Handbook of Psychopharmacology

Volume 17

Biochemical Studies of CNS Receptors

Edited by
Leslie L. Iversen
Susan D. Iversen
and Solomon H. Snyder

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PREFACE

It is now eight years since the first *Handbook* volumes on Basic Neuropharmacology were published, and there have been many important advances. As in many other areas in science, progress in this field has depended to a considerable extent on the availability of new experimental methods, and Volume 15 reviews some major recent developments, including new autoradiographic techniques that allow direct visualization of drug and transmitter receptors in the nervous system, and the pinpointing of the precise locations of the changes in brain metabolism elicited by various drug treatments. Volume 16 and 17 cover two of the most active areas for basic research in psychopharmacology at the moment: the characterization of drug and transmitter receptors in brain by radioligand binding techniques, and studies of the role of small peptides in brain function. The latter area, in particular, illustrates how rapidly progress continues to be made in basic research on the mechanisms of chemical communication within the nervous system. Eight years ago when the *Handbook* first appeared none of the opioid peptides (enkephalins and endorphins) had yet been identified. Since then a whole new area of basic biological research has focused on these substances, and in addition we know of more than thirty other neuropeptides with putative CNS transmitter functions.

We hope that these new volumes will help to keep the *Handbook of Psychopharmacology* abreast of the most recent advances in the field, and continue to make it a valuable reference work for all who are involved in research in this increasingly active field of science. The response to earlier volumes has been remarkably positive, and we remain indebted to the publishers for conceiving the original idea, and to the many contributors who have labored long and hard to bring it to fruition.

L.L.I.
S.D.I.
S.H.S.

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MOLECULAR ASPECTS OF NEUROTRANSMITTER RECEPTORS: AN OVERVIEW

Solomon H. Snyder

1. INTRODUCTION

It is axiomatic that following synaptic release neurotransmitters interact with specific sites on adjacent cellular membranes. Molecular approaches to neurotransmitter receptors are surprisingly recent, with most research on brain neurotransmitters having taken place within the past 5–8 years. During this relatively brief period, biochemical studies of receptors have burgeoned so rapidly that they form the most common theme of the chapters in this volume.

Much of the research described in these chapters deals with neurotransmitter receptor binding studies. Frequently, reports dealing with receptor binding are titled "Such and Such Neurotransmitter Receptor." There ensues discussion as to just what is meant by a neurotransmitter receptor. Some argue that binding studies do not deal with receptors at all but merely with binding sites which may not be associated with a physiological response and hence may not be functional. Accordingly, such entities do not deserve the name receptor.

Because of these controversies, it might be best to commence with some definitions. The concept of hormone or neurotransmitter receptors

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is largely a pharmacological one. Prior to the advent of molecular probes, pharmacologists measured physiological responses to drugs, hormones, and neurotransmitters, often monitoring contractions of smooth muscles. The "receptor" was that entity which was responsible for the "response." It was generally assumed that the total receptor apparatus must include a recognition site, some transducing mechanism, and an effector device. According to this view, one does not study receptors unless one investigates in each experiment all three elements. Thus, the only legitimate receptor research is that which measures smooth muscle contraction, secretion of a bodily substance, or some other physiological response.

Of course, this caricature applies only to an extreme point of view. However, it does address an important issue. In some instances, receptor recognition sites may not be linked to an effector apparatus and thus fit the designation "silent receptors." On the other hand, when we cannot detect a response associated with a receptor site, we may not be justified in concluding that there is no response but merely that we have been monitoring the wrong measure. This issue comes up in different experimental situations. For instance, the regional distribution of some neurotransmitter receptors does not parallel precisely the distribution of neuronal systems containing the transmitter. Thus, beta-adrenergic receptor binding sites are widely distributed throughout the brain and are highly concentrated in areas such as the corpus striatum which contains little or no norepinephrine (Bylund and Snyder, 1976). One may conclude either the beta-adrenergic receptor recognition sites are meaningless entities or that we are missing a subtlety of nature. For instance, perhaps there exists a hitherto unrecognized neurotransmitter other than norepinephrine which interacts with beta-receptors. Recently it has been possible to monitor by autoradiography the distribution of cholecystokinin (CCK) receptor sites using [^{125}I]-CCK-33, the 33 amino acid form of the peptide (Zarbin *et al.*, 1981). A number of very discrete localizations of the autoradiographically visualized grains, including discrete clusters in the optic tract and superior colliculus, differ markedly from the localization of CCK-containing neuronal systems mapped with antibodies to CCK. The rapidly accumulating evidence for multiple forms of CCK stored in distinct neuronal systems (Rehfeld, 1978) suggests that the visualized receptors are associated with neurons containing a form of CCK other than that which has been visualized in immunohistochemical studies.

It has been generally thought that the transducing element connecting neurotransmitter recognition to alterations in cellular function involves either changes in ion permeability or alterations in cyclic AMP formation. Recent evidence has greatly increased the number of possible second messenger or transducing mechanisms. Studies, especially from Axelrod's laboratory, suggest that in some instances adenylate cyclase may be a third messenger whose enhancement is provoked by an initial stimulation of

phospholipid methylation evoked by the hormone or neurotransmitter (Hirata and Axelrod, 1980). Beginning with the pioneering work of the Hokins, there has been a progressive accumulation of data linking formation of phosphatidylinositol with cholinergic, histamine, and substance P-associated synaptic activity. Alterations in calcium permeability may be important and linked to various types of messages. For instance, cyclic GMP formation is related to changes in calcium disposition. Calcium is also associated with specific binding proteins, most notably calmodulin, which in turn modulates numerous cellular responses. Calcium is also crucial for the activity of numerous enzymes, such as a protease which may be linked to glutamate receptors (Baudry and Lynch, 1980; Vargas *et al.*, 1980). Also, calcium is required for the activity of phospholipase A_2 which generates arachidonic acid, the precursor of prostaglandins which in turn mediate many receptor-associated responses.

How all these "second messengers" interact is unclear. One model holds that the rapid opening and closing of ion channels is responsible for classical excitation and inhibition in synaptic transmission. Biochemical alterations, such as changes in cyclic nucleotide, phospholipid, or prostaglandin formation may mediate slower changes. Some of these latter activities may be long-lasting "trophic" alterations involved in synaptic plasticity and other events associated with memory processes. Clearly one of the tasks of neurotransmitter research is to work out the molecular events which link receptor recognition to subsequent cellular events.

2. RECEPTOR RECOGNITION: ION AND NUCLEOTIDE REGULATION ASSOCIATED WITH "SECOND MESSENGERS"

The first biochemical approaches to receptor labeling for neurotransmitters dealt with the nicotinic cholinergic receptor in the electric organs of invertebrate fishes. These studies took advantage of the extremely high receptor content of these organs, amounting to 20% of membrane protein in some instances. Additionally, in these studies potent snake toxins were utilized which bound with high affinity and virtually irreversibly to the receptors. Such approaches could not be readily applied to the brain where receptor density in most cases is only about one-millionth by weight of brain tissue and in which unique irreversible, yet neurotransmitter-specific, toxins do not exist. Early studies using [^{3}H]atropine and intestinal smooth muscle indicated the feasibility of labeling receptors with reversible ligands, but technical difficulties, such as low signal–noise ratio, precluded any widespread development of these limited initial studies.

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