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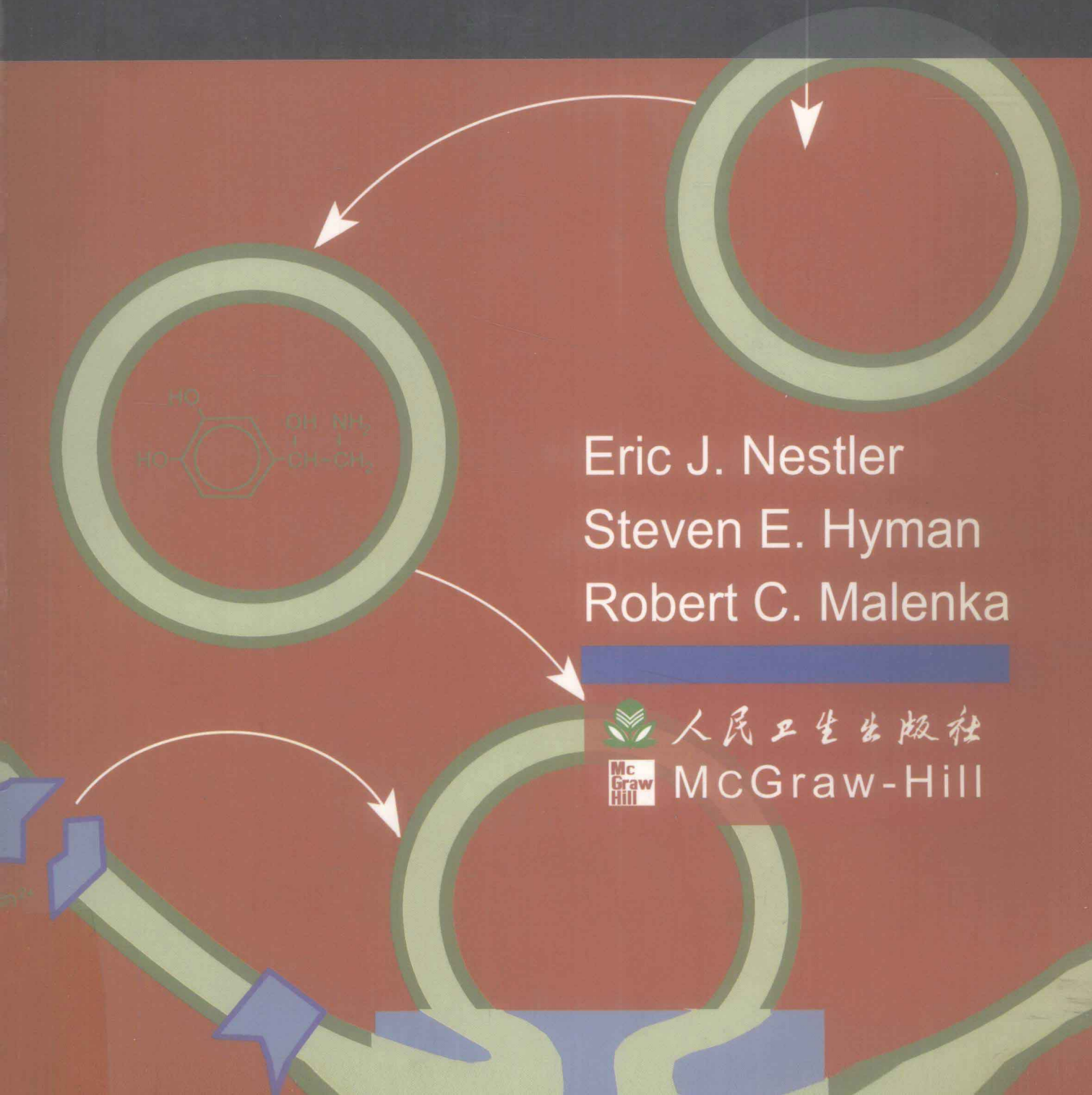
Molecular Neuropharmacology

A Foundation for Clinical Neuroscience

分子神经药理学



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Molecular Neuropharmacology:

A Foundation for Clinical Neuroscience

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MOLECULAR NEUROPHARMACOLOGY

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Notice

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This book is dedicated

to our wives and children:

Susan, David, Matt, and Jane

Barbara, Emily, Julia, and Charlie

Pam, Nick, and Ben

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PREFACE

Neuropharmacology, the study of drug actions on the nervous system, comprises several areas of investigation of critical importance to science and medicine. Neuropharmacology involves studies aimed at understanding the mechanisms by which drugs alter brain function. These include medications used to treat a wide range of neurologic and psychiatric disorders as well as drugs of abuse. A primary goal of neuropharmacology is to use this information to develop new medications with ever-improving efficacy and safety for diseases of the nervous system. In addition, neuropharmacologic agents are valuable tools with which to probe the molecular and cellular basis of nervous system functioning. For example, the mechanisms of drugs that produce their clinically relevant effects only after repeated administration, agents such as antidepressants in treating depression or drugs of abuse in causing addiction, provide a means of learning about neural plasticity. Overall, much of what we now know about the nervous system—how individual neurons work, how neurons communicate with one another, and how neurons adapt over time to external stimuli—has come from studies using pharmacologic probes.

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. 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. Thus, the action of a drug on the nervous system must be comprehended at many levels under both normal and pathologic conditions.

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 drug by drug or neurotransmitter 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 2–6), 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 7–10). 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 neurotrophic factors (Chapter 11), which over the last 10 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 12 focuses on the autonomic nervous system; Chapter 13 on neuroendocrine function, Chapter 14 on movement, Chapter 15 on emotion and mood, Chapter 16 on reinforcement and addiction, Chapter 17 on higher cognitive function and psychosis, Chapter 18 on attention and sleep, Chapter 19 on pain, Chapter 20 on memory and dementia, and Chapter 21 on stroke and seizures. 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 Parts 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 14) and sleep (Chapter 18).

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, 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. We also would like to thank Harvey Shoolman who originally recruited us for this project; Georgia Miller, who was an enormous help in numerous ways; and the folks at McGraw-Hill—Harriet Lebowitz, Janet Foltin, Pam Carley, Eve Siegel, and Susan Worley—who whipped this book (and us) into shape.

Eric J. Nestler
Steven E. Hyman
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CONTENTS

PART 1

Fundamentals of Neuropharmacology

CHAPTERS