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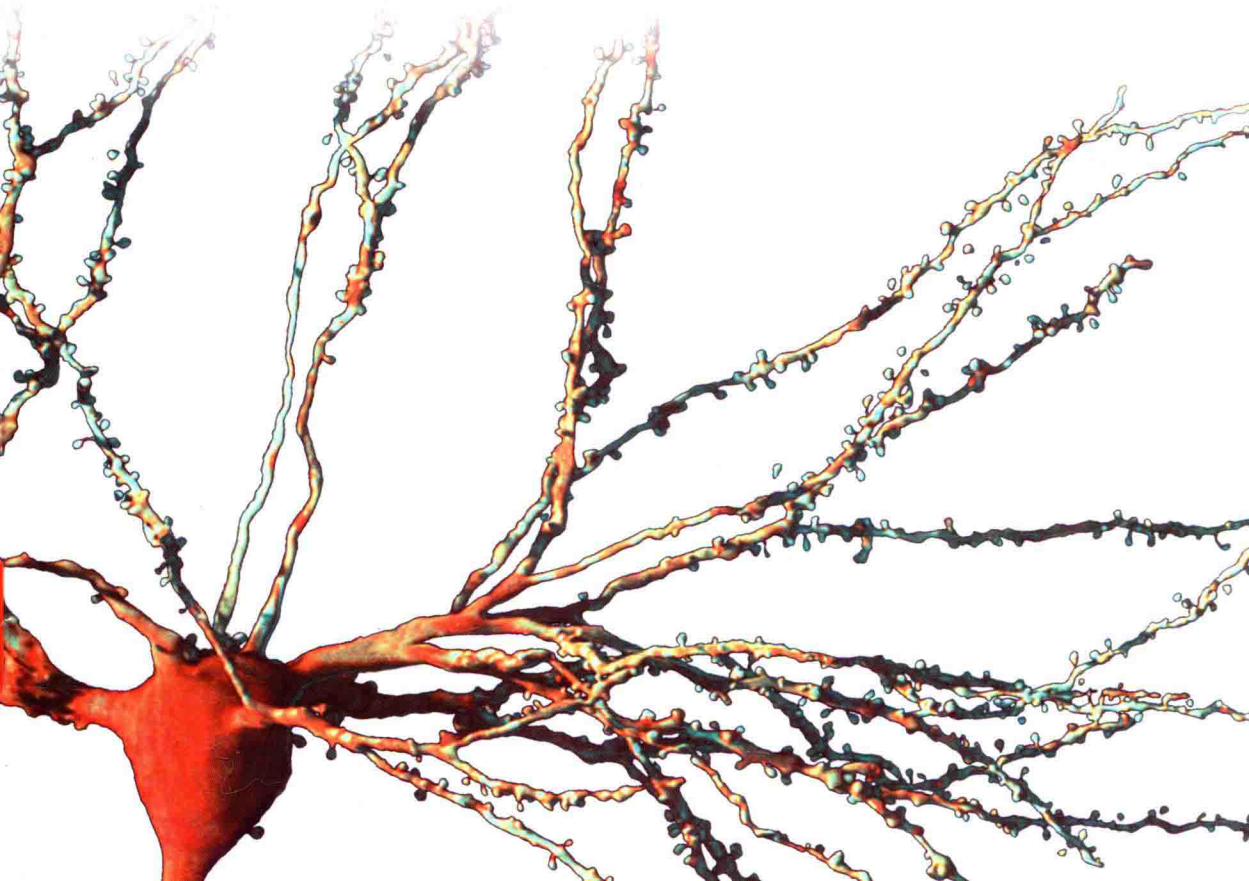
MOLECULAR NEUROPHARMACOLOGY

A Foundation for Clinical Neuroscience



Molecular Neuropharmacology

A Foundation for Clinical Neuroscience

THIRD EDITION

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PREFACE

Neuropharmacology, the study of drug actions on the nervous system, comprises several areas of critical importance to science and medicine. Neuropharmacology includes the translation of basic neuroscience into the discovery of new therapeutic agents, studies aimed at elucidating the mechanism by which drugs act in disease, and also the use of chemical compounds as tools to investigate the function of cells, synapses, and circuits in the nervous system. Much that we know about the nervous system has come from such studies. Indeed, numerous foundational discoveries in neuroscience, including the identification of many neurotransmitters and their receptors, transporters, and signaling molecules, came from investigation into mechanisms of drug action.

To comprehend the actions of a drug on the nervous system, a great deal more is needed than simply identifying the drug's initial target in the nervous system. Rather, one must understand the entire sequence of events that commences with the binding of a drug to an initial molecular target. The resulting alteration in the functioning of that target, the influence of that occurrence on the complex biochemical networks that exist within neurons, the subsequent changes in the output of the neuron, and their consequences for the functioning of circuits within which the targeted neuron exists are all important for gaining a real understanding of drug action. Likewise, it is crucial to delineate the actions of a drug on the many types of non-neuronal cells in the brain and spinal cord. Only with an awareness of the many steps in the process can we grasp how a drug changes complex nervous system functions such as movement, cognition, pain, or mood.

Neuropharmacology is entering an exciting new era as genetic analysis of many diseases of the nervous system is beginning to identify molecular mechanisms of pathogenesis that suggest new therapeutic targets. Even highly heterogeneous and genetically complex disorders, for instance, many forms of intellectual disability, autism, schizophrenia, epilepsy, and neurodegenerative diseases, among others, are beginning to yield to modern technologies. If these discoveries are ultimately going to yield effective therapeutics, new experimental approaches to neuropharmacology will be much in need.

The organization of this textbook represents an attempt to build an understanding of drug action by adding the different levels of explanation layer by layer. As a result this book differs significantly from many other pharmacology texts, which are usually organized by drug class or by neurotransmitter. In this book, information on fundamental molecular and cellular building blocks is provided first so that it can serve as the basis for the material associated with neural functions. This permits the reader to relate fundamental neuropharmacology to neural systems and ultimately to clinical neuroscience.

The book is divided into three parts. Part 1 includes a brief discussion of general principles of neuropharmacology (Chapter 1), followed by a detailed presentation of nervous system function (Chapters 2–4), from electrical excitability to signal transduction to gene expression. Drugs that act on these basic components of neuronal function are mentioned in these early chapters.

In Part 2 information about the major neurotransmitter systems in the brain and spinal cord is presented (Chapters 5–8). Highlighted in these chapters are the molecular details of neurotransmitter synthetic and degradative enzymes, receptors, and transporter proteins. These proteins represent the initial targets for the large majority of known psychotropic drugs. Also included in Part 2 is a discussion of several types of atypical neurotransmitters, eg, neurotrophic factors, adenosine, endocannabinoids, and nitric oxide, among others (Chapter 8), which in recent years have been shown to profoundly influence the adult nervous system and to be potentially important in therapeutics.

Part 3 uses the basic information contained in Parts 1 and 2 to build a systems-level description of the major domains of complex nervous system function. Chapter 9 focuses on the autonomic nervous system; Chapter 10 on neuroendocrine function, Chapter 11 on pain and analgesia, Chapter 12—new to this third edition—on neuroinflammation, Chapter 13 on sleep and arousal, Chapter 14 on cognition and behavioral control, Chapter 15 on emotion and mood, Chapter 16 on reinforcement and addiction, Chapter 17 on schizophrenia and other psychotic disorders, Chapter 18 on neurodegenerative diseases, in particular, Alzheimer disease and Parkinson disease, Chapter 19 on seizure disorders, and Chapter 20 on cerebrovascular illnesses such as stroke and migraine. Each chapter begins with a description of the normal neural mechanisms underlying a particular domain of nervous system functioning, followed by a discussion of the diseases that affect that domain. Drugs are discussed within the context of

their influence on the neural circuits involved in both normal function and specific disease states.

The organization of *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience* allows individual drugs to be discussed in several contexts. A drug is first mentioned when its initial target is described in Part 1 or 2. The drug is mentioned again in Part 3 in the context of its effect on complex neural functions. Many drugs are discussed in several chapters of Part 3 because they affect more than one domain; for example, first-generation antipsychotic drugs not only reduce psychosis (Chapter 17), but also affect motor function (Chapter 18), sleep (Chapter 13), and neuroendocrine function (Chapter 10).

The book's structure also permits the incorporation of a great deal of clinical information, much of it representing the integration of modern molecular genetics with neuropharmacology. New insights on the molecular mechanisms underlying such disorders as Parkinson disease, Huntington disease, depression, schizophrenia, Alzheimer disease, stroke, and epilepsy, to name a few, are provided. Our knowledge of the molecular underpinnings of normal brain function and disease, particularly in cases that have been successfully investigated by genetics, may be in advance of developments in pharmacology. Consequently, the book includes many molecular insights, even though drugs may not yet exist that exploit such molecular knowledge. In this regard the book can be seen as presenting a template for the future in identifying molecular mechanisms for novel therapeutic approaches. We anticipate that subsequent editions of this book will describe the development of such novel medications and thereby gradually fill in these gaps in pharmacology.

The scientific and clinical explanations in *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience* are written in a style that makes them accessible to a wide audience: undergraduate and graduate students as well as students in the medical and allied health professions. This book is also an excellent resource for residents in psychiatry, neurology, neurosurgery, rehabilitation medicine, and anesthesiology, and practicing clinicians and scientists in these areas. As a concise treatise of clinical information that provides descriptions of basic mechanisms and their clinical relevance, this book is suitable for both scientists and clinicians.

We would like to acknowledge the contributing authors who were instrumental in the initial phases of the preparation of this book for the first, second, and third editions, and we welcome David Holtzman as a new coauthor. We also would like to thank Anne Sydor and her colleagues at McGraw-Hill, and Ritu Joon and her team at Thomson Digital, for their crucial role in production of this third edition.

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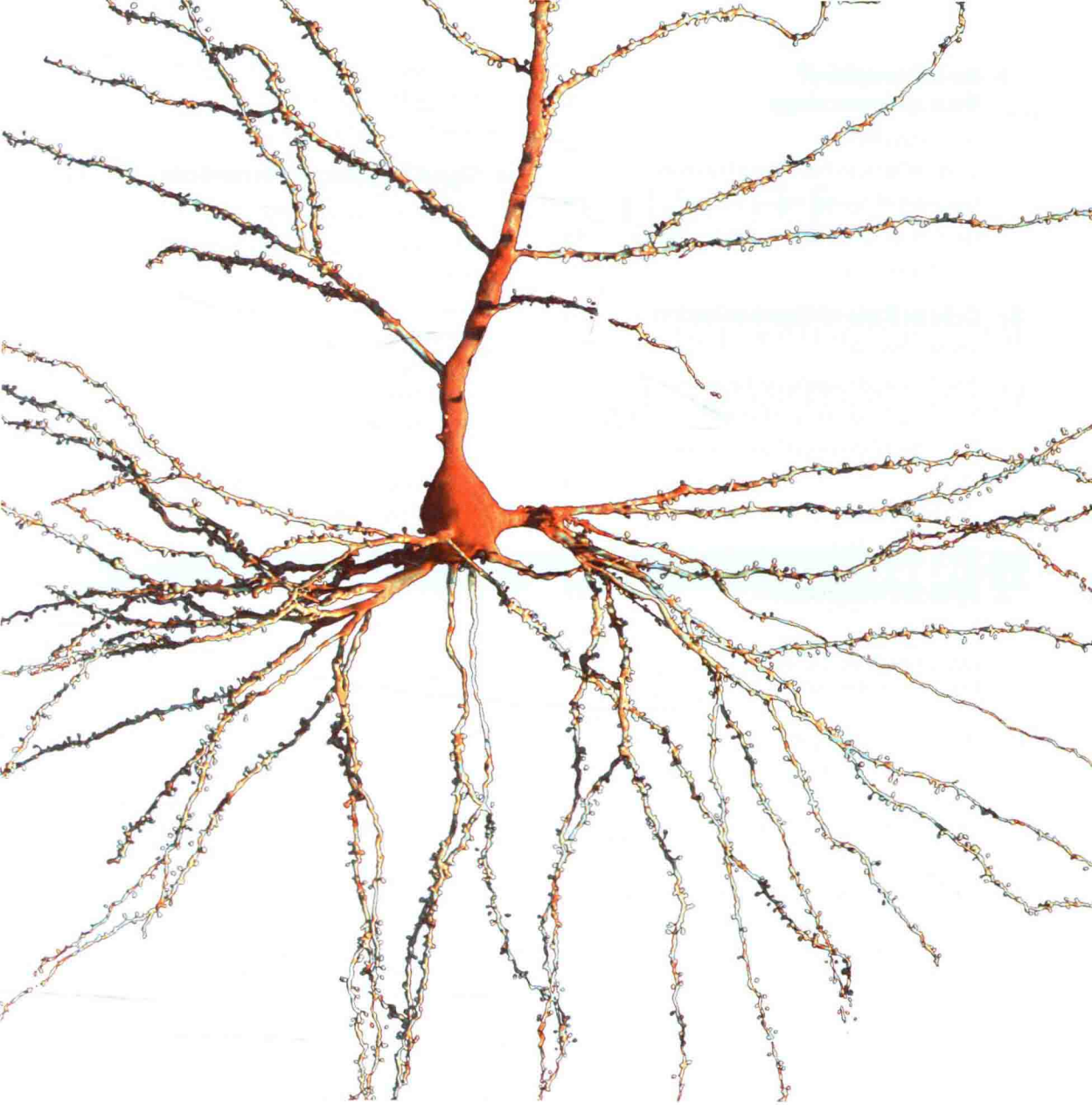

1 Fundamentals of Neuropharmacology

CHAPTER 1

Basic Principles of Neuropharmacology

KEY CONCEPTS

- An understanding of drug action in the brain must integrate knowledge of the molecular and cellular actions of a drug with their effects on brain circuitry.
- The clinical actions of a drug in the brain often are due to neural plasticity—the long-term adaptations of neurons to the sustained short-term actions of a drug.
- The binding of a drug to its specific target(s) normally is saturable and stereoselective.
- The specific binding of a drug to its target is quantified according to its affinity for the target, expressed as a dissociation constant (K_d), and the total amount of binding (B_{max}).
- Potency of a drug describes the strength of binding between the drug and its target; efficacy describes the maximal biologic effects that the drug exerts by binding to its target.
- Drugs can be classified as agonists, partial agonists, inverse agonists, partial inverse agonists, or antagonists.
- Modern neuropharmacology takes advantage of the tools of molecular biology, genetics, and cell biology as well as combinatorial chemistry, which is used to generate novel molecules that may function as new drugs.
- Functional genomics and proteomics will help identify novel drug targets.
- Pharmacogenetics will guide the choice of drug treatments based on an individual's genetic constitution.

Neuropharmacology is the scientific study of the effects of drugs on the nervous system. Its primary focus is the actions of medications for psychiatric and neurologic disorders as well as those of drugs of abuse. Neuropharmacology also uses drugs as tools to form a better understanding of normal nervous system functioning. The goal of neuropharmacology is to apply information about drugs and their mechanisms of action to develop safer, more effective treatments and eventually curative and preventive measures for a host of nervous system abnormalities. The importance of neuropharmacology to medical practice, and to society at large, is difficult to overstate. Drugs that act on the nervous system, including antidepressant, antianxiety, anticonvulsant, and antipsychotic agents, are among the most widely prescribed medications. Moreover, commonly prescribed medications that act on other organ systems often are associated with side effects that involve the nervous system and in turn may limit their clinical utility. In addition, a substantial number of individuals use common substances, such as caffeine, alcohol, and nicotine, that are included in the domain of neuropharmacology because of their effects on the central nervous system (CNS). In a much smaller fraction of the population, these and other drugs are used compulsively, in a manner that constitutes an addiction. Drug abuse and addiction exact an astoundingly high financial and human toll on society through direct adverse effects, such as lung cancer and hepatic cirrhosis, and indirect adverse effects—for example, accidents and AIDS—on health and productivity. Still other common afflictions of the nervous system, such as Alzheimer disease as just one example, are awaiting effective medications, further emphasizing the importance of neuropharmacology.

Neuropsychopharmacology is an all-encompassing term that typically is applied to all types of drug effects that influence nervous system functioning. The term *psychopharmacology* is often used to describe the effect of drugs on psychologic parameters such as emotions and cognition. Drugs that influence behavior are known as *psychotropic* agents. In this book we use the term *neuropharmacology* to describe the study of all drugs that affect the nervous system, whether they affect sensory perception, motor function, seizure activity, mood, higher cognitive function, or other forms of nervous system functioning.

HOW DRUGS WORK

The actions of drugs that affect the nervous system are considerably more complicated than those of drugs that act on other organ systems. To understand how drugs act on the nervous system, it is critical to integrate information about the molecular and cellular actions of a drug with knowledge of how these actions affect brain circuitry—a circuitry that is constantly changing in structure and function in response to both pharmacologic and nonpharmacologic input from the environment. The complexity that underlies such actions can be illustrated by consideration of **fluoxetine**, a widely prescribed antidepressant, and **furosemide**, a widely prescribed diuretic. The chemical actions of these drugs are fairly simple. Both drugs initially bind to their specific protein target: fluoxetine binds to and inhibits serotonin transporters, which normally inactivate the actions of the neurotransmitter serotonin (Chapter 6), and furosemide binds to and inhibits Cl^- channels located in the ascending loop of Henle in nephrons of the kidney. However, the relation between the chemical and clinical actions of these drugs—particularly those of fluoxetine—requires a more elaborate explanation.

The association between furosemide's chemical and clinical activity is relatively straightforward. By inhibiting Cl^- transport in Henle's loop, furosemide causes more Cl^- to remain in the lumen of the nephron tubule, which in turn requires more H_2O to remain in the tubule. Furosemide exerts this same effect on all nephrons in the kidney, and the increase in H_2O in individual nephron tubules combines to cause diuresis at the level of the kidney. Diuresis is achieved as soon as effective concentrations of the drug reach the kidney's extracellular fluid, and is maintained with repeated use of the drug—for example, in the treatment of chronic congestive heart failure.

The relationship between the chemical and clinical actions of fluoxetine is more intricate and also more speculative. Most drugs that act on the nervous system interact with only the minute subset of the brain's neurons that express the initial protein target of the drug. Fluoxetine directly affects only those neurons that use serotonin as a neurotransmitter—a few 100,000 out of approximately 100 billion neurons in the brain. By inhibiting serotonin reuptake by these neurons, fluoxetine enhances serotonergic transmission throughout the brain, but it is not

known with certainty where in the brain enhanced serotonin function causes an antidepressant effect. Similarly, little is known about which of serotonin's 14 known receptors must be activated to achieve an antidepressant response. Moreover, the mood-elevating effects of fluoxetine are not evident after initial exposure to the drug but require its continued use for several weeks. This delayed effect suggests that it is not the inhibition of serotonin transporters per se, but some adaptation to sustained increases in serotonin function that mediates the clinical actions of fluoxetine. However, where these adaptations occur in the brain and the nature of the adaptations at the molecular level have yet to be identified definitively.

The clinical actions of fluoxetine, like those of many neuropharmacologic agents, reflect drug-induced *neural plasticity*, which is the process by which neurons adapt over time in response to chronic disturbance. Consequently, to understand fully the effects of a neuropharmacologic drug, we must determine not only the initial effects of the drug but also the intraneuronal signals that control a neuron's adaptations over time, the interneuronal signals through which neurons communicate with one another, and the ways in which large groups of neurons operate in circuits to produce complex brain functions.

Parts I and II of this book explore the intraneuronal and interneuronal signals that enable communication among neurons, which are fairly well understood. Part III addresses the relationships between circuits of neurons and complex brain functions, about which much remains to be discovered.

DRUGS AS TOOLS TO PROBE BRAIN FUNCTION

Neuropharmacology has contributed to many important advances in the neurosciences during the past several decades. Drugs have been used as tools to dissect the functions of the brain and of individual nerve cells under normal and pathophysiologic conditions. Historically, neuropharmacology has involved the delineation of diverse molecules that function as neurotransmitters in the nervous system, including monoamines, amino acids, purines, and peptides. The identification of many of these neurotransmitters and the elucidation of their synthesis, degradation, and receptors occurred in conjunction with studies of synthetic and plant substances that were known to exert profound effects on behavior. The neuropharmacology of **ergot** alkaloids, **cocaine**, and **reserpine**, for example, led to the discovery and characterization of monoamine neurotransmitter systems; **opiate** alkaloids such as **morphine** led to endogenous opioid systems; **nicotine**, **muscarine**, and **cholinesterase inhibitors** led to cholinergic systems; and **caffeine** and related substances led to purinergic systems.

Neuropharmacology also played a fundamental role in the delineation of the numerous receptor subtypes through which neurotransmitters elicit biologic responses. The early idea that one neurotransmitter acts on only one receptor was replaced decades ago with the recognition that for each neurotransmitter there are multiple receptors. This discovery led to the development of synthetic drugs with increasing selectivity for individual types of receptors, and the evolution of these neuropharmacologic agents has represented important advances in clinical medicine. These advances include the use of selective **β_1-adrenergic antagonists** for cardiovascular disease, selective **β_2-adrenergic agonists** for asthma, **μ-opioid antagonists** for opiate overdose, and **$5HT_{1D}$-serotonin agonists** for migraine, to name just a few examples.

As well, the identification of multiple receptor subtypes for neurotransmitters contributed to the recognition of complex postreceptor signal transduction cascades through which receptors ultimately produce their biologic responses. From G proteins to second messengers to protein phosphorylation pathways to regulation of gene expression, studies of the effects of drugs on the nervous system have provided crucial windows onto the functioning of intracellular signaling. For instance, investigation of the mechanisms by which **organic nitrates** cause vasodilation in the treatment of angina led to the discovery of nitric oxide as a critical signaling molecule, and studies of **aspirin** and related nonsteroidal anti-inflammatory drugs (**NSAIDs**) led to the discovery of a host of signaling molecules derived from arachidonic acid, including prostaglandins and leukotrienes.

Drugs serve as prototypical external or environmental factors in determining how the brain adapts or maladapts over time in response to repeated perturbations. Many adaptations that occur in response

to repeated drug exposure are models for adaptations to other external exposures, including stress and experience.

PRINCIPLES OF GENERAL PHARMACOLOGY

The ability of a drug to produce an effect on an organism is dependent on many of its properties, from its absorption to its stability to its elimination. To briefly summarize these processes, the first factor to be considered is the *route of administration*, which can determine how rapidly a drug reaches its target organ and which organs it affects. *Oral* administration typically results in a relatively slow onset of action. *Parenteral* describes all other routes of administration, including *subcutaneous* (under the skin), *intraperitoneal* (into the peritoneal–abdominal cavity), *intravenous* (into the venous system), *intracerebroventricular* (into the cerebral ventricular system), *intrathecal* (into spinal fluid), and *intracerebral* (into the brain parenchyma) delivery. The *bioavailability* of a drug determines how much of the drug that is administered actually reaches its target. Bioavailability can be influenced by *absorption* of the drug from the gut if administered orally. It also can be affected by *binding* of the drug to plasma proteins, which makes the drug unavailable to bind to its target. Moreover, it can be influenced by a drug's ability to penetrate the *blood–brain barrier* if the drug acts on the brain (Chapter 2), or its ability to permeate cell membranes if the drug acts on intracellular proteins.

Drug action also depends on the *stability* of the drug once it is absorbed, that is, how rapidly it is metabolized to inactive congeners or eliminated from the body through urine, bile, or exhaled air. Some drugs (*prodrugs*) must be converted into active metabolites before they can exert their biologic effects.

Each of these factors, which can be categorized as *pharmacokinetic* considerations, is a critical determinant of drug action and influences both the clinical use of drugs and the process of developing new agents. However, these pharmacokinetic properties are not discussed in detail in this book because they are not, strictly speaking, related to the underlying mechanisms of drug action—the *pharmacodynamic* features that are the primary concern of these chapters. As an introduction to this topic, a brief description of the process by which a drug interacts with its initial protein target follows. *Pharmacogenetics*, which describes the influence of an individual's genes in determining the response to a given drug, is also critical, but still in the earliest phases of understanding (see below).

Drug Binding

Neuropharmacology is changing rapidly in response to the molecular revolution. In previous decades, neuropharmacology focused on the synapse and, more particularly, on the effects of drugs on neurotransmitters or neurotransmitter receptors. The action of drugs on synaptic targets remains an important field of investigation. The initial target of a drug generally determines the particular cells and neural circuits on which the drug acts and at the same time the potential efficacy and side effects of the pharmacologic agent. However, the molecular revolution has made it clear that the initial binding of a drug to its target—for example, the binding of a drug to a neurotransmitter receptor—is only the beginning of a signaling cascade that affects the behavior of cells and ultimately complex circuits.

When a drug binds to a protein, it affects the functioning of that protein, thereby establishing a form of *allosteric* regulation. A drug can conceivably bind to any site on a protein. A simple site may involve just a few contiguous amino acid residues in a protein's primary structure, while a relatively complex site may involve discontinuous residues from the protein's primary structure that are brought near each other by the protein's secondary and tertiary structures. Ultimately, the three-dimensional shape, or conformation, of a binding site and the electrostatic charges distributed across the site must complement the shape and charge of the drug. The interaction of a drug with its binding site can influence the intrinsic activity of the target protein, for example, the catalytic activity of an enzyme or the conductance of an ion channel, or it can influence the ability of the protein to interact with some other molecule, such as the ability of a receptor to bind to its neurotransmitter.

In classic studies of drug mechanisms of action, a mechanism is defined by a drug's ability to bind to an unknown receptor in tissue homogenates or on tissue sections. In these studies the drug, termed the *ligand*, is radiolabeled and incubated with a tissue preparation, which is washed extensively to remove loosely bound drug. A radioactive atom must be added to the drug without altering its ligand binding properties, a process that can be exceedingly difficult. The