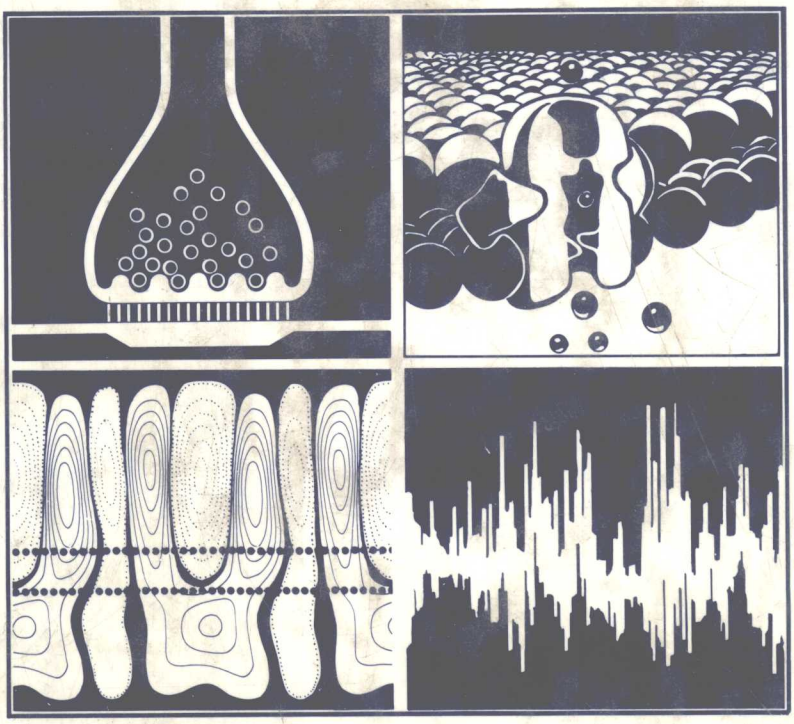
CLINICAL PHARMACOLOGY / 5

RECEPTOR BINDING IN DRUG RESEARCH



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Series Introduction

The remarkable degree of progress in receptor research reflected in this volume is brought home to me when I recall that as a student at New York University, one of my pharmacology professors was Otto Loewe, winner of the Nobel Prize. He had stimulated the vagus nerve of an animal, collected the released chemical substance (acetylcholine), and showed that it could slow the heart like vagus nerve stimulation itself. He had found and correctly described a specific chemical neurohumor that is recognized by a specific receptor on an effector structure and which, on binding to the receptor, initiates a chain of events of biologic importance.

Within the span of one life, a large number of additional neurohumors have been identified, and each has been shown to be capable of binding to several more or less specific receptors. A multitude of biologically active synthetic agents have been shown to owe their activity to the characteristics of their binding to particular receptors. No wonder that so much attention is now being paid to the generation, analysis, and interpretation of data concerning receptors.

This volume reviews not only neurohumors that are of major importance both centrally and peripherally, but also nonneurological systems that are critically dependent on receptors. It places particular emphasis on the application of such studies to the discovery, development, and understanding of drugs as well as previously unidentified endogenous ligands.

I have no doubt that a wide range of biological and medical professionals will find this volume of considerable interest.

Murray Weiner, M.D.

Foreword

With almost any scientific advance, "the proof is in the pudding." Most scientists, and certainly the greater part of the general public, regard scientific discoveries as genuinely important and mature when they have been demonstrated to do something "practical." Judged by these standards, this volume provides evidence that the binding techniques that have permitted the characterization of drug and neurotransmitter receptors are now truly relevant to the needs of mankind. With the demonstration of opiate receptor binding in 1973, it was apparent that one could judge the molar potencies of drugs at opiate receptors by simple binding techniques. The initial assays, using metal-free buffers, did not distinguish agonists from antagonists or successfully characterize agonist-antagonist mixtures and so could not be employed to identify the less-addicting, mixed agonist-antagonist opiates. Subsequent work showed that sodium ions reliably differentiate agonists from antagonists; since that time, receptor binding techniques could be productively employed in the drug industry for screening purposes.

While nicotinic cholinergic receptors had previously been identified with potent snake venom toxins in the electric organs of certain fish, opiate receptor techniques showed that successful receptor identification did not require a tissue extraordinarily enriched in receptors or a unique ligand. Instead, reversibly binding drugs could label receptors in crude tissue homogenates. The same general approach that had been successful with opiate receptors could be applied, with minor modifications, to receptors for almost all neurotransmitters in the brain and many classes of drugs (Snyder, 1984).

The present volume provides an elegant confirmation that receptor binding techniques are useful for assessing a chemical's true potency at its pharmacological target. By contrast, drug potency in intact animals is determined by a combination of absorption into the general circulation, metabolism, penetration to the target organ, and receptor affinity. By monitoring a drug's affinity for receptor binding sites one can pursue structure-activity studies to escalate potency systematically, a strategy that can result in more-potent and more-selective agents than would be possible utilizing only in vivo screens (Snyder, 1983).

The chapters in this volume describe the applications of receptor techniques in many different areas in addition to conventional drug and neurotransmitter binding sites. Humoral modulators such as a leukotrienes, interferon, platelet-derived growth factor, and novel endogenous ligands are reviewed. To emphasize the relevance of receptor techniques to practical development of drugs, the authors describe detailed experimental strategies that may be employed with each receptor.

Though receptor research has become a "mature" field in its application to drug discovery, major conceptual and technical advances continue. Receptor binding techniques are now applied to the characterization of enzymes using potent inhibitors for ligands as with [^{3}H]captopril labeling of angiotensin converting enzyme (Strittmatter et al., 1984a) or [^{3}H]guanidinoethylmercaptosuccinic acid ([^{3}H]GEMSA) and enkephalin convertase (Strittmatter et al., 1984b). In this way one can literally count the numbers of enzyme molecules in crude tissue homogenates, something exceedingly difficult with conventional catalytic enzyme assays. It is likely that receptor binding techniques will be used more and more frequently to characterize elements of second messenger systems, both cyclase-linked systems and the phosphoinositide cycle. It is quite possible that similar strategies will prove useful in identifying target sites for actions of viruses, perhaps presaging a new generation of antiviral drugs.

The many elegantly written contributions in this volume render it a unique source book for this rapidly developing area of basic and applied research.

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Solomon H. Snyder, M.D.

Preface

Within the pharmaceutical industry, the primary goal of drug research is, without question, the discovery and development of new and novel compounds. They should be efficacious in previously untreatable disease modalities or possess a more beneficial therapeutic and side effect profile than already marketed drugs. Central to rational drug discovery is the application of modern pharmacological findings to directed research on new chemical agents' pharmacological mechanisms of action as well as concerted investigations of the biological and pathophysiological mechanisms operating in disease. New knowledge in the area of receptor pharmacology has greatly aided our investigations of biological and chemical mechanisms. Advances in computer modeling, biotechnology, monoclonal antibody production, and radioisotopes and imaging have all increased the potential of receptor research programs for identifying new leads and research directions. Biologists and chemists today can better correlate drug receptor affinities and mapping profiles with chemical structure and pharmacological activity.

Over the last several years, the pharmaceutical industry has come to utilize receptor technology in a more pragmatic fashion. The great expense of drug discovery and the characterization and eventual evaluation of a drug in human clinical trials in man has caused significant introspection into ways to decrease the cost of developing new therapeutic agents. Apart from the now-accepted use of computer modeling in the process of drug design, probably the implementation of receptor binding technology has been most responsible for the expanded screening and characterization of drug candidates. A company's receptor biochemist working in close concert with chemists and pharmacologists can rapidly assess potential therapeutic activity as well as predict the profile of side effect liability largely on in vitro data.

The aim in assembling the chapters for this text was to put together, from the industrial drug development perspective, a number of receptor binding approaches to finding and characterizing new, therapeutically interesting chemical entities. The goal has not been to exhaust the vast literature or all of the specific methodologies in use, but to present some philosophies for use of receptor pharmacology in drug screening. Some of the most challenging therapeutic areas were chosen, and examples of receptor binding information and future prospects based on research in these areas are discussed.

Special thanks and appreciation to my wife, Lee Rae, and my sons, Sean and Chris, for their patience, encouragement, and understanding. Thanks also to the staff at Marcel Dekker, Inc. I am gratefully indebted to Sally Burd and Faith Belverio for their assistance with the index.

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Receptor Binding Methodology and Analysis

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