Handbook of Psychopharmacology

Volume 6

Biogenic Amine Receptors

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

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AMINE RECEPTORS IN CNS I. NOREPINEPHRINE

Floyd E. Bloom

1. INTRODUCTION

Among the neurochemicals considered to be candidates for synaptic transmitter function within the central nervous system, the conceptual link to psychopharmacological actions has been particularly strong for norepinephrine (NE). Basic research in psychiatry has concentrated on the changes in brain monoamine metabolism produced by psychoactive drugs (see Snyder, 1974) to develop catecholamine theories of mental diseases. In such a psychopharmacological model, NE is presumed to be a central synaptic transmitter, but the actual functional controls (i.e., excitation or inhibition) exerted by such synapses, their exact cellular location, and their mechanism of action have not been known. This chapter will focus on the methods by which the central receptors for NE may be characterized as to location, function, and pharmacological significance.

At the outset, it is important to distinguish between two classes of operationally defined receptors. The most rigorously defined NE receptor would be that receptor which initiates the response of postsynaptic neurons to the NE released by activity in NE-containing presynaptic terminals. Specific interactions of behavior-altering drugs at these receptor sites might

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be expected to reflect some of the changes in cellular activity which result in the behavioral changes these same drugs can produce. However, as will be described below, localization and functional characterization of NE central receptors have generally stopped short of direct examination of a NE-mediated pathway, and sought mainly to demonstrate microreceptivity to NE; receptors on cells such that when NE is administered, as by microiontophoresis (see Chap. 2, Vol. 2), the electrical discharge pattern of the cells is altered.

Early microiontophoretic studies assumed that such responses were meaningful and that quantitative assessment of the proportion of neurons which would or would not respond to NE in a given region could be taken inferentially to reflect the "importance" of noradrenergic transmission. After a dismally poor potency in some early studies (for review, see Bloom, 1968), NE has now been demonstrated to alter the discharge patterns of neurons in almost every region of the brain tested.

There are only two possible general types of positive responses which neurons can manifest to microiontophoretic administration of NE: the cell can fire either faster or slower. Thus, depending on the cell type tested, NE can either depress discharge rates, as it does in several cortical areas, or facilitate discharge rates, as with certain groups of hindbrain and spinal neurons (Bradley and Wolstencroft, 1962; Boakes *et al.*, 1971; Couch, 1970; Weight and Salmoiraghi, 1967).

However, some problems of interpretation arise when apparently similar neurons under apparently identical conditions are reported to have opposite qualitative responses. For example, the earlier reports of Krnjević and Phillis (1963*a*,*b*) had indicated only a few relatively unimpressive and generally depressant effects of NE (for review, see Bloom, 1974), while Straughan and his colleagues observed excitatory responses of cortical neurons (Johnson *et al.*, 1969*a*,*b*), and Phillis with newer collaborators (Phillis *et al.*, 1973) and Stone (1973) observed frequent depressant actions of NE.

By proper regard for each of the necessary experimental controls peculiar to microiontophoresis (Bloom, 1974), it has been possible to observe reproducible effects of NE on neuronal discharge. However, such data do not necessarily indicate the responses to be a reflection of an underlying NE-mediated input to the cells being tested. To corroborate this inference requires that selective stimulation of the afferent NE axons will reproduce the effects produced by microiontophoresis of NE. Since the cells of origin for the cortical NE projections have only recently been established (Olson and Fuxe, 1971; Ungerstedt, 1971; Segal *et al.*, 1973), the next best evidence has been to establish that the cells being tested do receive NE-containing synapses. In the absence of such corroborative data, responses cannot be functionally interpreted.

2. LOCALIZING NOREPINEPHRINE-CONTAINING SYNAPSES

The varicosities of the axons demonstrated by fluorescence histochemistry indicate presumed sites of transmitter release. However, because of the limited resolution of the optical microscope relative to the very fine nature of the complexly interrelated cellular processes of the neuropil, electron microscopic methods are needed to determine precisely which neurons in a given region receive synaptic contact from NE-containing axons.

No single electron microscopic histochemical method has yet achieved the consistency and selectivity of localization desired for analysis of NE-transmitting synapses. Permanganate fixation methods (Hökfelt, 1967; Richardson, 1966) offer the most direct approach to the successful visualization of small granular synaptic vesicles, which seem identical morphologically and pharmacologically to the storage vesicles of NE in peripheral sympathetic nerve terminals. However, technical problems (such as poor penetration yielding small usable tissue samples) generally limit this method to regions with a high density of NE axons (e.g., pons, hypothalamus). Recently it has been possible to observe permanganate-positive terminals within the cerebellar cortex of certain mouse mutant stains (Landis and Bloom, 1974).

We have found most useful for our purposes a combination of two methods: autoradiographic localization (see Iversen and Schon, 1973) of processes which accumulate tracer amounts of [^{3}H]NE *in vivo* (Aghajanian and Bloom, 1967) or *in vitro* (Lenn, 1967), and the acute degeneration which occurs in NE terminals within 8–48 h after injection of 6-hydroxydopamine (6-OHDA) into the cerebrospinal fluid (see Bloom, 1971; Malmfors and Thoenen, 1971).

For these reasons, we have attempted to apply as many of the available methods as possible when seeking to localize NE-containing synaptic terminals, and find the most satisfactory localizations to be based on complementary results from multiple approaches (Bloom *et al.*, 1971; Bloom, 1973). A promising auxiliary line of investigation is based on the exploitation of axoplasmic transport. The distribution of a specific NE axonal pathway can now be revealed by autoradiographic localization of labeled macromolecules which are synthesized exclusively in a few perikarya after a restricted microinjection of labeled precursor (Cowan *et al.*, 1972) directly to the NE-containing neurons (Segal *et al.*, 1973; Pickel *et al.*, 1974*a,b*).

By application of the combination of fluorescence histochemistry, autoradiography of [^{3}H]NE, and acute degeneration after 6-OHDA, NE-containing synapses have been identified as projecting to olfactory mitral cells (Dahlström *et al.*, 1965; Bloom, unpublished results), to hypothalamic neurons of the supraoptic nucleus (Barker *et al.*, 1971; Nicoll and Barker, 1971), to a portion of the neurons of the raphe nuclei in cat and rat (Loizu, 1969; Bloom and Costa, 1971; Chu and Bloom, 1974), as well as to particular neurons in certain cortical regions described below.

3. EFFECTS OF NOREPINEPHRINE ON CENTRAL NEURONS

A number of different procedures have been employed to study the effect of NE on central neurons. For example, injection of precursors parenterally (see Salmoiraghi and Stefanis, 1971) has been reported to alter both cortical slow waves and unit potentials. However, the most useful technique for evaluating the effects of NE on central neurons utilizes microiontophoretic application from multibarreled micropipettes, thus circumventing many of the temporal, chemical, and structural restrictions suffered with other test procedures (see Chap. 2, Vol. 2).

3.1. Overview of Microiontophoretic Studies

In contrast to earlier studies which indicated negligible NE effects on cortical (Krnjević and Phillis, 1963*a,b*) and spinal (Curtis *et al.*, 1961) neurons, recent experiments have indicated that NE can affect nerve cells at virtually all levels of the neuraxis (see Table 1). The critical parameters underlying the presence or absence and qualitative nature of responses to NE have been clarified by a number of studies. Thus, in the cerebral cortex, the response to iontophoresis of NE depends partially on the type of anesthesia: excitatory responses are more prevalent with halothane or in certain unanesthetized preparations (Johnson *et al.*, 1969*a,b*). The pH of the drug solution also may be critical: unidentified cortical neurons are reported to be excited by NE ejected from solutions with pH less than 4.0 and inhibited by NE from solutions greater than 4.0 (Frederickson *et al.*, 1972). We have not observed a strict pH dependency for NE responses in other brain areas including the unanesthetized squirrel monkey cortex (S. L. Foote, unpublished); in fact, with pH 4.5, NE, tests by Weight and Salmoiraghi (1966, 1967) on spinal interneurons revealed both excitatory and inhibitory responses to NE on the same cell. These responses were antagonized selectively by α-adrenergic antagonists, so that they could not have been due to "proton" receptors.

3.2. Identification of Test Neurons

When attempting to evaluate the results of iontophoretic tests in any brain region, the primary concern is the identity of the cells tested. Such

TABLE 1

Studies on the Pharmacological Characterization of Norepinephrine Receptors Throughout the Mammalian CNS as Studied by Microiontophoresis in Various Regions and Cell Types

Brain region	Receptor studies	Reference
a. Cortex		
1. Cerebral (general)	Excitations blocked by α- and β-blockers, depressions not blocked by either	Johnson *et al.* (1969*a*)
	Depressions blocked by "calcium antagonists"	Phillis *et al.* (1973), Yarborough *et al.* (1974)
2. Polysensory cells	Depressions potentiated by desmethylimipramine	Nelson *et al.* (1973)
3. Pyramidal cells	Depressions blocked by MJ-1999 and potentiated by monoamine oxidase inhibitors	Stone (1973)
B. Limbic system		
1. Hippocampus, pyramidal cells	Depressions blocked by MJ-1999 and prostaglandins E_1 and E_2, potentiated by phosphodiesterase inhibitors and desmethylimipramine	Segal and Bloom (1974*a*)
2.* Olfactory bulb, mitral cells	Depressions blocked by Dibenamine and LSD	Bloom *et al.* (1964)
C. Diencephalon		
1. Medial geniculate	Depressions blocked by strychnine	Tebēcis (1970)
2. Hypothalamus supraoptic	Depressions blocked by MJ-1999, potentiated by DMI	Barker *et al.* (1971)

TABLE 1—*continued*

Brain region	Receptor studies	Reference
D. Brain stem		
1. Paramedian reticular nucleus	Excitations blocked by chlorpromazine	Avanzino *et al.* (1966), Bradley *et al.* (1966)
2. Unidentified cells	Amphetamine sensitivity correlated with NE response	Boakes *et al.* (1971)
	Excitation blocked by α-methyl-NE	Boakes *et al.* (1968)
E Spinal cord, interneuron	Depressions and excitations blocked by phenoxybenzamine	Biscoe and Curtis (1966), Weight and Salmoiraghi (1966)
F Cerebellum, Purkinje cells	Depressions blocked by MJ-1999, prostaglandin E_1, nicotinate; potentiated by DMI, methylxanthines, papeverine	Hoffer *et al.* (1969, 1971*a,b*, 1973), Siggins *et al.* (1971*a,b,c,d*)

identifications can be made during the test on the basis of characteristic discharge patterns or from the response of the test cells to stimulation of specific antidromic or orthodromic projections, or by marking recording sites with any of several methods and examining the recording sites cytologically after the experiment.

Such identifications offer several interpretative advantages. First, the cells tested can then be categorized into homogeneous functional or cytological groupings for cleaner interpretation of heterogeneous responses. The differences in responsiveness to NE between "all-cells-in-a-region" and specific identifiable cell types within a region have been described for olfactory bulb (von Baumgarten *et al.*, 1963; Bloom *et al.*, 1964), hypothalamus (Bloom *et al.*, 1963; Barker *et al.*, 1971; Hori and Nakayama, 1973), cerebral cortex (Krnjević and Phillis, 1963*a,b*; Stone, 1973), cerebellum (Hoffer *et al.*, 1971), thalamus (Curtis and Davis, 1962; Satinsky, 1967), limbic system (Salmoiraghi and Stefanis, 1971; Segal and Bloom, 1974*a,b*), pons (Avanzino *et al.*, 1966; Couch, 1970), and spinal cord (Weight and Salmoiraghi, 1967; Curtis *et al.*, 1961). In all of these cases, the response to NE of identified cells is inhibitory, with the exception of border cells in the ventromedial nucleus of the hypothalamus (Krebs and Bindra, 1971), the cells of the paramedian reticular nucleus (Bradley *et al.*, 1966), and some cells in the pontine raphe nucleus (Couch, 1970), which respond to NE with excitatory responses. In no case do identified cells exhibit significant instances of mixed responses (i.e., some cells faster, some cells slower) as seen when "all-cells-in-a-region" are artificially lumped together.

Second, identification of tested cells is even more important when drug responses are to be compared to a specific synaptic input to a test cell, or in attempts to determine the molecular basis of the synaptic or drug response. Here, the cells must be identified so that it can be established cytologically (Bloom, 1973) that the pathway under examination does, indeed, synapse with the cells to be tested. However, in the case of catecholaminergic synaptic projections, precise source neurons to specific postsynaptic cells can be stimulated only for a very few synaptic targets. Nevertheless, a synaptic inference to iontophoretic responses requires that the cells tested be shown to receive this chemical class of synaptic inputs whether or not their nucleus of origin can at present be stimulated.

Third, identification of the test cells can define which of the iontophoretic responses observed may never be utilized by normal synaptic connections (e.g., the excitatory β-receptors of neurons in the deep cerebellar neurons of the cat where no evidence for catecholaminergic synapses exists, Yamamoto, 1967). Finally identification of test cells is required so that data may be accumulated on homogenous cell populations for evaluation of the antagonists or potentiators of the test synapses or test substances.