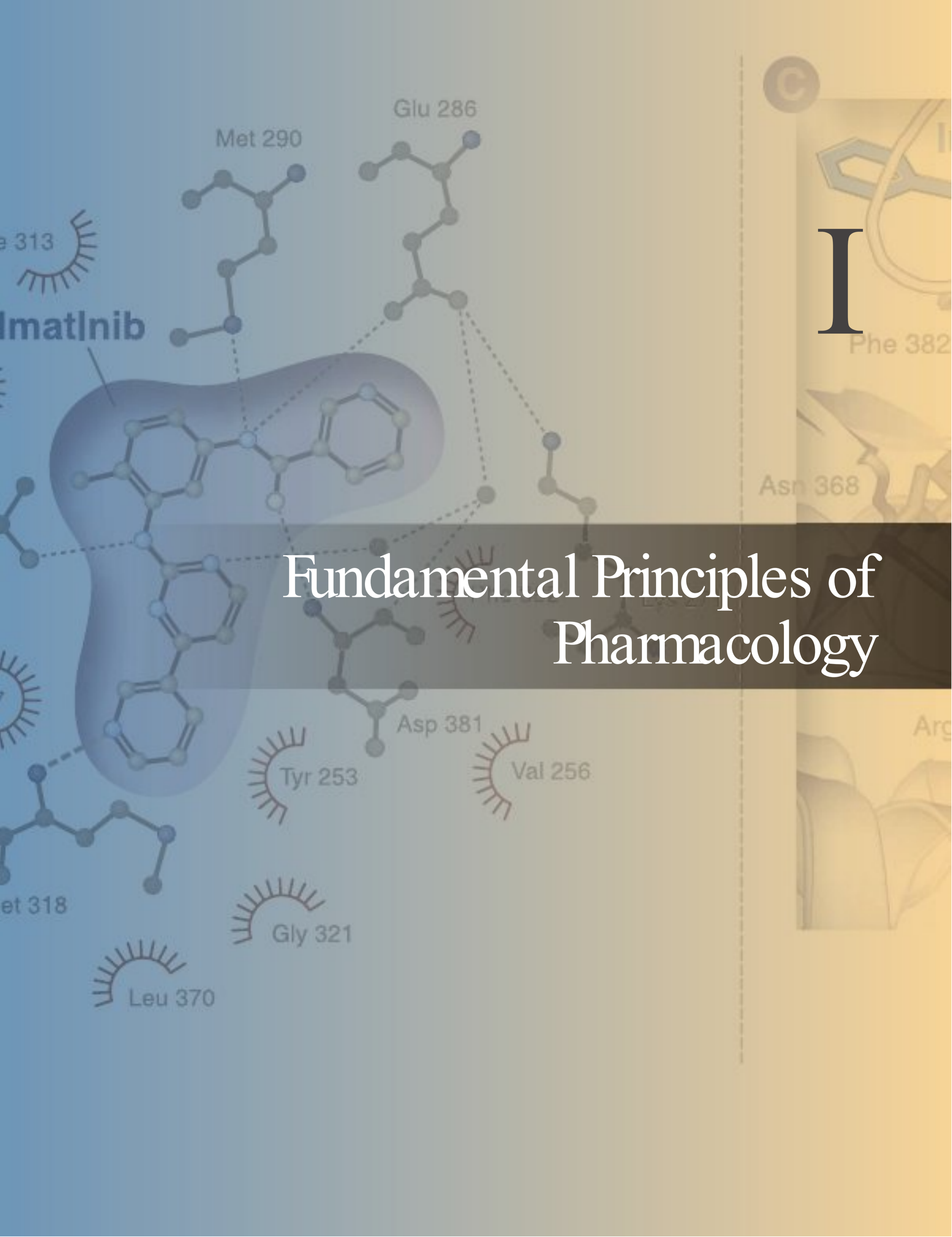
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Met 313
Imatinib

Met 290

Glu 286

Fundamental Principles of Pharmacology

Tyr 253

Val 256

Asp 381

Gly 321

Leu 370

Met 318

Phe 382

Asn 368

Arg

I

Drug–Receptor Interactions

Francis J. Alenghat and David E. Golan

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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 ($70,000 \text{ cells/mm}^3$) 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,

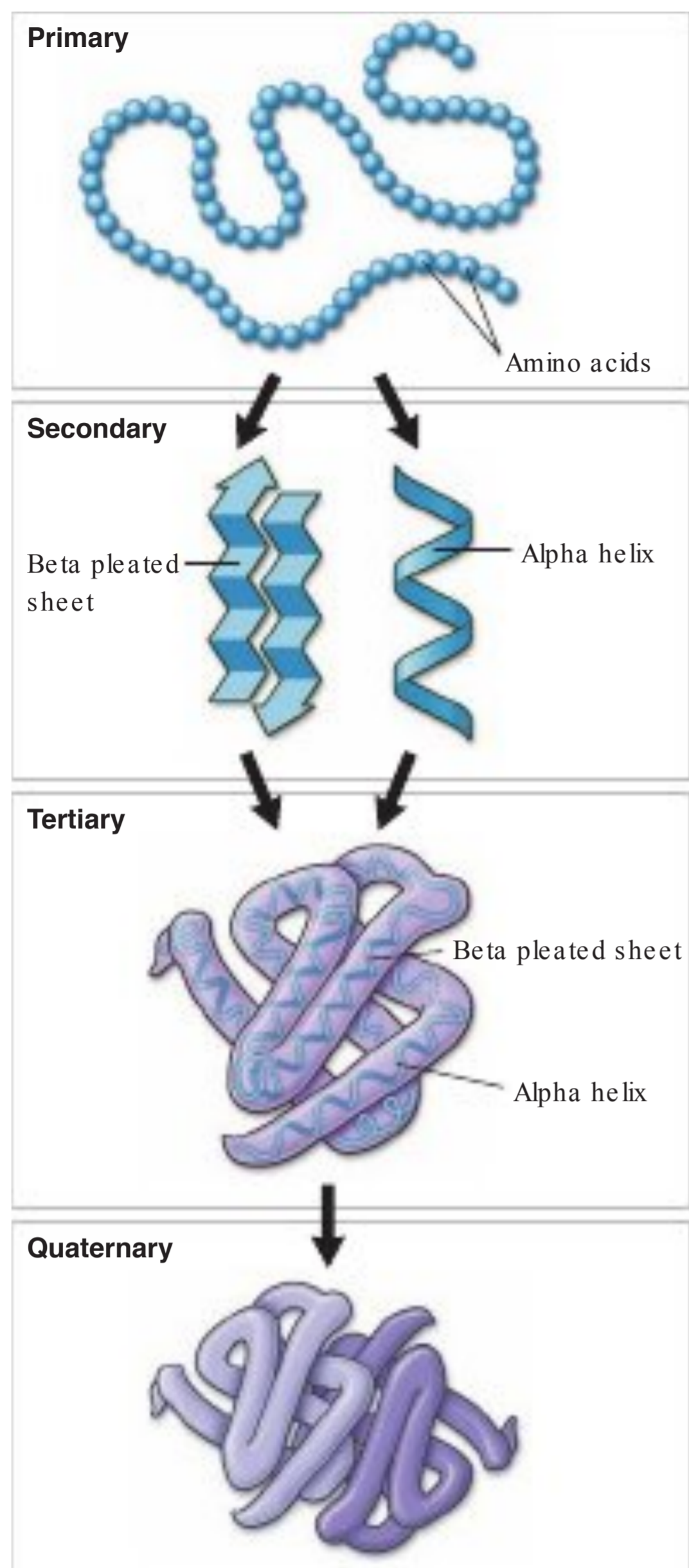


FIGURE 1-1. Levels of protein structure. Protein structure can be divided into four levels of complexity, referred to as primary, secondary, tertiary, and quaternary structure. Primary structure is determined by the sequence of amino acids that make up the polypeptide chain. Secondary structure is determined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

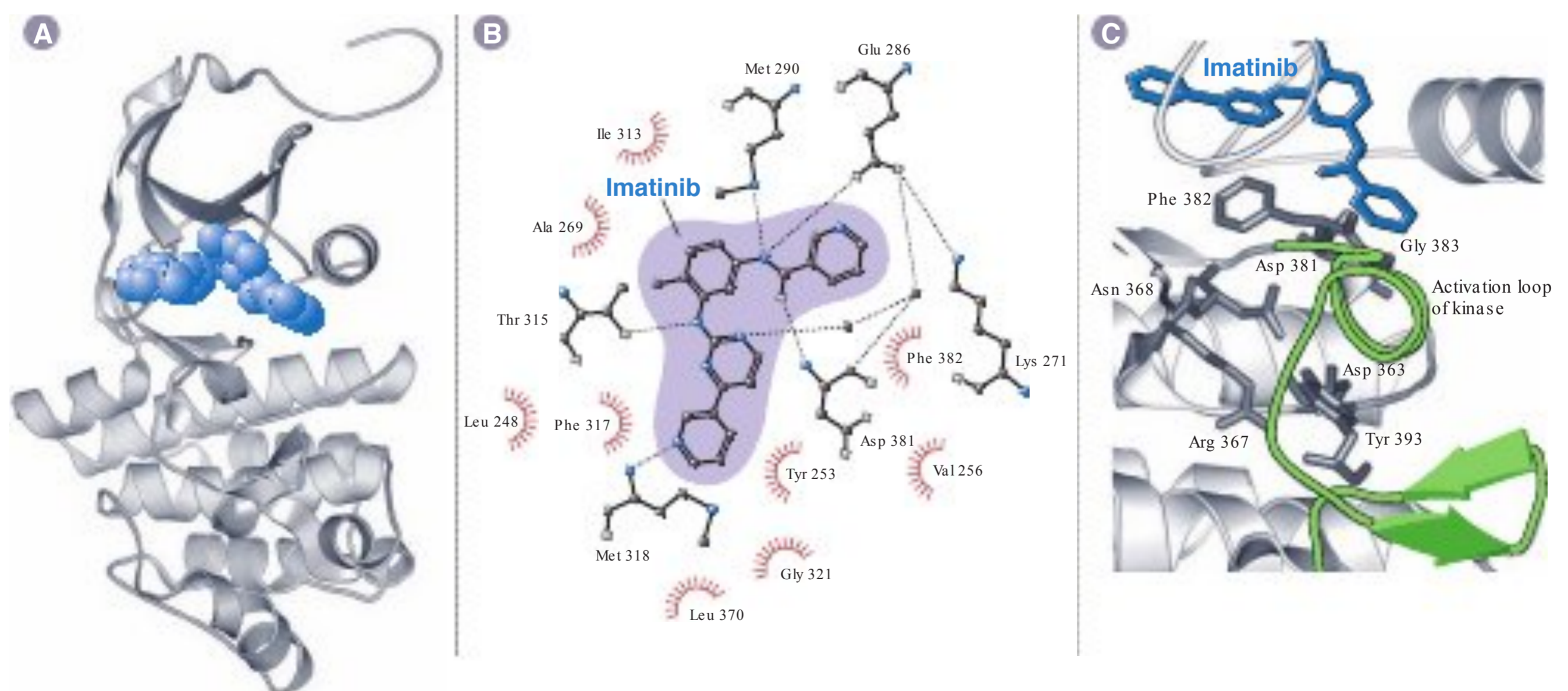


FIGURE 1-2. Structural basis of specific enzyme inhibition: imatinib interaction with the BCR-Abl kinase. A. The kinase portion of the BCR-Abl tyrosine kinase is shown in a ribbon format (gray). An analogue of imatinib, a specific inhibitor of the BCR-Abl tyrosine kinase, is shown as a space-filling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

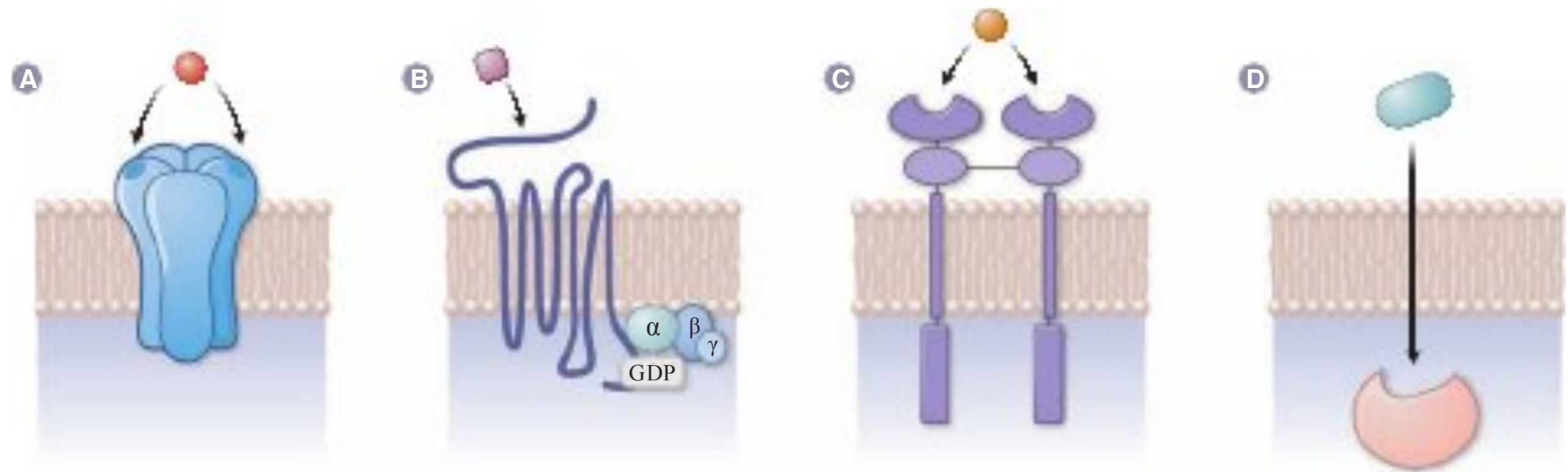


FIGURE 1-3. Major types of interactions between drugs and receptors. Most drug–receptor interactions can be divided into six groups, four of which are shown here. **A.** Drugs can bind to ion channels spanning the plasma membrane, causing an alteration in the channel’s conductance. **B.** Heptahelical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

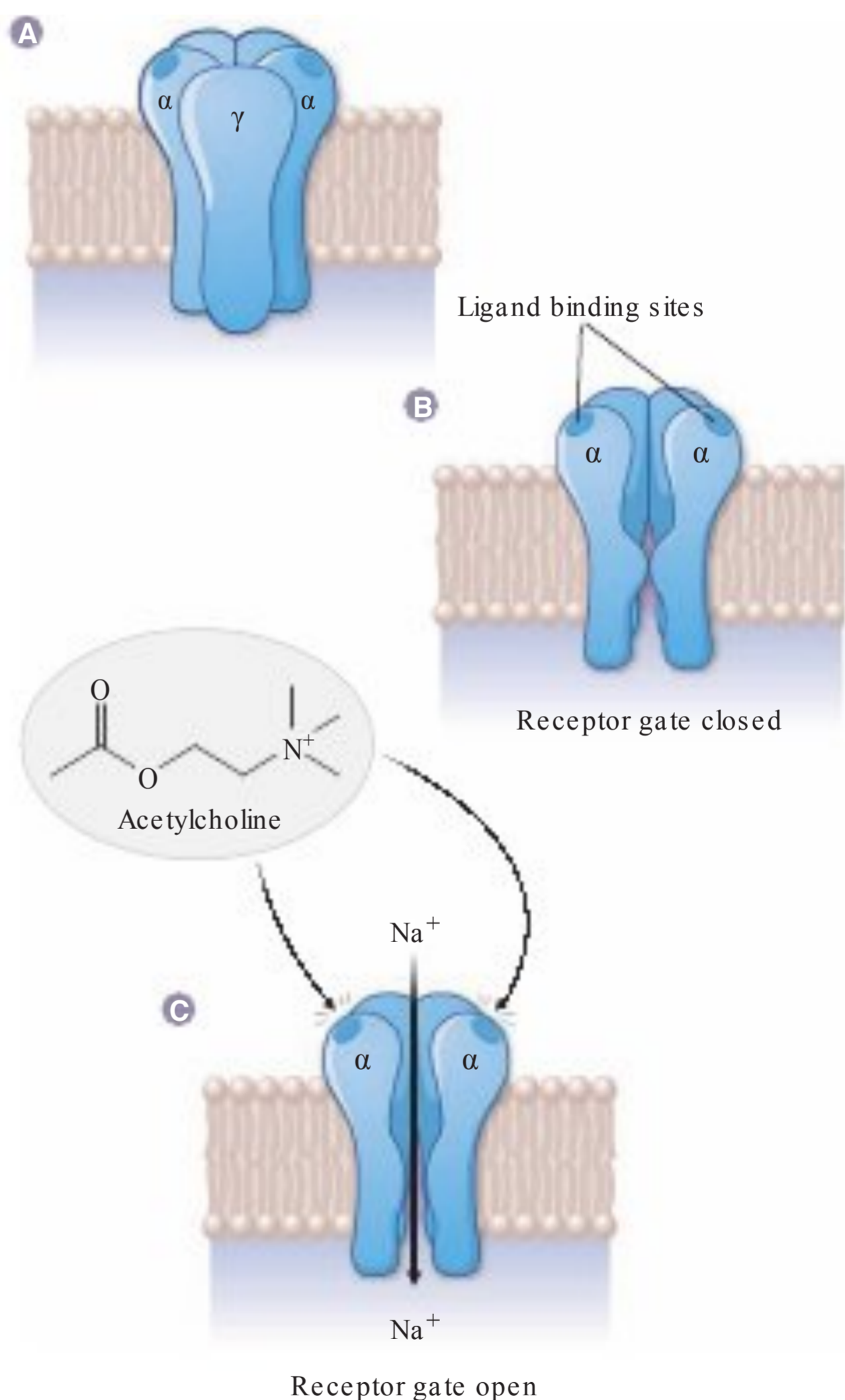


FIGURE 1-4. Ligand-gated nicotinic acetylcholine receptor. A. The plasma membrane acetylcholine (ACh) receptor is composed of five subunits—two α subunits, a β subunit, a γ subunit, and a δ subunit. B. The γ subunit has been removed to show an internal schematic view of the receptor, demonstrating that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

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

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 $\beta\gamma$ 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 $\beta\gamma$ subunit, and the α or $\beta\gamma$ 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

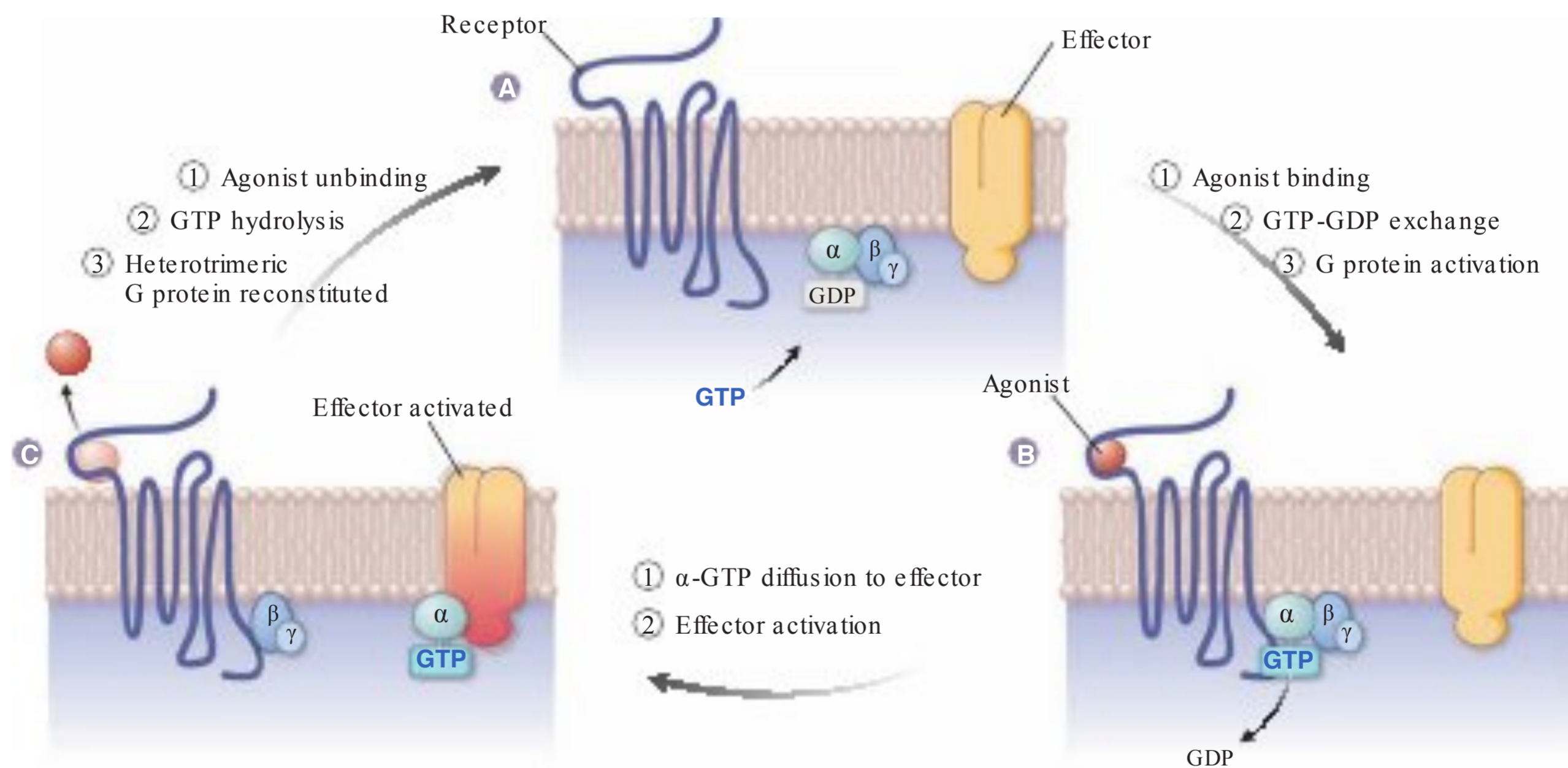


FIGURE 1-5. Receptor-mediated activation of a G protein and the resultant effector interaction. A. In the resting state, the α and $\beta\gamma$ subunits of a G protein are associated with one another, and GDP is bound to the α subunit. B. Binding of an extracellular ligand (agonist) to a G protein-coupled receptor causes the exchange of GTP for GDP on the α subunit. C. The $\beta\gamma$ 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 $\beta\gamma$ subunit can also activate effector proteins. Depending on the receptor subtype and the specific $G\alpha$ isoform, $G\alpha$ 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 $\beta\gamma$ subunit, and the cycle can begin again.

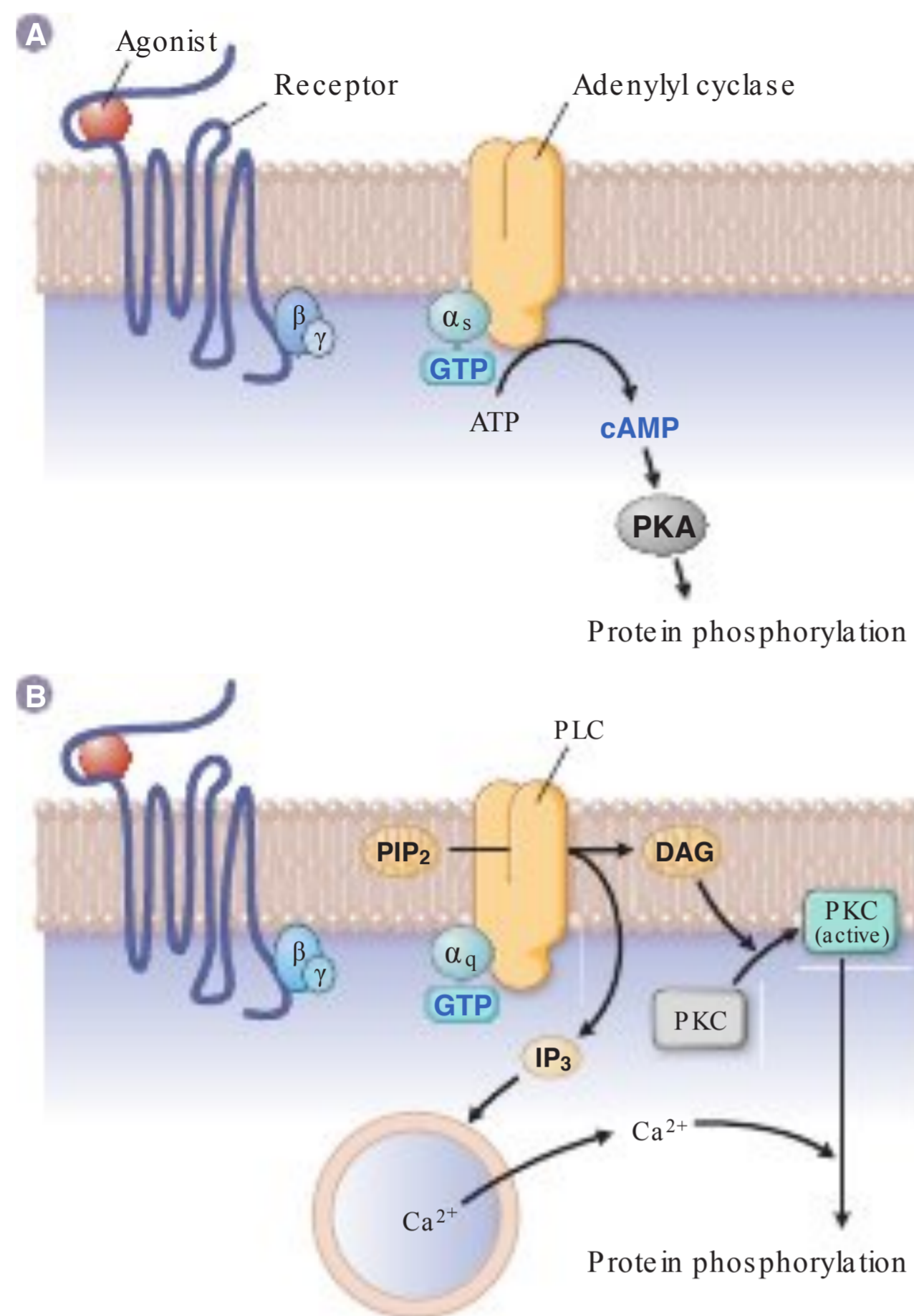


FIGURE 1-6. Activation of adenylyl cyclase (AC) and phospholipase C (PLC) by G proteins. G proteins can interact with several different types of effector molecules. The subtype of $G\alpha$ protein that is activated often determines which effector the G protein will activate. Two of the most common $G\alpha$ 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 $\beta\gamma$ 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 $G\alpha$ protein isoforms have been identified, each with unique effects on its targets. Based on the primary sequence of the $G\alpha$ subunit, these isoforms can

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

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 $\beta\gamma$ 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 1-5 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

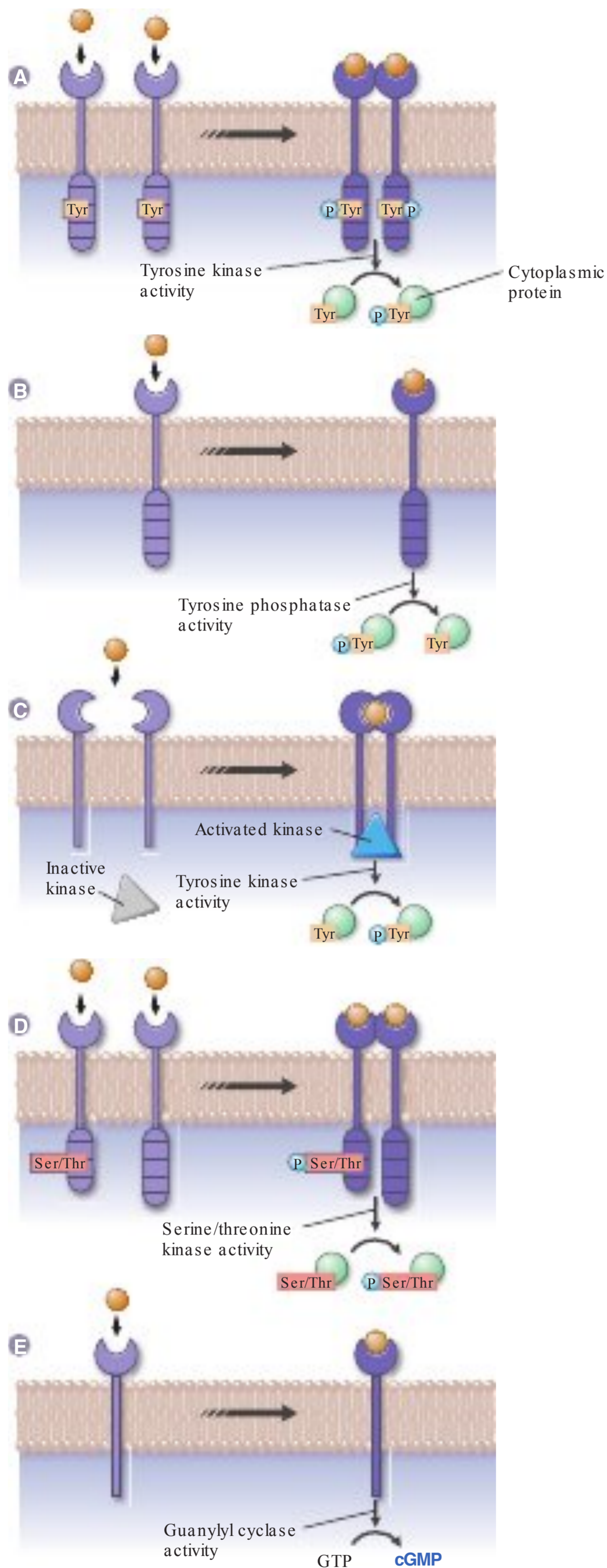


FIGURE 1-7. Major types of transmembrane receptors with linked enzymatic domains. There are five major categories of transmembrane receptors with linked enzymatic domains. **A.** The largest group is composed of receptor tyrosine kinases. After ligand-induced activation, these receptors dimerize and 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 specific 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 $G\alpha$ 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 modification 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 first 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 co-activator 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

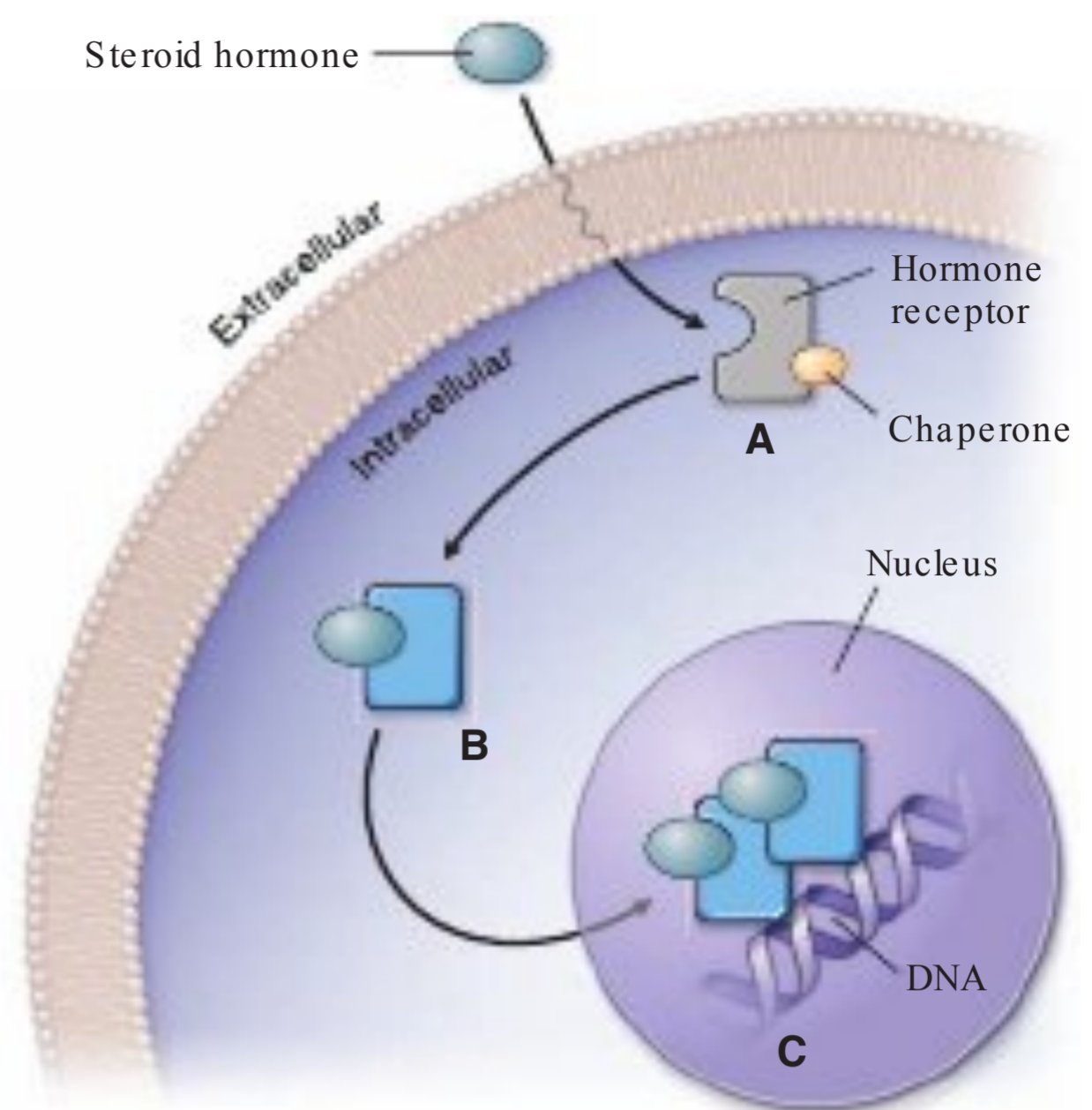


FIGURE 1-8. Lipophilic molecule binding to an intracellular transcription factor. A. Small lipophilic molecules can diffuse through the plasma membrane and bind to intracellular transcription factors. In this example, steroid hormone binding to a cytosolic hormone receptor is shown, although some receptors 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.

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.

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, eptifibatid), 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

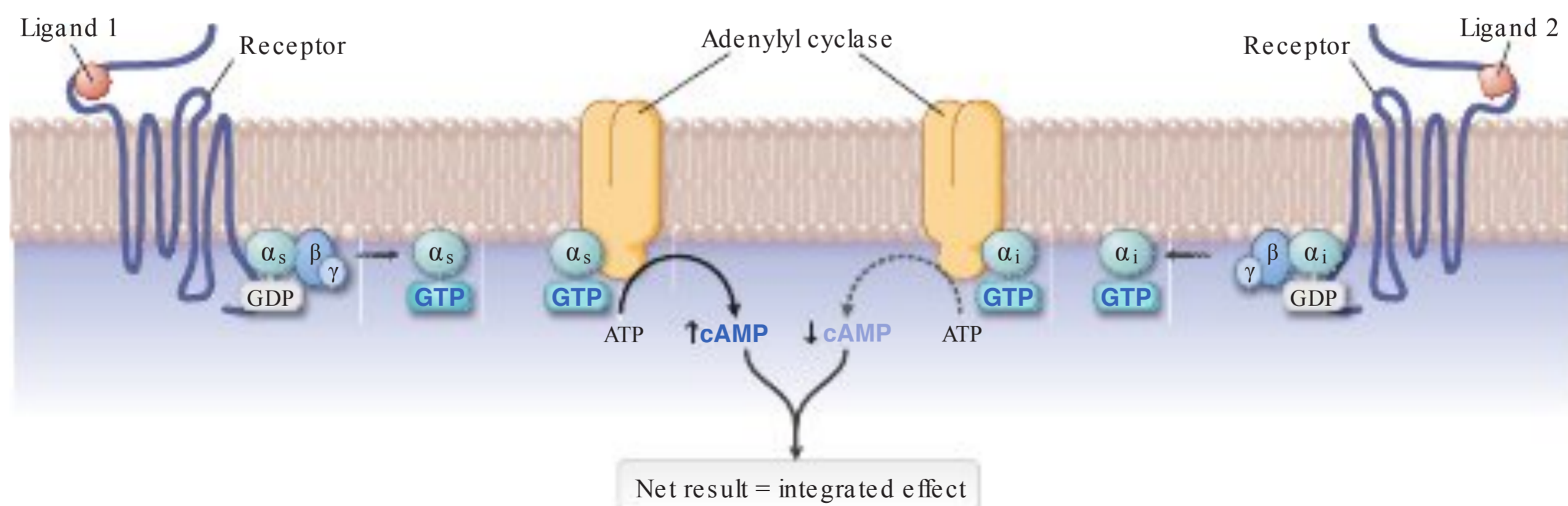


FIGURE 1-9. Signaling convergence of two receptors. A limited number of mechanisms are used to transduce intracellular signal cascades. In some cases, this allows for convergence, where two different receptors have opposite effects that tend to negate one another in the cell. In a simple example, two 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

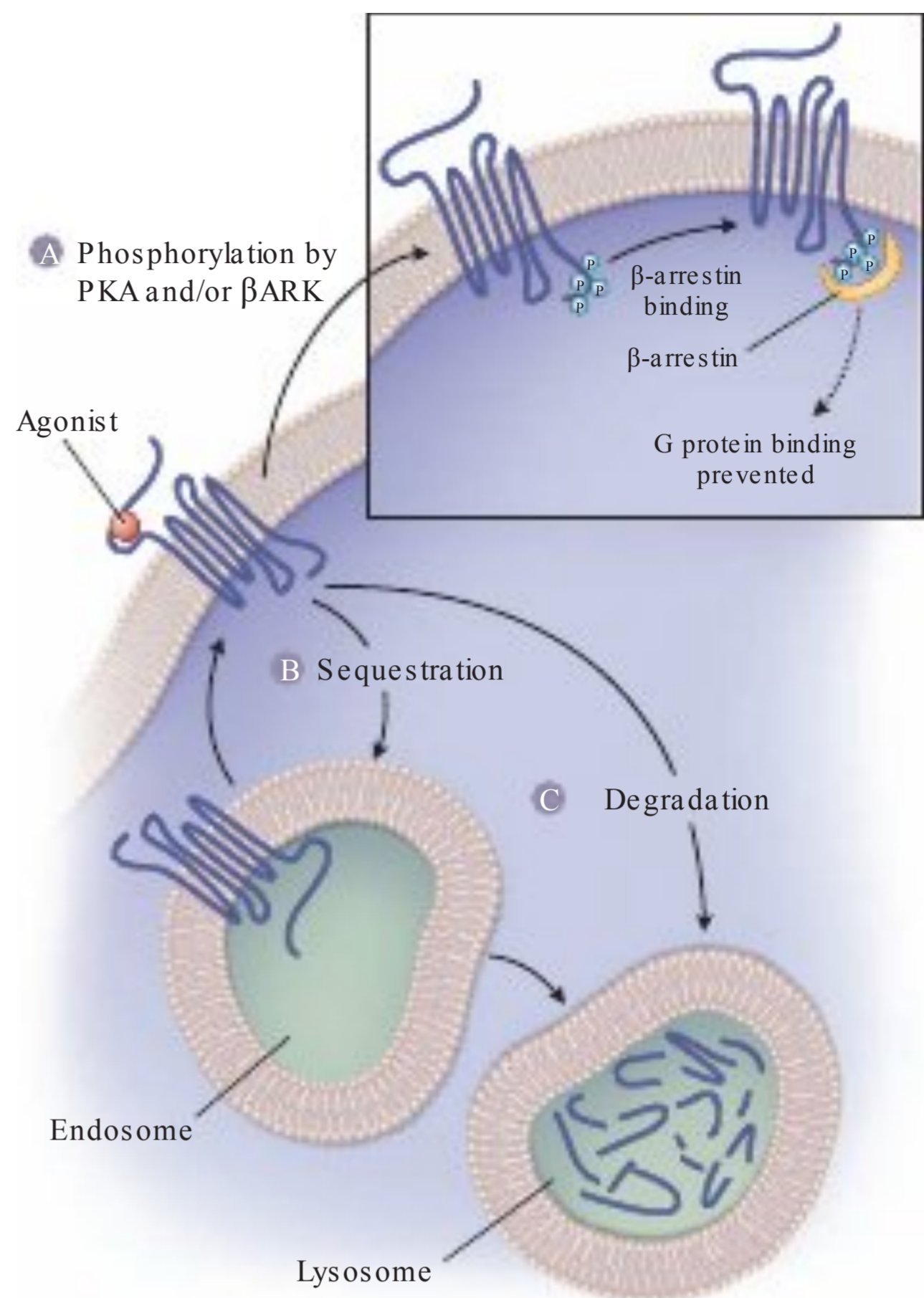


FIGURE 1-10. β -Adrenergic receptor regulation. Agonist-bound β -adrenergic receptors activate G proteins, which then stimulate adenylyl cyclase activity (not shown). A. Repeated or persistent stimulation of the receptor by agonist results in phosphorylation of amino acids at the C-terminus of the receptor by protein kinase A (PKA) and/or β -adrenergic receptor kinase (β ARK). 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).

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.

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 fit 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 nonspecifically by absorbing or chemically neutralizing stomach acid. Examples of these agents include bases such as NaHCO_3 and $\text{Mg}(\text{OH})_2$.

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* specificity of a drug with the *genetic* and *pathophysiologic* specificity of the drug target to provide more and more selective therapies.

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