American Handbook of Psychiatry

Linkage of Basic Neuropharmacology and Clinical Psychopharmacology

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LINKAGE OF BASIC NEUROPHARMACOLOGY AND CLINICAL PSYCHOPHARMACOLOGY

Introduction

The investigative efforts and consequent production of new information in basic neuropharmacology and clinical psychopharmacology in recent years has been enormous. In the relatively short period of the preceding twenty years specific pharmacological treatments for the major psychopathological states have become available. Clinically effective psychopharmacological agents have not only been helpful to patients, but they have also turned out to be powerful investigative tools for the elucidation of basic neurobiological processes that in turn have led to the development of specific hypotheses as to the biological genesis of psychopathological states. The literature dealing with linkages between basic neuropharmacology and clinical psychopharmacology is huge in that almost any paper dealing with a drug which affects the psyche or a neurobiological process could be rightfully included in this chapter, given its title. Such a review would be not only beyond the authors' abilities but also redundant in that many excellent reviews of the relationship of a variety of classes of psychopharmacological agents to neurobiological processes, and vice versa, have been written. For these reasons the choice of a more focused review of a particular area of relationship between basic and clinical psychopharmacology was chosen.

Such a choice inevitably depends upon the judgment of the writers, but it is felt that a great many investigators would agree that the publication by Dahlstrom and Fuxe in 1965 indicating that the biogenic amines DA, NE, and 5-HT[1] are to be found in discrete and specifically identifiable groups of neurons was seminal. Subsequent work indicated that these amines, and probably their synthetic enzymes, are made in discrete groupings of cell bodies and then transported down the axons, which themselves are found in specific tracts, to nerve endings existing at a considerable distance from their cell bodies in some cases. It is now clear, although the specifics are only beginning to emerge, that the different aminergic systems regulate or modulate separable and to a certain extent discrete kinds of behavior. Further, it has been found that some clinically useful classes of psychopharmacological agents have specific actions on one of these aminergic systems but not others. Since studies of the relationships of specific brain amine systems, behavior, and psychopharmacological agents are relatively recent and because the implications of such studies for increasing our understanding of the biological genesis of psychopathological states is clear, it is this area of brain amine systems, drugs, and behavior that has been chosen for review.

Briefly, the general scheme of presentation is to first review our present knowledge as to the existence and localization of brain amine systems, to describe some kinds of behavior that may be modulated by them, to review

the experimental evidence that indicates that some clinically useful psychopharmacological agents have specific actions upon these brain amine systems, to describe possible amine system interactions, and, finally, to conclude with suggestions as to the possibility that specific amine systems are centrally involved in the genesis of specific psychopathological states.

The Neuroanatomy of the Brain Amine Systems

History of Development of Techniques

The development of techniques for the localization of groups of cells responsible for DA, NE, 5-HT, and ACh production and release has added a new dimension to the study of neurotransmitters. For the first time amine-specific, cell-body areas can be defined, their axonal bundles can be demonstrated, and their terminal areas, at which there is release of specific neurotransmitter and activation of receptor site, can be localized and studied chemically, ultra-structurally, and electrophysiologically. Further, the behavioral effects that occur as a consequence of altering these systems by a variety of techniques may be studied.

Attempts at defining pathways of monoamine systems began with the work of Heller and Moore who, by making small lesions in various parts of the brain, could differentially effect whole brain levels of NE, DA, and 5-HT. Their

work suggested that major tracts connecting with 5-HT and NE rich areas in the forebrain ran in the dorsomedial brainstem tegmentum and through the median forebrain bundle in the lateral hypothalamus. Ventrolateral tegmental lesions reduced only brain NE and central gray lesions lowered 5-HT only. Their inability to trace degenerating fibers to the cortex and other structures that showed marked decreases in amine levels after lesions suggested to them that the monoamine systems might be multisynaptic with the reduction in amine content being secondary to a lesion of neurons which transsynaptically activated monoamine neurons.

A further development in technique for mapping out the catecholamine and indoleamine systems (NE, DA, 5-HT) began with the work of Falck and Hillarp who devised a method of condensing these monoamines in tissue sections with formaldehyde vapor to produce an intense fluorophore, which could be visualized by fluorescence microscopy. Recent developments in microspectrophotofluorimetry have permitted excitation and emission differentials for the NE, DA, and 5-HT fluorophores, permitting species identification for each of the catecholamines (NE and DA) and 5-HT.

Fluorescence histochemistry, together with lesioning techniques, provided the tools for clarifying some of the issues raised by the work of Heller and Moore, i.e., since monoamines accumulate proximal to axonal lesions, terminal and axonal regions can be destroyed selectively and specific

pathways can be defined by following the development of increased fluorescence proximal to the lesioned stump. This approach, for example, has been used in studies in which the neostriatum was ablated with the subsequent accumulation of fluorescence in axons of the internal capsule and in the DA cells of the pars compacta of the substantia nigra, allowing definition of the now well-known nigro-striatal DA pathway. Conversely, lesions in the DA cell-body area, the substantia nigra, caused a substantial loss of DA fluorescence in the neostriatum. Using the same approach it has also been found that many of the catecholamine containing nerve endings in the cerebral cortex are terminals of axons whose cell bodies are to be found in the brainstem. Alpha-m-NE also proved to be a useful tool in mapping amine systems as it is taken up and produces an intense fluorescence when injected into terminal areas and the fluorescence spreads retrograde toward the cells of origin.

The fluorophores from 5-HT terminals and cell bodies are more difficult to visualize than those of catecholamines with the routine Falck-Hillarp method. In order to localize 5-HT more easily, pretreatment with a monoamine oxidase inhibitor is frequently used to increase tissue concentrations of 5-HT, which then makes recognition of the structures more possible. Even with such treatment many areas of the telencephalon and diencephalon, which are known from biochemical determinations to contain 5-HT, do not show fluorescence and this is probably in part due to the fact

that the 5-HT terminals are very fine and many are probably submicroscopic. For these reasons negative findings in any given experiment, as to the 5-HT systems when the Falck-Hillarp method is used, must be interpreted with caution. While this problem is of particular concern with 5-HT systems, it may also occur with smaller terminals of the NE and DA systems. In terms of the limitations of this approach, it should also be noted that direct application of the histochemical-fluorescence method allows visualization only of those areas within the neuron that contain high concentration of monoamines. Highest concentrations of amines are found in terminal areas and adequate concentrations for visual recognition are also found in cell bodies, but axonal pathways contain too little monoamine to fluoresce, unless special manipulations are employed.

Fluorescence histochemical mapping of several of the amine systems in rat brain, including the defining of cell bodies of origin, axonal pathways, and terminal areas, has been developed during the past several years by a group of investigators at the Karolinski Institute, and these findings recently have been summarized and extended by Ungerstedt. As of this writing this technique has permitted definition of six reasonably well-defined monoamine systems, i.e., two NE, one 5-HT, and three DA systems that supply primarily the diencephalon and telencephalon; and five of these have their cell bodies of origin in the medulla, pons, or mesencephalon. In this section, available data as to anatomical loci and possible interactions with other amine systems,

including ACh systems, also defined herein and located in proximity, will be summarized. The following section will examine, when known, the behavioral effects of selective pharmacologic manipulations for each of these systems.

The assumption that identical monoamine systems as described in the rat are also present in higher species, including primates, must be approached with some caution. Preliminary evidence from work in progress suggests that although widespread similarities of cell-body and terminal areas exist, some interspecies dissimilarities in distribution of cell bodies and terminals in cat and Rhesus brainstems (J. R. Sladek, Jr., personal communication) and squirrel and monkey brainstems (D. Felton, personal communication) are also present. Axonal pathways in species other than the rat have not as yet been systematically reported.

The Norepinephrine Systems (Figure 20-1.)

The Dorsal NE System

The dorsal NE system arises from the cell bodies of the pontine nucleus locus coeruleus (Ag according to the nomenclature of Dahlstrom and Fuxe) and after giving off axons both to the cord and cerebellum, it ascends in the mid-reticular formation of the pons just ventral to the nucleus tractus solitarius. It passes in the dorsal part of the combined catecholamine bundle (dorsal and ventral bundle) between the pregenual fibers of the seventh

cranial nerve. The dorsal NE fibers then separate from the ventral system, turning dorsomedially, ascending in a tight bundle just lateral to the oculomotor nucleus. Some axons leave the bundle to cross in the posterior commissure before it dives sharply ventrolaterally into the zona incerta at the junction of the mesencephalon and diencephalon and rejoins the ventral NE system already in the median forebrain bundle. It gives off some branches dorsolaterally in the area of the nucleus subthalamus supplying NE terminals in the geniculate bodies and some branches dorsomedially to terminals in the nucleus anterior ventral thalamus and nucleus paraventricularis rotundocellularis. After contributing a small number of terminals (both crossed and uncrossed) to the hypothalamus, the bundle gives off, at a mid-hypothalamic level some axons which enter both the ansa lenticularis and the dorsal supraoptic commissure. There the axons spread both laterally toward the amygdala and basal cortical terminals, and medially, crossing the midline to end in the contralateral cortex. The bulk of the axons, however, ascend toward the septal region, where they give off terminals and then continue on in the cingulum on their way to terminals in the cortex and hippocampus. Terminal areas of the dorsal NE system are summarized in Table 20-1.

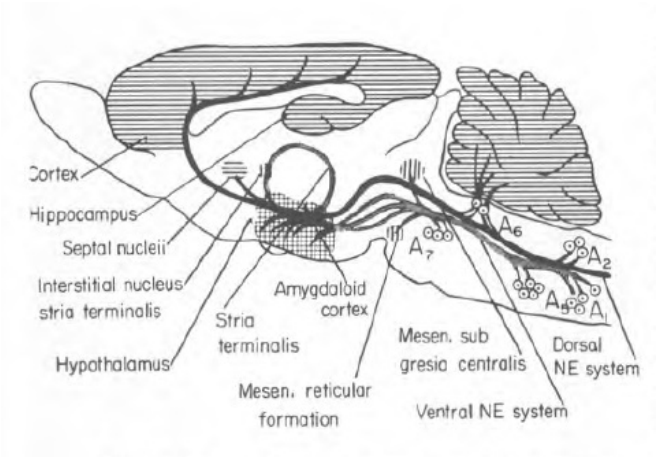

Figure 20-1.
Saggital projection of the ascending norepinephrine (NE) pathway of the rat. Horizontal stripes indicate major terminal areas of the dorsal NE system. Vertical stripes indicate major terminal areas of the ventral NE system.

The Ventral NE System

The ventral NE system arises from cell bodies at A_1, A_2, A_4, A_5, A_7 in the medulla and pons—there are very few cell bodies in the squirrel monkey A_3, A_4 and A_7, (D. Felton, personal communication)—and it ascends in the mid-reticular formation. Its axons remain slightly ventral to the dorsal bundle in the pons and then they spread ventromedially along the medial lemniscus and continue rostrally, mainly in the median forebrain bundle in the mesencephalon. In the mesencephalon, it gives rise to NE terminal areas dorsally, in the ventrolateral part of the substantia griseum centralis (which

are in intimate contact with 5-HT cells of group B_7 and to a lesser extent B_8) and to part of the mesencephalic reticular formation dorsal and dorsolateral to the medial lemniscus at the caudal level of the interpeduncular nucleus. The ventral NE system gives off terminals to the whole hypothalamus (especially the dorso-medialis hypothalami, nucleus periventricularis, area ventral to fornix, nucleus arcuatus, inner layer of median eminence, retrochiasmatic area, nucleus paraventricularis, nucleus supraopticus, preoptic area) both ipsilaterally and contralaterally. Continuing in the median forebrain bundle, it ascends rostrally in the stria terminals, giving off NE terminals to the ventral part of the nucleus interstitialis stria terminalis before continuing on to supply terminal areas in the amygdaloid cortex. Terminal areas of the ventral NE system are summarized in Table 20-1.

The Dopamine Systems (Figure 20-2.)

Nigrostriatal System

The nigrostriatal system originates in the *substantia nigra* (A_9) especially the *zona compacta,* adjacent tegmental area, and an area just caudal to the substantia nigra and dorsal to the medial lemniscus (A_8) and it sends dopaminergic axons rostral in the lateral hypothalamus, entering the cerebral peduncle in the mid-hypothalamus, ascending in the internal capsule, fanning out in the globus pallidus, and finally entering and terminating in the caudate

and putamen. DA terminals in the central amygdaloid nucleus are extensions of DA axons in the putamen and originate from axons running lateroventrally in the internal capsule. Terminal areas of the nigro-striatal DA system are summarized in Table 20-1.

Meso-limbic Dopamine System

DA cell bodies that are located at A_{10} (around the interpeduncular nucleus and extending in the midline up to the level of the dorsal motor nucleus of the third cranial nerve) contribute axons that run just dorsal to the median forebrain bundle in the lateral hypothalamus and, at the level of the anterior commissure, give off a series of branches to supply terminals in the nucleus accumbens, the dorsal part of the interstitial nucleus of the stria terminalis, and in the olfactory tubercle, (DA fibers to the amygdala arise from the adjacent A_9—substantia nigra—and enter the internal capsule, diving through the putamen to central amygdaloid nucleus.) Terminal areas of the meso-limbic DA system are summarized in Table 20-1.

Table 20-1. Major Terminal Areas of Monoamine Systems

	SYSTEMS						
TERMINAL AREAS	Dorsal NE	Ventral NE	Meso-Limbic DA	Nigro-Striatal DA	Tubo-Infundibular and Intrahypothalamic DA	5-HT	ACh
Cerebellar Cortex	X					X	X

Brainstem: Pons and Medulla	X	X				X	X
Limbic Midbrain Area and Tectum		X				X	X
Thalamus	X					X	X
Hypothalamus	X	X			X	X	X
Preoptic-Suprachiasmatic Area	x?*	X?*				X	X
Septum	X					X	(X)**
Interstitialis Nucleus Stria Terminalis		X	X				
Nucleus Accumbens	x?*	X?*	X				X
Tuberculum Olfactorium			X				X
Neostriatum				X		X	X
Amygdala and Amygdaloid Cortex	X	X		X		X	X
Hippocampus	X					X	X
Cerebral Cortex	X					X	X

* Cells of origin of innervation uncertain.

** Although cell bodies are present, terminals have not been described except more anteriorly in the diagonal band. However, intraseptal ACh

produces rage that is antagonized by atropine. See discussion below.

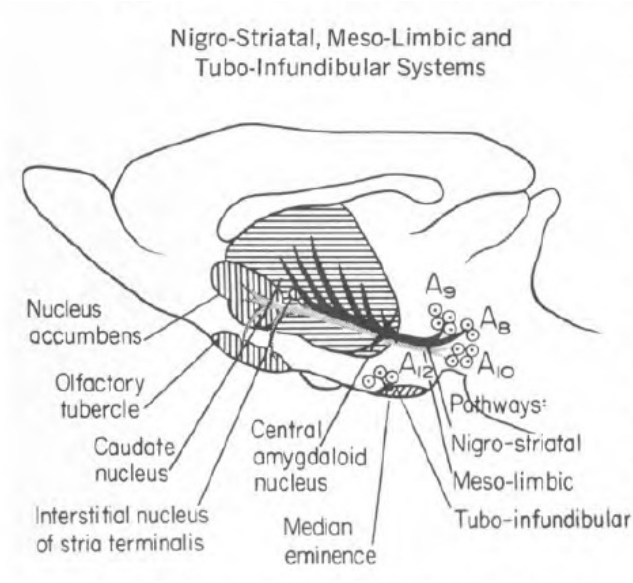

Figure 20-2.
Saggital projection of DA pathways in the rat brain. Horizontal stripes indicate major terminal areas of the Nigro-striatal system. Vertical stripes indicate major terminal areas of the Meso-limbic system. Sloped stripes indicate major terminal areas of the Tubo-infundibular system.

Tubo-Infundibular System

The cell bodies of the dopaminergic tubo-infundibular system are located within the nucleus arcuatus (A_{12}) and along the lateral border of the periventricular nucleus. A_{12} innervates the external layer of the median eminence and is concerned with neuroendocrine control, discussion of which is beyond the scope of this chapter. The cells along the periventricular border

give rise to Intrahypothalamic A terminals and are noted in Table 20-1.

Catecholamine Terminal Areas and Cell-body Areas With Unknown Pathways

Noradrenergic terminals have recently been described in the posterior medial part of the nucleus accumbens, bordering on the septal nuclei, and the interstitial nucleus of the stria terminalis. The cells of origin and pathways to these terminals are not known, although the adjacent septal nuclei are innervated by the dorsal NE system and the adjacent ventral part of the interstitial nucleus of the stria terminalis is innervated by the ventral NE system. Their function in the accumbens has not been studied.

A dense group of DA cell bodies (A13) has been reported just dorsolateral to the dorsomedial hypothalamic nucleus. This group has been reported to give rise to ascending axons in the median forebrain bundle. Terminal areas have not been described and the function of this group of DA cells has not been studied.

Serotonin System(s) (Figure 20-3.)

Owing to the difficulties noted above concerning the insensitivity of the fluorescence-histochemical technique in demonstrating 5-HT, such systems have been less clearly defined than those of catecholamines. The following description of known pathways is based on the work of Anden, Dahlstrom and Fuxe, Fuxe, Fuxe et al., Heller and Moore, and Ungerstedt.

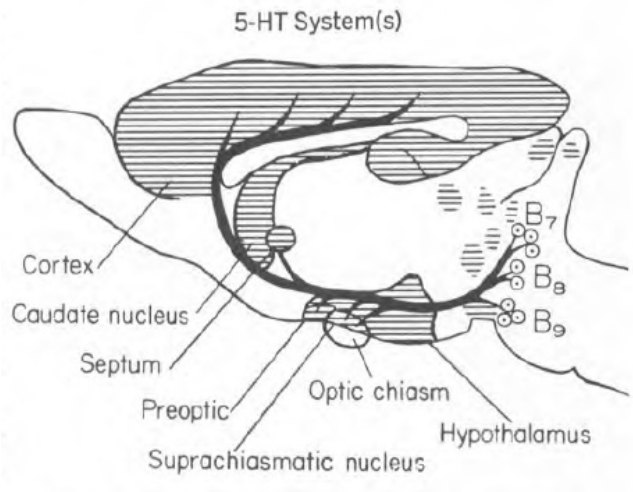

Figure 20-3.
Saggital projection of ascending 5-HT pathway(s) of the rat. Horizontal stripes indicate terminal areas of the 5-HT system. Pathways to many of these areas are as yet undefined.

Although there exist a large number of bulbo-spinal 5-HT neurons that arise from 5-HT cells, many of which are innervated by NE terminals to the raphe nuclei and to the surrounding pyramidal tract of the medulla, our interest here will be confined primarily to ascending 5-HT pathways.

An ascending system of 5-HT neurons arises from the 5-HT cell bodies in the raphe nuclei of the mesencephalon (nucleus of the dorsal raphe, B_7, and the nucleus of the median raphe, B_8). The axons run ventrally and then turn rostrally in the midbrain tegmentum as they approach the interpeduncular nucleus. Most of the axons lie close to the midline and become aggregated in a

bundle lying medial to the fasciculus retroflexus on the border between the mesencephalon and diencephalon. The axons enter the median forebrain bundle by passing, laterally, close to the ventral outline of the fasciculus retroflexus, and most become aggregated close to the lateral surface of the fornix. At least one other smaller tract is seen running more laterally in the lateral hypothalamus ventral to the cerebral peduncle, and just dorsal to the lateral part of the optic tract. The cells of origin of the secondary tract have not been clearly defined, but it may be possible that this secondary tract amounts for the remaining 20 percent of tryptophan hydroxylase and 30 percent of the 5-HT that persists in the telencephalon and diencephalon after the complete electrolytic destruction of the raphe (B_7 and B_8) nuclei that leaves the more lateral 5-HT group (B_9) in the mesencephalic reticular formation intact. The terminal area of the lateral secondary bundle has not been distinguished from that of the more medial primary bundle except as noted below. The primary bundle continues its route through the hypothalamus in the median forebrain bundle, running just ventral to the combined NE bundles, moving dorsally in front of the septal area, partly by the diagonal tract, and into the cingulum and toward the superficial part of the white matter to supply the cortex. Lesions of both raphe nuclei produce electron microscopic signs of degeneration in the 5-HT rich suprachiasmatic nucleus and reduce the overall 5-HT in whole brain by 70 percent, tyrosine hydroxylase by 80 percent. Ventromedial tegmental lesions reduce

tryptophan hydroxylase in at least caudate, anterior perforated substance, and septal area. From these studies, the only clear localization of cell body to terminal area is that of the raphe (B_7 and B_8) supplying the suprachiasmatic nucleus. In addition to 5-HT terminals mentioned above (suprachiasmatic nucleus, cortex, septum, caudate, anterior perforated substance), the mesencephalon, telencephalon, and diencephalon show by fluorescent 5-HT terminals widespread areas of 5-HT innervation encompassing the dorsal tegmental nuclei, the zona reticulata of the substantia nigra, between the interpeduncular area and the median raphe nucleus, the interpeduncular nucleus, cranioventral to the interpeduncular nucleus, both colliculi, pretectal region, both geniculates, habenular nuclei, many of the thalamic and most of the hypothalamic nuclei, two of the preoptic nuclei, anterior amygdaloid nuclei, hippocampi and globi pal-lidus. 5-HT cell bodies have not been reported anterior to the mesencephalon. It should be remembered, especially with 5-HT, that terminal areas may have relatively high amounts of monoamines and yet be invisible by fluorescent microscopy, i.e., that 5-HT terminals may be even more widespread than those noted. Demonstrated terminal areas of the 5-HT system(s) are noted in Table 20-1.

The Acetylcholine Systems[2] (Figures 20-4 and 20-5.)

Unlike the catecholamines and indoleamines the neurotransmitter acetylcholine (ACh) does not form a fluorophore that can be visualized by

fluorescent microscopy. The most successful attempts to define ACh pathways have depended not on the demonstration of ACh itself, but upon the presence of choline acetylase and especially acetyl cholinesterase in cell bodies, axons, and terminals of ACh neurons. Using the thiocholine method for esterase and light microscopy, Shute and Lewis mapped out ACh systems in the rat brain. They demonstrated three pathway systems of ACh with numerous interconnections, the terminal innervations of which are also summarized in Table 20-1.

The Dorsal Tegmental Pathway

The dorsal tegmental pathway is a system of fibers that runs rostrally from the midbrain tegmentum and supplies the tectum, pretectal area, geniculate bodies, and thalamus. It arises primarily from the mesencephalic nucleus cuneiformis and supplies the inferior and superior colliculus (the latter transsynaptically), pretectal nuclei, medial and lateral geniculate bodies (especially the ventral nucleus of the lateral geniculate body), specific thalamic nuclei, including the centromedian and intralaminar thalamic nuclei, and especially the anteroventral thalamic nuclei of the anterior thalamic group. By long circuitous routes also supplied is the anterior colliculus and the pretectal nuclei, via the supraoptic decussation, and the lateral geniculate body via the medial strial bundle.

The Ventral Tegmental Pathway

The ventral tegmental pathway arises from the ventral tegmental area and the pars compacta of the substantia nigra and supplies the oculomotor nucleus, mammillary bodies, subthalamus, anterior thalamic nuclei, especially the anteroventral thalamic nucleus, entopeduncular nucleus, and globus pallidus, the posterior and lateral hypothalamic areas, lateral preoptic area, paraventricular and supraoptic hypothalamic nuclei and olfactory tubercle, and, circuitously via the stria terminalis, the lateral amygdaloid nucleus. These fibers as they pass through the diencephalon enter the zona incerta, supra-mammillary region, and the lateral hypothalamic area, where there are many ACh-containing cells, before running rostrally to the basal areas of the forebrain.

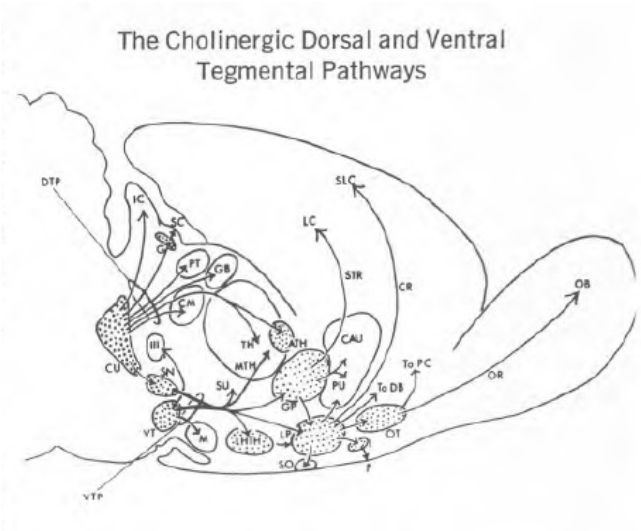

Figure 20-4.
Diagram showing the constituent nuclei (stippled) of the ascending cholinergic reticular system in the mid-brain and fore-brain, with projections to the cerebellum, tectum, thalamus, hypothalamus, striatum, lateral cortex, and olfactory bulb. Abbreviations: ATH, antero-ventral and antero-dorsal thalamic nuclei; CAU, caudate; CM, centromedian (parafascicular) nucleus; CR, cingulate radiation; CU, nucleus cuneiformis; DB, diagonal band; DTP, dorsal tegmental pathway; G, stratum griseum intermediale of superior colliculus; GB, medial and lateral geniculate bodies; GP, globus pallidus and entopeduncular nucleus; I, islets of Calleja; IC, inferior colliculus; III, oculomotor nucleus; LC, lateral cortex; LHTH, lateral hypothalamic area; LP, lateral preoptic area; M, mammillary body; MTH, mammillo-thalamic tract; OB, olfactory bulb; OR, olfactory radiation; OT, olfactory tubercle; P, plexiform layer of olfactory tubercle; PC, precallosal cells; PT, pretectal nuclei; PU, patamen; SC, superior colliculus; SLC, supero-lateral cortex; SN, substantia nigra pars compacta; SO, supraoptic nucleus; STR, striatal radiation; SU, subthalamus; TH, thalamus; TP, nucleus reticularis tegmenti pontis (of Bechterew); VT, ventral tegmental area and nucleus of basal optic root; VTP, ventral tegmental pathway. Source: C. C. D. Shute and P. R. Lewis, Brain, 90 (1969), 529. By permission of the author.

The ventral tegmental system continues cholinergically from cell bodies

located in nuclei already supplied by cholinergic terminals giving rise to centrifugal radiations to the neocortex, olfactory cortex and bulb, and to subcortical nuclei. The entopeduncular nucleus and globus pallidus give rise to cholinergic fibers that innervate the anteroventral nucleus of the thalamus, the caudate, and putamen and also give rise to striatal radiations to the lateral cortex above the rhinal fissure. The lateral preoptic (and anterior amygdaloid) areas give rise to cholinergic fibers supplying the amygdaloid nuclei—especially the pars ventralis of the lateral amygdaloid nucleus—give rise to fibers that run in the stria terminalis to the cortical and medial amygdaloid nuclei (olfactory part), and give rise to the amygdaloid radiation that pierces the amygdala, enters the ventral part of the external capsule and is distributed to the inferno-lateral cortex below the rhinal fissure. Arising also from the lateral preoptic area and augmented by contributions from the olfactory tubercle are innervations to the nucleus accumbens and fibers of the olfactory radiation that turn laterally from the preoptic area and travel rostrally in the lateral olfactory tract and in the olfactory peduncle and supply the nucleus of the lateral olfactory tract, the olfactory tubercle, and the olfactory bulb and the olfactory cortex (ventrolateral aspect of the hemisphere below the rhinal fissure). The lateral preoptic area also provides cholinergic innervation for the cortex on the superior aspect of the hemisphere through the cingulate radiation that ascends from the lateral preoptic area, anterior to the genu of the corpus callosum, and travels

caudally in the cingulum and below the corpus, the latter piercing upward more caudally and reaching the cingulum on their way to the cortex.

The Cholinergic Limbic System

The cholinergic limbic system consists of an intermingling of cholinergic and noncholinergic neurons. It arises from cholinergic cell bodies, located in the medial septum, and the nucleus of the diagonal band, and it projects to the hippocampal formation via the septal radiation through the dorsal fornix, the alveus, and fimbria. Hippocampal efferents (non-cholinergic) traveling via the fornix project directly or indirectly onto cholinergic neurons in the hippocampal commissure, anterior thalamus, habenular nuclei, dorsal and deep tegmental nuclei via the mammillo-tegmental tract, and in the nucleus accumbens. These cholinergic cell-body areas then project cholinergic fibers: from hippocampal commissure to the precallosal cells and on to the frontal cortex and olfactory bulb; from anterior thalamus to the cingulate cortex; from habenular nuclei to the interpeduncular nucleus that connects with the ventral tegmentum area (ventral tegmental pathway); from dorsal tegmental nuclei to the cholinergic nucleus reticularis tegmenti poitis (that connects with the ventral tegmental pathway), to latero-dorsal tegmental nuclei (cholinergic) that send fibers to the nucleus cuneiformis (dorsal tegmental pathway); and from both dorsal and deep tegmental nuclei to the dorsal and medial nuclei of the raphe that, through another cholinergic connection in the

interpeduncular nucleus, also connect back to the ventral tegmental pathway; and from the accumbens nucleus to the olfactory tubercle.

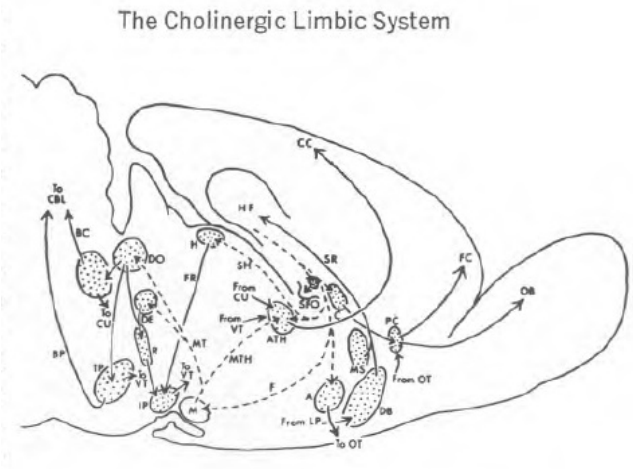

Figure 20-5.
Diagram showing cholinesterase-containing nuclei of the mid-brain and fore-brain (indicated by stipple) connected with the hippocampus, their projections to the medial cortex, and their connexions with the ascending cholinergic reticular system. Abbreviations: A, nucleus accumbens; ATH, antero-ventral and antero-dorsal thalamic nuclei; BC, brachium conjunctivum; BP, brachium pontis; C, interstitial nucleus of the ventral hippocampal commissure; CBL, cerebellum; CC, cingulate cortex (cingular and retrosplenial areas); CU, nucleus cuneiformis; DB, diagonal band; DE, deep tegmental nucleus (ventral tegmental nucleus of Gudden); DO, dorsal tegmental nucleus; F, fornix; FC, frontal cortex (area infra-limbica and anterior limbic area); FR, fasciculus retroflexus (habenulo-interpeduncular tract); H, habenular nuclei; HF, hippocampal formation; IP, interpeduncular nucleus; LD, latero-dorsal tegmental nucleus; LP, lateral preoptic area; M, mammillary body; MS, medial septal nucleus; MT, mammillo-tegmental tract; MTH, mammillo-thalamic tract; OB, olfactory bulb; OT, olfactory tubercle; PC, precallosal cells; R, dorsal and median nuclei of raphe (nucleus centralis superior); SFO, subfornical organ; SH, stria habenularis; SR, septal radiation; TP, nucleus reticularis tegmenti pontis (of Bechterew); VT, ventral tegmental area. Source: P. R. Lewis and C. C. D. Shute, Brain, 90 (ig6g) 508. By permission of the author.

The Amine Brain Systems and Behavior

The demonstration of specific aminergic systems innervating specific loci within the brain opens the avenue to clarification of monoamine function in the regulation or modulation of behavior controlled at specific loci. Such clarification of function at specific loci can be expected to increase our understanding of the genesis of certain kinds of psychopathology. (See section on Specific Brain Aminergic Systems, p. 451.) Only a few experimental studies have been reported in which the relationship of these specific amine systems to behavior have been studied. There is, however, a great deal of activity in this area and it is expected that by the time of publication of this chapter much more experimental data will be available. To date, data as to the behavioral consequences of altering, by a variety of techniques, one or more portions of the aminergic systems are summarized below.

Dopaminergic Systems

The Nigrostriatal Pathway

The dopaminergic, nigrostriatal pathway, with the exception of its projection to the amygdala, has been studied more extensively than any other of the catecholamine pathways, probably because this system is reasonably discrete and because of its demonstrated involvement in a well-defined pathological condition, Parkinsonism.

Experimentally the nigrostriatal pathway can be lesioned so as to produce an ipsilateral deficiency in the terminals of the neostriatum of both DA and the synthetic enzymes, tyrosine hydroxylase and Dopa decarboxylase. Unilateral lesions of the substantia nigra produce an ipsilateral hypokinesia and cause rats to rotate toward the lesioned, DA-depleted side, particularly after treatment with a monoamine oxidase inhibitor and reserpine or with amphetamine, both of which treatments presumably increase the quantities of DA at receptors on the nonlesioned side. Haloperidol, which blocks DA receptors (see below), very quickly interrupts such rotation as produced by amphetamine. The development of a postsynaptic receptor supersensitivity on the denervated side allows DA receptor agonists, such as apomorphine, to activate differentially the denervated side and produce a rotation away from the lesioned side when given systemically. DA or apomorphine, injected directly into the neostriatum, produces rotation away from the side of injection.

Stereotyped movements (interruption of normal grooming, feeding, and drinking, and the appearance of continuous sniffing, licking, gnawing, repetitive motor movements of the head extremities) are also seen after intraneostriatal administration of DA and amphetamine, and are antagonized by systemic administration of haloperidol. Intraneostriatal administration of chlorpromazine antagonizes the stereotyped behavior induced by systemic administration of amphetamine. That phenothiazines and butyrophenones

exhibit DA blocking properties is suggested by the above and by their secondary effect of increasing DA turnover after presumed blockade of receptor sites. (See section on Actions of Clinically Useful Pharmacological Agents, p. 434.)

That the nigro-striatal DA systems control more than motor behavior is shown by Ungerstedt's recent work with the "lateral hypothalamic syndrome." He was able to produce adipsia and aphagia by total destruction of the nigro-striatal pathway bilaterally. Moreover, in animals so lesioned he noted severe hypokinesia, difficulty in initiating activity, and loss of exploratory behavior and curiosity. He concluded that it is probable that the nigro-striatal DA system may control the general arousal or drive level that is necessary for performing a number of vital activities such as eating and drinking.

Of considerable interest is the possibility that the dopaminergic systems may have a role in mental function beyond that of regulating movement per se. The association of the antipsychotic actions of the phenothiazines, butyrophenones, etc., with extrapyramidal reactions in man and the antagonism of these same drugs to stereotyped behavior in animals (and perhaps stereotypy in schizophrenia) suggests that all of these kinds of behavior may be related to DA systems. In terms of this issue, it should be remembered that the antipsychotic or neuroleptic drugs probably block DA

receptors related to the terminals of the meso-limbic DA system as well as the nigrostriatal.

The Mesolimbic Pathway

As noted above, one might speculate that it is the blockade of DA receptors in meso-limbic terminals that is responsible for the antipsychotic action of some neuroleptics. An attempt to separate the function of the dopaminergic meso-limbic terminals in the nucleus accumbens and olfactory tubercle from the dopaminergic nigro-striatal terminals has been made by removing the neostriatum of rats by bilateral electrocoagulation and then treating the animals with cataprezen, a NE receptor stimulating agent, both with and without apomorphine, which would be expected to activate the remaining DA receptors on the meso-limbic terminals (but not the destroyed DA terminals of the neostriatum). In such a preparation, apomorphine elicits a peculiar behavior consisting of jerky, very rapid movements with periods of complete rest.

The Tubo-infundibular System

The dopaminergic tubo-infundibular system is believed to be concerned primarily with neuroendocrine function and is beyond the scope of this chapter. The reader is referred to recent reviews by Fuxe and Hokfelt, and by Fuxe et al.

The Norepinephrine Systems

The Dorsal NE System

The dorsal NE system can clearly be implicated in but one type of behavior: bar pressing for electrical self-stimulation. An electrode placed in the area of the locus coeruleus of the pons and just lateral to the central gray in the mesencephalon (the site of passage of the dorsal NE bundle) produces reinforcement, "reward," or "pleasure" when a small current is passed through it into the tissue; that is, a rat will bar press to receive electrical stimulation to his dorsal NE bundle at rates over 500/hr.

It is clear, however, that fibers other than those of the dorsal NE bundle may also produce self-stimulation-reinforcing behavior since similar self-stimulation can be produced by stimulating the median forebrain bundle from its origin in the mesencephalon to the septal area.-

Ventral NE System

The specific functions of the ventral NE system have been sparsely studied. The intimate contact of its terminal area in the ventral substantia gresia centralis with 5-HT cell bodies of the (B_7) group implies an interrelation between the ventral NE system and the 5-HT system, but the functional significance of such direct communication is obscure.

To date a single study has appeared involving a lesion of the ventral NE bundle. A behavioral response in rats to such a lesion was a hyperphagia, with increases in food consumption by 40 percent. Moreover, the animals so lesioned were refractory to the anorexogenic action of amphetamine.

The Serotonin Systems

Electrical stimulation of the raphe nuclei (B7 and B8) of the mesencephalon produces behavioral signs of calmness and an EEG pattern similar to that found in sleep. It also produces an increase in brain 5-HIAA and a decrease in 5-HT levels. Destruction of mesencephalic raphe nuclei in cats caused a decrease in slow wave sleep, which significantly correlated with selective diminution of cerebral 5-HT (but not with NE content). Behaviorally, these lesioned animals showed increases in spontaneous motor activity, aimless rotatory movements, and hypersensitivity to auditory stimuli.

The Acetylcholine Systems

As mentioned previously (see nigro-striatal system) stereotyped behavior, felt by some to be the animal model of psychosis, occurs after a systemic administration of a number of psychostimulant drugs (especially amphetamines), and after microinjections of DA into the neostriatum, but this stereotypy can also be produced by injection of anticholinergics into the

neostriatum. Further, the stereotypy induced by psychostimulants is antagonized by the administration of anticholinesterases or by choline esters as well as by injections of chlorpromazine and haloperidol into the neostriatum.

Systemic administration of the anticholinesterase physostigmine depresses self-stimulation behavior and such effects are antagonized by atropine, although the area of brain involved in stimulation may be a critical variable. This suggests that ACh predominance results in decreased bar pressing for electrical stimulation (the operational paradigm for "reward") by increasing CNS cholinergic tone. Cholinergic agents (carbachol, muscarine, and physostigmine) injected into the medial hypothalamic area decreased the rate of punished behavior. Anticholinergic agents (scopolamine, atropine) similarly injected caused disinhibition of punished behavior.

Margules has demonstrated that the anticholinergic atropine *lessens* the effect of punishment in the passive-avoidance-deficit paradigm when injected into the entopeduncular nucleus. Introduction of cholinergic and cholinesterase inhibitors to certain sites may produce aggressiveness or even killing behavior in animals. Such aggressiveness and hyperactivity results from local application of amitone (an anticholinesterase agent) in the lateral septal nucleus of the rat and such behavior was inhibited by pretreatment with atropine. Killing behavior in mice is induced by intrahypothalamic

injection of carbachol or neostigmine and is antagonized by prior intrahypothalamic administration of methyl atropine. Such demonstrations of the multiple effects of a single neurotransmitter (ACh) in various areas should not be surprising in view of the various functions of different discrete parts of the brain.

Specificity of Actions of Clinically Useful Psychopharmacological Agents upon Brain Amine Systems

The Tricyclic Antidepressants (Thymoleptics)

In this section the terms tricyclic drugs or tricyclic amines are used to refer to a group of drugs that are chemically similar and that have been demonstrated to be of use in the treatment of depression in man. The structure of four of these tricyclic drugs, which are frequently referred to in this chapter, are shown in Figure 20-6. It is of interest that the secondary amines, desipramine and nortriptyline, are natural metabolic products of the tertiary amines and there is evidence that a part or all of the antidepressant actions of the tertiary amines are mediated via their desmethylated products. Some of the published data as to structure-activity relationships will be briefly reviewed in this section and then considerable attention will be given to the differential effects of these drugs upon specific brain aminergic systems.

Structure-activity Relationships for the Tricyclic Antidepressants

Bickel and Brodie noted that treatment of animals with a benzoquinolizine produced a reserpine-like syndrome and that desipramine blocked all signs of this syndrome and, in higher doses, desipramine was even able to produce a hyperactive animal. Taking this as a model situation, these investigators tested a large number of drugs, as well as a number of structurally altered analogues of desipramine, in terms of their potency in reversing the benzoquinolizine syndrome. They noted the following. Activity was restricted to compounds having two or three carbons on the side chain whereas compounds with branch chains or chains containing more than four carbons tended to be inactive or toxic. In terms on N-substitution it was noted that activity was confined to methyl-substituted or un substituted amines, whereas ethyl or higher alkyl groups on the side chain nitrogen resulted in compounds that were either inactive or toxic. A number of ring-substituted compounds were active, i.e., the 3-chloro, 10-methyl, or the 10, 11-dimethyl. Changes in the bridge between the two phenyl groups from CH_2-CH_2 to CH=CH did not change activity. Removal of the ring nitrogen and substitution with a carbon made little difference in terms of activity. Given work that will be reviewed later as to the differential effects between tertiary and secondary tricyclic amines on uptake of 5-HT and NE, it is of interest that Bickel and Brodie noted that “almost all antidepressant compounds are primary and secondary amines .. .” and, “The possibility exists that the antidepressant

action of the two active tertiary amines are mediated through the rapid formation of their secondary analogues in the body."

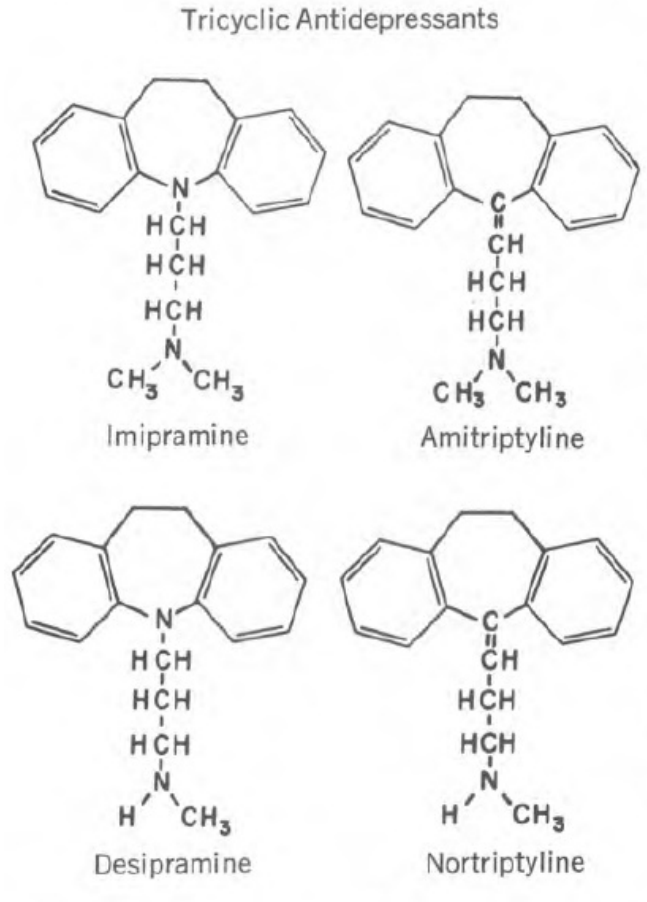

Figure 20-6.
Structures of tricyclic anti depressant drugs frequently referred to in the text.

Maxwell et al. explored in some detail the molecular features of the tricyclic antidepressants as they may affect the inhibition of the uptake of NE. Although most of the work of this group has been done with rabbit aortic strips, .there is one publication that suggests that the general conclusions reached by these workers can be applied to brain. Their data agree with other work that has been or will be cited as to the greater potency of desipramine, as compared to imipramine, in blocking the uptake of NE, and they also found that at lower concentrations of NE the inhibition of NE uptake by desipramine departs markedly from linearity. For example, at a concentration of NE of 1 X 10^{-7} M there was a much more marked inhibition of uptake of NE than at a concentration of 4 X 10^{-7} M. This deviation from linearity was not observed for imipramine, nortriptyline, or a primary amine derivative. They note that at lower concentrations of NE the potency of desipramine in blocking NE uptake relative to imipramine may be therefore much greater than the factor of ten, which is usually quoted (q.v.). This group has also made some interesting and important observations about mechanisms by which structural differences may alter the inhibition of uptake. They compared systems in which the bridge between the two phenyl groups was either absent or was formed by sulfur, a — CH^{-2}—CH^{-2}—, a —CH=CH—, an oxygen, or a bond between two carbons of the phenyl groups. They found that high potency (in blocking uptake of NE)occurs with tricyclic compounds in which the phenyl groups are held at considerable angles to one another (examples

of this would be, imipramine, amitriptyline, phenothiazines, or protriptyline); intermediate potency occurs with tricyclic drugs in which the two phenyl groups are held at slight angles or in which there is no bridge between the diphenyl systems. Tricyclics in which the phenyl rings are coplanar, such as carbazole, are only weakly active. They suggest that if the assumption is made that the receptor site is the best fit by the extended confirmation of phenylethylamine, then the presence of two phenyl rings that are not in the same plane will allow the side chain amine group of the drug to be inserted into the receptor site, and, further, that the phenyl ring that is above the plane can occupy a position somewhat analogous to that of the hydroxyl group on the carbon of NE. Theoretical considerations led to the suggestion that the fit of the secondary amine into the receptor site is a tight one of the lock and key type. They calculated the difference in total free energy of binding for desipramine and its primary amine analogue and noted that the difference is of the order of — 1.4 KC, which is quite close to the sum of —700 calories, occurring with the transfer of a methyl group from water to a nonaqueous phase, and —600 calories, the maximal increment for Van der Waals interactions of a methyl group with methylene groups in an enzyme. It is also apparent that since these drugs are not capable of blocking the uptake of DA (q.v.) which lacks a hydroxyl group on the carbon, the interaction of the raised phenyl ring with another portion of the receptor must be of considerable importance.

Studies Dealing with the Uptake of Dopamine, Norepinephrine, and Serotonin as Influenced by Tricyclic Antidepressant Drugs

Glowinski and Axelrod demonstrated that desipramine and imipramine, but not chlorpromazine, decreased the uptake of intra-ventricularly administered NE. Subsequent studies, in which a variety of techniques have been used, have in general supported these original observations, but it has also been found that there are differences in the degree to which the various tricyclic antidepressants are able to block the uptake of NE within brain and further that there are differential effects upon specific amines and aminergic systems. Some of the published reports bearing upon this specificity of drug action are summarized in the following portion of this chapter.

Carlsson et al. pretreated rats with reserpine to deplete brain stores of biogenic amines and administered a monoamine oxidase inhibitor, nialamide, and then gave L-Dopa and studied the reappearance of catecholamine fluorescence. It was found that the reappearance of fluorescence was blocked in both brain and heart by desipramine and protriptyline and that these effects were restricted to NE fibers, in that the drugs did not alter the reappearance of fluorescence in DA fibers. Similar results as to differential drug effects on DA and NE neurons were obtained with the use of an in vitro, brain slice technique. Glowinski et al. also found that while desipramine decreased the uptake of intraventricular administered H — NE into several areas of brain, this drug was without effect on DA uptake. Ross and Renyi,

however, noted that the differential effects of the tricyclic drugs on blockade of uptake on DA and NE systems were not absolute. For example, desipramine in the incubating media produced a 50 percent inhibition of uptake of NE in brain slices at a concentration of 3×10^{-8} and a 50 percent inhibition of uptake of DA into striatal slices at a concentration of 5×10^{-5}, i.e., a blockade of DA uptake equal to that of NE required an approximate one thousand-fold increase in drug concentration. Similar differences in the concentration of imipramine required to produce a 50 percent inhibition of uptake in noradrenergic and dopaminergic systems were found. These workers also made the interesting discovery that there were marked differences in the concentrations of desipramine and imipramine that were needed to block uptake of NE into cerebral slices by 50 percent, whereas there was relatively little difference in the quantities of these two drugs required to give a 50 percent blockade of uptake of DA into striatal slices. They calculated, for example, that a 50 percent inhibition of uptake of NE by brain slices could be produced by incubating the slices with 3×10^{-7} M imipramine or 3×10^{-8} M desipramine (to produce the same degree of blockade of uptake by pretreatment of the animals it was necessary to give 6 mg/kg of imipramine but only 2 mg/kg of desipramine). These in vivo and in vitro biochemical findings were buttressed by physiological data, i.e., the amount of imipramine required to give significant inhibition of a reserpine produced ptosis was 7 mg/kg, and for hypothermia 5 mg/kg, whereas desipramine in doses of 0.8

mg/kg and 0.5 of mg/kg respectively produced the same antagonistic effects. (These dose-blockade relationships suggest that the finding by Schanberg et al. that desipramine and imipramine both significantly block the uptake of H-NE into the cisterna magna was due to the dosage used, i.e., 25 mg/kg.) Haggendal and Hamberger also produced data that is in essential agreement with the preceding work. They pretreated rats with reserpine and nialamide, prepared slices from cerebral cortex and neostriatum, and examined the uptake of NE in both of these areas with and without desipramine. They demonstrated that the amine pump in the straitum was quite active for NE, i.e., NE was concentrated against a gradient, as it was in cerebral cortex, but that the blockade of the uptake in these two areas by desipramine and chlorpromazine was rather different, i.e., at a concentration of 1×10^{-5} there was a significant blockade of uptake of NE by cortical slices, but that this effect was much reduced in slices of striatum. That these actions of tricyclic drugs on the uptake of NE also occur in an in vivo situation was established by Sulser et al. This group pretreated rats with reserpine and desipramine and, with the use of a push-pull cannulae implanted in the hypothalamus, assayed labeled NE and NM in the perfusate. As expected desipramine produced an increase in both NE and NM in the perfusate.

In general, the cited studies as a group are consistent in that they indicate that the tricyclic drugs, desipramine and imipramine, markedly block the uptake of NE by neural tissues and that these effects are either absent or

much less marked in DA systems, viz., the concentration of desipramine or imipramine required to give a 50 percent inhibition of uptake in striatum is one hundred to one thousand times greater than that for the cerebral cortex. In addition to the differential effects on DA-versus-NE neurons, there is also agreement that desipramine is a more potent inhibitor of NE uptake than is imipramine, i.e., depending upon the experimental conditions, the amount of desipramine required to give the same effect is three to ten times less than that of imipramine.

Interestingly, in most of these studies the effects of these drugs upon the uptake of 5-HT was ignored. This omission, however, was soon rectified with some interesting results. Blackburn et al., using rat brain slices, found that at concentrations of 1×10^{-4} and 1×10^{-5}, imipramine, desipramine, and chlorpromazine were all inhibitory of 5-HT uptake. However, at the 1×10^{-5} concentration imipramine blocked uptake by 38 and 30 percent. In partial contradiction to this work, Palaic et al. found that desipramine in doses of 10 mg/kg, when given intraperitoneally twenty minutes before sacrifice, did not affect the uptake of labeled 5-HT in an experimental situation in which the brain was perfused with labeled 5-HT and later assayed for both 5-HT and 5-HIAA. (They did find, however, that drug treatment produced a decrease in endogenous 5-HIAA, which is of interest in terms of work described in another section of this chapter regarding the effects of these drugs on amine turnover.) Other published reports by different groups of investigators gave

information relevant to the apparent discrepancy between the work of Blackburn et al. and Palaic et al. For example, Alpers and Himwich, using slices from rat brainstems, estimated the concentrations of imipramine, amitriptyline, and desipramine required to give a 50 percent inhibition of 5-HT uptake. The concentrations required for imipramine and amitriptyline were essentially the same, i.e., 3 to 4.5 X 10^{-5}, whereas for desipramine the concentration required was ten times greater, i.e., 3 X 10^{-5}. Ross and Renyi and Carlsson also found that the tertiary tricyclic amines, imipramine and amitriptyline, were more potent in blocking 5-HT uptake than were their demethylated derivatives, desipramine and nortriptyline. For example, the latter authors found that a 50 percent inhibition of uptake of 5-HT by brain slices occurred at a concentration of imipramine of 6 X 10^{-7} M, whereas the concentration required for desipramine was 4 X 10^{-6} M. A similar difference, albeit not as marked, was found between amitriptyline and nortriptyline. Both Ross and Renyi and Carlsson noted that the difference in the inhibitory potency for the uptake of 5-HT by brain slices was exactly the opposite of that which had been found for NE. Carlsson further investigated the structural specificity for the inhibition of 5-HT uptake by cerebral slices obtained from mice that had been pretreated with reserpine and nialamide and found that chlorimipramine was somewhat more potent than imipramine. Glowinski and coworkers have used a somewhat different but important technique to assess the differential effects of the secondary and tertiary tricyclic amines on

serotonergic, noradrenergic, and dopaminergic systems. Their approach has been to dissect out specific structures such as the hypothalamus, medulla oblongata, or striatum, to make slice preparations from these areas and incubate the tissues for fifteen minutes with labeled tyrosine or tryptophan. Given the short period of incubation, they feel that they may be specifically focusing on the release and reuptake of newly synthesized amines that may be preferentially released during nerve stimulation. The data as obtained with this technique are essentially in agreement with the work that has been reviewed above, i.e., desipramine markedly increased the content of labeled NE in the media in which slices of medulla oblongata were incubated, whereas there were no effects on the quantities of labeled DA found under similar conditions with slices of striatum. Similarly, with slices of hypothalamus, imipramine resulted in marked increases in the quantities of labeled 5-HT found in the media. In general, these results were obtained whether the drugs were administered in vivo or were added to the incubating media.

Given the agreement among the studies cited above as to the differential effects of the secondary and tertiary tricyclic amines on blockage of uptake of the three amines DA, NE, and 5-HT, a logical inference is that these different drugs might have specific effects on aminergic systems as morphologically defined. As expected this issue has been explored with the use of histochemical-fluorescent techniques. Fuxe and Ungerstedt pretreated

experimental animals with reserpine and then gave intraventricular injections of DA, 5-HT, or NE. In some cases, prior to the injection of the amines, the animals were pretreated with desipramine or imipramine. They found that with the control animals, i.e., those which had been pretreated with reserpine but not with the tricyclic drug, there was a partial to marked increase in fluorescence following injection of DA, NE, or alpha-methyl-NE, in areas close to the ventricle. They further found that pretreatment with desipramine or protriptyline prevented the increase in fluorescence in NE terminals, but not in DA terminals. This effect was dose dependent. The blockage was greatest in those terminals just beneath the fourth ventricle and in the subarachnoid space of the medulla and pons, but little blockage was observed in NE nerve terminals of the hippocampal formation or septal area, where the concentration of injected amine would have been expected to be high. In contrast to the findings with desipramine or protriptyline, they found that pretreatment with imipramine only slightly decreased the return of fluorescence following the injection of the DA or NE. Further, pretreatment with desipramine did not block the accumulation of fluorescence following the injection of 5-HT in any of the areas examined, whereas there were partial effects following pretreatment with imipramine. While these findings agree with and extend those obtained by biochemical or pharmacological approaches there remains the problem of the unphysiological route of administration of the amines. To avoid this potentially confounding problem

Carlsson et al. injected rats and mice intraperitoneally with 4, alpha - dimethyl-meta-tyrosine (H77-77), which causes the depletion of NE and DA in both central and peripheral pools, and by the use of biochemical-and histochemical-fluorescent techniques examined the effects of imipramine, desipramine, or protriptyline on the drug-induced amine depletions. The H77-77 induced depletion of NE, but not DA, was prevented by pretreatment with desipramine and protriptyline, and this blocking effect appeared to be dose dependent. In contrast, pretreatment with imipramine or amitriptyline blocked NE nerve-terminal depletion by H77-77 only at the highest doses. Data obtained by biochemical analysis of brains for NE and DA content were, in general, in agreement with those obtained with the histochemical-fluorescence technique. Carlsson also found that an analogue of H77-77, 4-methyl-alpha-ethylmeta-tyrosine (H75-12), was capable of causing depletion not only of catecholamines but also of 5-HT stores in the brain and, as before, he used this agent to examine the action of the tricyclic drugs on serotonergic systems in the brain. In these investigations the 5-HT nerve terminals examined were mainly in the mesencephalon and diencephalon, particularly the nucleus suprachiasmaticus. It was found that chlorimipramine and imipramine were the most potent drugs in blocking the H75/12 induced amine depletion in 5-HT nerve terminals, whereas drugs such as protriptyline, desipramine, and nortriptyline had little blocking activity in the doses studied. The biochemical data was supportive of and consistent with

the histochemical-fluorescent data.

In summary, the available biochemical data indicate that the tricyclic antidepressant drugs do not block, or do so only weekly, the uptake of DA. Further, while the tricyclic drugs block the uptake of both 5-HT and NE by brain tissue there are differential effects in that the tertiary tricyclic amines, such as imipramine, are more potent inhibitors of 5-HT uptake than are the secondary amines, such as desipramine. In contrast, the secondary amines are more potent blockers of NE uptake than are the tertiary amines. As might be expected from this biochemical data, histochemical-fluorescent studies indicate that the tricyclic drugs are without effects upon dopaminergic systems per se, whereas the secondary and tertiary tricyclic drugs exert their principal effects respectively upon noradrenergic and serotonergic brain systems.

Effects of Tricyclic Antidepressants on Turnover of Dopamine, Norepinephrine, and Serotonin

In 1966, Neff and Costa published data that indicated that if rats were given protriptyline (20 mg/kg) or desipramine (10 mg/kg) X 5 over a three-day period, an increase of turnover of brain NE, but not DA, was produced. In terms of issues to be discussed in other parts of this chapter, it should be noted that these investigators also found that in contrast to the lack of an effect of the tricyclic drugs on DA turnover, chlorpromazine in doses of 5

mg/kg did increase the turnover of DA. Corrodi and Fuxe pretreated experimental animals with imipramine and inhibitors of tyrosine hydroxylase or tryptophan hydroxylase and by biochemical-and histochemical-fluorescent techniques estimated the rates of disappearance of catecholamines and indoleamines. They found that, even with high doses of imipramine, there were no changes in the rates of depletion of NE or DA, whereas there was a significant slowing of the decrease in the disappearance of 5-HT. This finding as to an effect of imipramine on the turnover of 5-HT and the lack of an effect on NE or DA systems, of course, "fits" with studies cited earlier in this chapter indicating that the tertiary tricyclic amines act primarily on serotonergic systems, whereas the secondary amines have a more specific action on noradrenergic systems. In later work Corrodi and Fuxe examined the effects of amitriptyline, chlorimipramine, and nortriptyline on brain 5-HT turnover by assessing the effects of these agents on the depletion of brain 5-HT and the rates of disappearance of fluorescence in serotonergic areas following the administration of a tryptophan hydroxylase inhibitor. They found that it was necessary to use extremely high doses to obtain significant slowing of turnover of 5-HT, and even then the results were very modest. (These findings are in contrast to the rather marked effects of some of these drugs in blocking 5-HT uptake, as noted in studies cited elsewhere in this chapter.) Using a somewhat different technique and approach, Meek and Werdinius found that, following the administration of chlorimipramine and probenecid,

there was a decrease in the accumulation of 5-HIAA in the brain, which is consistent with and supportive of the earlier suggestion that the imipramine-like drugs slow the turnover of 5-HT.

Schubert et al. approached the problem of turnover time, as influenced by the tricyclic drugs, by giving labeled tryptophan or tyrosine, either as a single pulse or as an infusion, and then measuring the amount of labeled 5-HT, DA, or NE that accumulated during the infusion or the amount of labelled amine that was found in brain at some point after the pulse was given. Drugs evaluated were imipramine, desipramine, amitriptyline, and nortriptyline. It was very clear from their data that none of these drugs affected DA accumulation or disappearance. For 5-HT the disappearance was decreased by imipramine and amitriptyline, but was unaltered by desipramine or nortriptyline. The accumulation of 5-HT was decreased by imipramine, but not by the other drugs. In general these findings may be considered to be consistent with the notion that imipramine slows the turnover of 5-HT, whereas desipramine or nortriptyline are without an effect. The accumulation of NE was not increased by any of the drugs, but the disappearance was increased by desipramine and nortriptyline, which would suggest that these two drugs may increase the turnover of this amine. Since only single time points are available, however, these conclusions as to effects of these four agents on turnover must be quite tentative, and it can only be firmly concluded that these drugs appear to be without effect on DA systems, but do

have effects on the quantities of labeled 5-HT and NE found in brain.

In an investigation of the effects of psychoactive drugs on 5-HT metabolism, Schildkraut et al. noted that when C-5-HT was administered by intracisternal injection and imipramine was subsequently injected intraperitoneally (the animals were sacrificed two hours following the injection of the labeled amine) there was a significant increase in levels of C-5-HT in those animals which had been treated with imipramine. This finding is consistent with the work noted above, which indicates that imipramine results in a slowing of the turnover of brain 5-HT. Schildkraut has also presented data that indicates that the length of time of drug administration is a significant factor in determining potential effects on turnover time of the amine under study. For example, he noted that when rats were given imipramine (10 mg/kg) twice daily for three weeks, there appeared to be an increase in the rate of disappearance of H-NE from the brain, following an intracisternal injection of the labeled amine. Again, this data is difficult to interpret with certainty, in that only two time points were presented and there were alterations in the endogenous NE content and, as such, specific activities were probably altered.

Glowinski and coworkers, using a technique that was described earlier in this chapter, examined the effects of some tricyclic antidepressant on the synthesis of NE, DA, and 5-HT from labeled precursors. They found that the

total labeled 5-HT found (media and tissue) was decreased if imipramine was present in the media or if tissue was obtained from animals that had been pretreated with this drug. Desipramine produced marked increases in NE synthesis in slices of medulla, but no effects on the synthesis of DA in striatum were noted.

In summary, the available data indicate that the tricyclic drugs, whether of the tertiary or secondary amine type, do not alter the turnover or disposition of DA. Tricyclic drugs of the tertiary amine type produce effects that are consistent with a slowing of the turnover of 5-HT. In contrast, tricyclic drugs of the secondary amine type produce effects on NE that are consistent with an increase in turnover of this amine. These differential effects (or lack thereof) of the tertiary and secondary tricyclic amines on the turnover of DA, NE, and 5-HT are also consistent with the demonstrated differential blockage of uptake of these three biogenic amines as produced by the tertiary and secondary tricyclic amines.

Actions other than those on Uptake and Turnover

As is indicated by the foregoing there has been a great deal of attention paid to the effects of tricyclic drugs on the neuronal membrane pump for NE, DA, and 5-HT. It should be noted, however, that this may reflect the focus of the investigating spotlight rather than a total description of modes of action.

For example, Mandell has presented data that indicates that imipramine in doses of 25 mg/kg (two times per day) for three days and at 10 mg/kg (two times per day) for eight days produces significant decreases in midbrain tyrosine hydroxylase activity. It is also probable that the tricyclic drugs have some effects upon the uptake of amines into organelles within the neurons. The magnitude of this effect in determining the pharmacological actions of the drugs is uncertain, but it should not be overlooked. Brodie et al. found that desipramine blocks the uptake of small doses of tyramine by a rat heart, but if the tyramine is given in doses of 20 mg/kg, desipramine (20 mg/kg) does not alter the intracellular concentrations of tyramine, but it is able to prevent the depletion of NE by the tyramine. Similarly, Leitz showed that while desipramine was able to prevent the efflux of NE from heart slices, following treatment with metaraminol, this effect was much greater than the blockage of the uptake of metaraminol per se. He interprets this data to indicate that while desipramine blocks the uptake of metaraminol at the neuronal membrane, it also blocks the entrance of metaraminol into the granules and thus has an intraneuronal action. Steinberg and Smith, using rat-brain slices, found that low doses of desipramine did not prevent the uptake of H-tyramine at the neuronal membrane and subsequent synthesis of H-parahydroxyphenlyacetic acid, but that it did prevent the uptake of H-tyramine into intraneuronal sites, as indicated by the decreased formation of labeled octopamine.

The Neuroleptic or Antipsychotic Drugs

These classes of drugs, for example, the butyrophenones and phenothiazines, are of particular interest in that although they differ chemically, they share the ability to decrease manifest psychotic behavior and ideation in schizophrenic subjects, whereas they are not particularly helpful in reversing depressive mood and psychomotor retardation in the depressive disorders.[3] Because of this specific clinical usefulness in the neuroleptics, a demonstrated action on specific aminergic systems would assume importance in that leads might be provided as to the possibility that one or more of the brain aminergic systems has a central role in the genesis of some, if not all, components of schizophrenia. This general line of pharmacological reasoning, of course, is similar to that which has been used to develop hypotheses as to the involvement of specific biogenic amines in the affective disorders. Investigation of the specificity of action of the neuroleptics has, however, posed methodological problems in that these drugs have a multiplicity of biological effects, and the manipulation of a particularly important effect, receptor blockage, requires in vivo, function-type preparations, in contrast to other types of studies in which homogenates, brain slices, synaptosomes, ventricular-perfusion techniques etc., may be used. In general, studies of receptor blockage within specific amine systems have either utilized “functional-test” methods or a biochemical marker, i.e., amine turnover time, which changes as a consequence of drug administration.

Studies Using "Function" Type Methods

Anden et al. examined the effects of a variety of drugs on rats in which the DA pathway had been destroyed by either an electrolytic lesion in the crus cerebri at the level of the mammillary bodies or by unilateral removal of the corpus striatum. Reserpine produced a turning of the tail and head to the side opposite from the lesion as did haloperidol and chlorpromazine, whereas promethazine was without effect. Pretreatment with a monoamine oxidase inhibitor accentuated the reserpine effect, but the turning was now toward the operated side and this was blocked by haloperiodol. Similarly, pretreatment with a monoamine oxidase inhibitor followed by L-Dopa, but not 5-hydroxytryptophan, resulted in a turning toward the operated side. These findings can be taken as supporting the possibility that ehlorpromazine and haloperidol block dopaminergic receptors, but the question as to an effect on other types of central receptors is left unanswered.

Snyder et al. noted that d-amphetamine is a more potent inhibitor of NE uptake than is 1-amphetamine, whereas the two isomers are about equally active in inhibiting DA uptake, and, as such, suggested that this differential effect might be used to dissect out the noradrenergic versus dopaminergic-mediated behavior that is produced by amphetamine. It was found that d-amphetamine was about ten times more potent than the 1-isomer in producing locomotor stimulation and only twice as potent in producing

stereotypical gnawing and mouthing movements. It was concluded that the locomotor activity was predominantly mediated via noradrenergic systems, whereas the stereotypy was due primarily to dopaminergic systems with some contribution from the noradrenergic. These data can be used to reinterpret some earlier reports as to the effects of a variety of neuroleptic agents on the amphetamine-induced behavior. For example, Randrup et al. found that chlorpromazine, haloperidol, and ethoxybutamoxane were all effective antagonists of amphetamine-induced behavior that, as described by them, seems to be similar to gnawing and mouthing movements. In terms of later work to be reviewed, it is of particular interest that they found haloperidol was effective at lower doses than chlorpromazine." Janssen et al. studied an amazingly large number of drugs of the neuroleptic type in terms of their ability to antagonize amphetamine- or apomorphine-induced chewing and agitation. Given the correctness of Snyder s interpretation of his data as indicating that stereotyped gnawing behavior is due primarily to DA systems and the agitation to the noradrenergic, the data of Janssen can be used to categorize a large number of neuroleptics in terms of their potency for blockage of dopaminergic and/or noradrenergic receptors. For example, Janssen et al. noted that haloperidol is a more potent antagonist of amphetamine- or apomorphine-induced chewing than it is of agitation, which would imply a greater potency in blocking dopaminergic receptors. Despite the great detail of the Janssen et al. report, however, it is clear that

conclusions regarding the blockage of dopaminergic-versus-noradrenergic receptors rests upon inference, and it is for this reason that a relatively recent report by Anden et al., in which information was obtained as a specificity of receptor blockage by a more direct experimental approach is of particular interest. As noted, Anden et al. found that rats which had been unilaterally striatomized, when treated with apomorphine, turn toward the operated side. The dosages of a variety of neuroleptic agents required to block this behavior were noted, and this data was then taken as a measure of potency of dopaminergic-receptor blockage. For a test of central, noradrenergic-receptor blockage the ability of a series of neuroleptics, in varying dosages, to block the hind-limb flexor-reflex activity of a spinal animal after NE receptor stimulation, as produced by L-Dopa, was examined. It was found that two drugs of the diphenylbutylamine class, pimozide and fluspirilene, blocked only DA receptors, and even at very high dosage these drugs did not block NE receptors. A second group of drugs, among which were haloperidol, spiroperidol, and fluphenazine, had marked blocking activity for DA receptors, but only small to modest activity in blocking NE receptors. A third group of neuroleptics were reasonably good blockers of both dopaminergic and noradrenergic receptors and an example from this group is chlorpromazine.

The detailed report by Janssen et al. regarding the pharmacology and toxicology of pimozide contains data, which is consistent with the work of

Anden et al., that indicates that this drug is a potent blocker of DA receptors. Further, there is a report that indicates that this drug is a potent antipsychotic, and that, in terms of regional distribution, the highest concentrations in the brain are to be found in the caudate nucleus and pituitary, which, given the anatomy of aminergic systems, supports the concept that this drug has its primary effects on dopaminergic systems.

In summary, the available data indicate that the neuroleptic drugs as a group block DA and/or NE receptors in the brain, but some of these drugs which have antipsychotic properties have been found to be selective blockers of dopamine receptors. This, of course, raises the possibility that brain DA systems, and not NE systems, are involved in the production of psychotic behavior.

Effects of Neuroleptic Drugs on the Disposition of Dopamine, Norepinephrine, and Serotonin

In 1963, Carlsson and Lindquist published data that indicated that chlorpromazine or haloperidol did not alter endogenous brain NE and DA levels, but that these agents did produce increases in NM and 3-methoxytyramine. Furthermore, these changes were not produced with either phenoxybenzamine or promethazine. This report was seminal in that it suggested that chemically different drugs that have in common antipsychotic effects alter the turnover of two important brain amines, whereas a

phenothiazine, promethazine, which does not have antipsychotic properties, was without effect. These findings led the authors to postulate that these drugs produce a receptor blockage that, via a neuronal feedback mechanism, results in increased transmitter release and, consequently, an increased turnover. Work compatible with and supportive of the increased turnover of DA, as induced by these neuroleptic drugs, was published by Anden et al. in 1964. Laverty and Sharman also published data that were generally supportive of these earlier observations, but which raised questions as to problems of dosage and the capacity of neuroleptics to deplete amine stores. These investigations examined the effects of four different phenothiazines on brain levels of DA, NE, 5-HT, 5-HIAA and HVA. They noted that chlorpromazine when given acutely did not alter brain NE, 5-HT, or 5-HIAA, but that it did significantly decrease DA and increase HVA. Thioridazine, in contrast, did not affect 5-HIAA or DA, but it did increase NE and, in higher doses (50 mg/kg), treatment with this drug produced decreased brain 5-HT and increased HVA. In chronic experiments in which animals were treated with either chlorpromazine (20 mg/kg for fourteen days), trifluoperazine (8 mg/kg for twelve days) or thioproperazine (100 mg/mg for fourteen days) it was found that all drugs resulted in an increase in brain HVA, whereas there were no effects on brain NE, DA, 5-HT, or 5-HIAA (NE was measured in the hypothalamus, DA, and HVA in the caudate nucleus, and 5-HT and 5-HIAA in the thalamus). Atropine in doses of 25 mg/kg in cats had no effects on any of

the assayed amines or metabolites. Da Prada and Pletscher reported that chlorpromazine markedly increased, in a dose-dependent fashion, brain HVA but not 5-HIAA, and that this increase of HVA could be abolished by treatment with a monoamine oxidase inhibitor. They noted that the endogenous content of DA was not changed by chlorpromazine.

Neff and Costa, using a nonisotopic method, found that while treatment with chlorpromazine (5 mg/kg twice a day for three days) produced a significant increase in the turnover of brain DA, there was no change in the turnover of brain NE. This report represents the first direct demonstration that chlorpromazine does indeed alter the turnover of brain DA inasmuch as previous methods relied upon the analysis of changes in the metabolites of brain amines. Furthermore, the data in this paper, in terms of drug amine system specificity, set the stage for a controversy, which has not as yet been completely resolved, i.e., Neff and Costa found no change in the turnover of brain NE due to chlorpromazine, whereas the work of Carlsson suggested that this drug induced changes in the turnover of both DA and NE. Burkard et al. found that pretreatment of animals with chlorpromazine resulted in an increased conversion of peripherally administered tyrosine to H catechols in brain. The increase was major, being of the order of 80 to 100 percent, and lasted for one and a half to six hours. In an extension of this work, Gey and Pletscher found that the increase in labeled catechols that occurred as a function of treatment with chlorpromazine was due to an increase in the

specific activity of DA, whereas there was no change in the specific activity of NE. Also, these investigators found that if they gave C-Dopa and then gave chlorpromazine, the specific activity of DA at one hundred and twenty to one hundred and eighty minutes was significantly decreased, whereas that of NE was decreased less markedly and only at one hundred and twenty minutes as compared with controls. (The chlorpromazine treatment produced significant decrements in brain tyrosine levels, but this decrease was not of sufficient magnitude to negate the finding regarding turnover.) This data then supports the results of Neff and Costa as to an increase in DA turnover and a lack of change in NE turnover after chlorpromazine treatment.

Corrodi et al. presented both biochemical- and histochemical-fluorescence data that indicated that with rats acutely treated with haloperidol or chlorpromazine and sacrificed four hours after tyrosine-hydroxylase inhibition, there was a greater depletion of NE as a function of the neuroleptic drugs, whereas this was not found for DA. Treatment of rats for three days with chlorpromazine, followed by sacrifice six hours after enzyme inhibition, resulted in there being significantly less brain NE and DA in comparison to a control group. It should be noted that this latter "multiple" treatment schedule of Corrodi was similar to that of Neff and Costa; both groups used an inhibitor of tyrosine hydroxylase to assess the effects of neuroleptics on brain amine depletion, but Neff and Costa assayed for DA and NE at multiple time points, after tyrosine hydroxylase, and as such were able

to calculate the actual slope of the rate of disappearance of amines following enzyme inhibition, whereas the Corrodi group had only one or two time points.

Nyback and coworkers published a series of articles'' dealing with the problem of alterations in the turnover of brain amines as induced by neuroleptic drugs, using a technique in which rats or mice were pretreated with neuroleptic drugs and then either infused with labeled tyrosine or given a pulse of this catecholamine precursor. Immediately following infusion, or one and a half hours after the pulse, animals were sacrificed and the brains assayed for labeled tyrosine, DA or NE. Their data indicate that chlorpromazine resulted in an increased accumulation of C-DA, no change in C-tyrosine, and a small increase in the accumulation of C-NE. Further, this result for DA was maximal if the chlorpromazine was given one hour before the infusion and absent if the chlorpromazine was given twelve hours previously. If they gave chlorpromazine one hour after the labeled tyrosine, there were no effects on labeled tyrosine or NE, but C-DA was decreased. They also found that haloperidol increased the accumulation and disappearance of C-DA. The disappearance, but not the accumulation of C-NE, was increased by haloperidol, and promethazine did not alter the accumulation of labeled amines but did slightly increase the disappearance of C-NE. It was also demonstrated that analogues of phenothiazines, possessing neuroleptic activity (chlorpromazine, levomepromazine, perphenazine, and

chlorprothixene), in comparison to promethazine, altered the incorporation and loss of labeled DA from the brain, and that there was a tendency for the clinically most potent neuroleptics to have marked effects on DA formation and disappearance. At the highest dosages all drugs, except promethazine, increased the disappearance of NE and, at lower dosages, three of the four did.

Anden et al., as noted, classified drugs in terms of their ability to block DA and NE receptors within the central nervous system and then examined the effects of these same neuroleptic agents on the turnover of DA and NE, as assessed by the rates of decrease of DA and NE in the rat brain following treatment with a tyrosine-hydroxylase inhibitor, as well as by following changes in histochemical fluorescence due to catecholamines. The authors found that the two drugs of the diphenybutylamine type (pimozide and fluspiridene) which blocked only central DA receptors increased DA turnover and, in somewhat higher doses, NE turnover. In general, there was a relationship between the type and degree of receptor blockage and increased turnover of DA and/or NE.

Although the above reports clearly indicate that the neuroleptics alter brain DA turnover, the mechanism by which this change is induced is uncertain. As noted, in 1963 Carlsson and Lindquist originally speculated that this increase in turnover occurred as the consequence of receptor blockage

that, via a direct or indirect neural feedback, initiated increased neural activity, increased transmitter (DA) release, and then increased synthesis. Anden et al. investigated the problem as follows. It was noted that chlorpromazine, haloperidol, and an alpha receptor blocker, all prevented the Dopa-induced increase in the hind-limb flexor reflex in spinal animals. These drugs (but not a blocker) also resulted in increased disappearance of NE after tyrosine hydroxylase inhibition above the lesion, but not below, which led to the suggestion that the effect on NE turnover was due to an increase in nerve-impulse flow and not due to a direct action of the drugs themselves, i.e., the experimental data was consistent with Carlsson's original hypothesis. Tagliamonte et ah, however, have suggested a somewhat different mechanism. These authors found that chlorpromazine, in doses ranging from 5 to 20 mg/kg, was able to produce significant decreases in DA in the caudate nucleus with a corresponding increase in HVA. They further noted that with chlorpromazine there was a decrement in the 3-methoxy-tyramine content of brain. They concluded that it is probable that chlorpromazine may, like reserpine, produce an increased intraneuronal destruction of DA and that this then leads to the increase in turnover. Himwich et al. found that haloperidol even in the lowest doses used (1 mg/kg), produced significant decreases of dopamine in the caudate nucleus whereas with the same dosage no effect was noted in the rabbit. Other authors have also noted that chlorpromazine or haloperidol at higher doses produces decreases in brain DA (see Laverty and

Sharman), and these data give some support to Tagliamonte's suggestion. In contrast, much of the data reported by Swedish workers indicate that increases in turnover of brain DA can occur without decreases in endogenous DA content.'' It is of interest that amphetamine is able to diminish the rate of DA synthesis from H-tyrosine in brain slices in vitro, which raises the possibility that the effects observed are due to factors other than neural feedback mechanisms.

Relative to DA and NE, the biochemical effects of neuroleptics on brain 5-HT has not been intensively studied. Gey and Pletscher found that chlorpromazine and chlorprothixene did not alter the endogenous content of rat brain 5-HT, but it did counteract the increase of this amine after monoamine oxidase (MAO) inhibition or following 5-hydroxytryptophan as well as the decrement in 5-HT produced by reserpine. They conclude that the drug may affect the intracellular disposition of 5-HT. Anden et al. found that 5-HT content in cell bodies and nerve endings were unchanged as assessed by the histochemical-fluorescent method, nor were there changes demonstrated with biochemical assays. Giacalone and Kostowski found that for both forebrain and brainstem chlorpromazine (5 mg/kg) did not alter 5-HT content, but it did result in significant increases in 5-HIAA. Guldberg and Yates found that chlorpromazine in dosages of 2.5 to 10 mg/kg resulted in increases of 5-HIAA in the ventricular-cerebrospinal fluid and caudate nuclei of dogs (but not of other brain areas) whereas higher doses (10 to 15 mg/kg)

were without effect on 5-HIAA in either CSF or brain tissues. Gumulka et al. found that chlorpromazine in doses of x, 5, and 10 mg/kg did not alter brain 5-HT, but, in confirmation of Guldberg and

Yates, they found that the 5 mg/kg of chlorpromazine increased brain 5-HIAA, whereas this was not found with the lower or higher dose of the drug. As noted elsewhere, Laverty and Sharman found that acute chronic administration of chlorpromazine (at doses of 10 and 20 mg/kg respectively) did not alter brain 5-HT or 5-HIAA. It thus appears that the phenothiazine neuroleptics do not alter brain 5-HT, whereas, within a selected dose range, they do produce increases in 5-HIAA. However, because of the possibility that chlorpromazine will alter intraneuronal processes that are involved in the disposition of 5-HT and because of dose relationship, it cannot be assumed that this drug affects turnover. The relationship of neuroleptics to the 5-HT systems awaits more definitive investigation.

In summary, whether the brain DA systems have been examined in terms of alterations in brain metabolites, changes in DA content as produced by tyrosine-hydroxylase inhibition, or by the rates of formation of labeled DA, or disappearance of labeled DA following an intravenous pulse of labeled tyrosine, the results are consistent and in good agreement, i.e., treatment with neuroleptic drugs that may differ chemically but share antipsychotic effects, all produce increases in turnover of DA in brain. In contrast to DA, the data

dealing with the effects of these antipsychotic or neuroleptic drugs on the turnover of brain NE is less consistent. Some authors have found 110 alterations in turnover of brain NE as a function of treatment with neuroleptics, whereas others have found small but statistically significant changes, depending upon the type and amount of drug administered. In comparison to DA, the effects on NE turnover produced by the neuroleptics would appear to be minimal. It has been postulated that the neuroleptic-induced increases in amine turnover occur as a consequence of receptor blockage, but definitive experimental data as to the exact mechanism by which the neuroleptics alter turnover is not available. Studies dealing with the effects of the neuroleptics on 5-HT systems are few, and this area needs further exploration.

Lest We Forget

The function of specific aminergic systems has been approached artificially by the dissection, as much as methods allow, of each system from the influence of other amine systems. While the role of each system can be studied thereby, it is easy to lose the perspective that the brain is a complex organ or group of organs, all of whose component systems operating *together* yield the final measurable end product, behavior. Moreover, the aminergic systems described herein (NE, DA, 5-HT, ACh) make up only a small portion of brain neurons. While they may be the more critical neurotransmitter systems

so far as psycho-pathologic states are concerned, it can be appreciated readily that other candidates also exist but as yet have not been either defined or investigated.

The relationships among the presently described systems are of considerable interest, especially the relationships of cholinergic to dopaminergic and noradrenergic systems. Recently, clinical studies in which brain ACh systems were altered by the anticholinesterase physostigmine have shown the induction of a short-lived depressive state with lethargy, withdrawal, and psychomotor retardation. Physostigmine was also able to move manic patients toward the euthymic state. For the moment these studies must remain a curiosity, since there is no evidence implicating a defect in ACh metabolism in the brain in depressive states, but the frequent coincidence of terminal areas of ACh and NE systems, noted in Table 20-1, raises the possibility that ACh and NE systems may be acting at specific sites, balancing one another's inhibitory or facilitatory effect on a postsynaptic neuronal system that mediates affect, depression occurring when ACh receptor activation predominates over NE receptor activation.

The stereotypy induced by increasing DA in the neostriatum has been shown to be antagonized by ACh and by physostigmine as well as by haloperidol. Here again the coincidence of DA and ACh terminals in the neostriatum suggest that the two monoamines, DA and ACh, may be balancing

one another's inhibitory or facilitatory effect on a postsynaptic neuronal system that mediates stereotypy, stereotypy appearing when DA receptor activation predominates over ACh receptor activation.

A specific neuronal system may also terminally innervate another neuronal system. The intimate contact of ventral NE terminals with

HT raphe cell bodies (B_7) as seen by fluorescent histochemistry suggests such innervation. Such innervation of one system by another may not be unique to the raphe, but as yet it has not been described in other areas. The functional significance of such innervation is unknown at this time, but such findings open the possibility of further relationships among specific aminergic systems.

Specific Brain Aminergic Systems and the Genesis of the Affective and Schizophrenic Disorders—Some Speculations

In this final section an attempt is made to integrate data, from previously cited reports, around the possibility that specific amine systems within the brain are crucially involved in the production of specific psychopathological states. Before proceeding, however, a couple of caveats about this approach are needed. First, the comments and paradigms herein give short shrift to the issue of interactions between amine systems that are, without question, of importance in the regulation of behavior. It is, for

example, clear that there are cholinergic and dopaminergic nerve endings in the neostriatum and that these two transmitters produce antagonistic effects. It is also well-known that the tricyclic antidepressant drugs, in addition to their actions on other amines, possess anticholinergic properties. Secondly, given the complexity of the brain and of behavior, it is likely that a one-amine-one-psychiatric-disease[4] concept is too simple, but it is felt that from the investigators' standpoint there is heuristic value in constructing reasonably simple paradigms that may contain at least partial truths.

Aminergic Brain Systems and Depression

If one tabulates the data reviewed above, there are some remarkably consistent findings that emerge from the studies with the tricyclic antidepressant drugs. These can be used to develop and buttress the idea that specific aminergic systems within the central nervous system are (or are not) involved in the production of severe depressive states in man.[5] Some of this data has been tabulated in Table 20.2. Perhaps the most consistent finding is that the tertiary and secondary tricyclic amines, when administered in doses used clinically, are without effect on the uptake of DA into dopaminergic fibers. Further, these drugs do not have a significant effect on the turnover of DA. In contrast, drugs such as the phenothiazines and butyrophenones, which are without significant antidepressant activity, do have pronounced effects on the turnover of DA (q.v.). By inference then, it seems possible to exclude the

dopaminergic systems as having a central role in the genesis of some depressive states, and, given the experimental data as reviewed, the question arises concerning the role that noradrenergic and/or serotonergic systems may play in depression. There also appears to be general agreement among different workers that tertiary amines are more potent inhibitors of the uptake of 5-HT than of NE, whereas the effectiveness of the blockage of uptake of 5-HT and NE is reversed with the secondary tricyclic amines. The data as to alterations in turnover of NE and 5-HT that occurs as a consequence of administration of the tertiary and secondary tricyclic amines is not quite as clear as that for blockage of uptake. But, on the balance, the available information indicates that the turnover of 5-HT is slowed by the tertiary tricyclic amines, whereas the turnover of NE is increased by the secondary tricyclic amines.

Table 20-2. The effect of secondary and tertiary tricyclic antidepressants on DA, NE and 5-HT uptake and turnover.

Amine	Blockade of Uptake		Effects on Amine Turnover	
	Tertiary Tricyclic Amine (viz Imipramine)	Secondary Tricyclic Amine (viz Desipramine)	Tertiary Tricyclic Amine (viz Imipramine)	Secondary Tricyclic Amine (viz Desipramine)
DA	No Effect	No Effect	No Effect	No Effect
NE	+	+ + +	—	Increases
5-HT	+ + +	+	Slows	—

Given the above findings, one might reasonably conclude that both noradrenergic and serotonergic, but not dopaminergic brain systems, are involved in depressive disorders. This is essentially the position that Carlsson has taken, in that he posits a role for 5-HT in regulating mood and for NE in regulating drive energy and activity. While such a view cannot, of course, be disproved and must be respected until definitive data is available, we feel that if one examines the situation a bit more closely, the evidence favors an involvement of noradrenergic rather than the serotonergic systems in the genesis of depression. The reasoning behind this position briefly is as follows. It is by now well-established that the tertiary tricyclic amine, imipramine, following administration to animals, undergoes rapid demethylation to form the secondary amine, desipramine. Direct experimental evidence has been obtained from a human subject who died as a result of an accidental overdose of imipramine, indicating that significant quantities of the demethylated product were formed. There are species differences, in that rat and man rapidly metabolize imipramine to desipramine, which is then itself metabolized less rapidly, with the net result being that there is a gradual accumulation of desipramine in tissues. In those animals in which rapid metabolism of imipramine, and the less rapid metabolism of the demethylated product, do not occur, one finds that the ability of the tertiary amine to antagonize the effects of reserpine, or the experimental drug benzoquinolizine, is less marked. Further, the available data on turnover

would indicate that while the secondary tricyclic amines may increase NE synthesis, there is a decrease in turnover of 5-HT induced by the tertiary tricyclic amines. A slowing of turnover, accompanied by a blockage of reuptake, may produce a system in which quantities of amine available at receptors is the same as that found before drug treatment. An increase in synthesis, accompanied by blockage of reuptake as probably occurs with NE as a consequence of the tricyclic drug administration, should, on the other hand, make more amine available to the receptor. This data, particularly that dealing with the metabolism of the tricyclic drugs, suggests that the secondary tricyclic amine is the therapeutic agent. Given the data as summarized in Table 20-2, it is inferred that the noradrenergic rather than the serotonergic brain systems are primarily involved with depression. However, there are obvious problems with this reasoning, in that small amounts of the tertiary amine could still be available for changing the 5-HT systems. Against this argument is the fact that there is now a great wealth of clinical data available as to the effects of desipramine per se in the treatment of depressive states. The available information indicates that desipramine is as effective as imipramine in the treatment of depressive disorders. Since it is known that N-methylation of desipramine (to form imipramine) does not occur to any significant degree, it is suggested that the clinical effectiveness (in terms of mood and activity) of this secondary tricyclic amine, when coupled with its effects upon NE versus 5-HT systems (see Table 20-2)

provides perhaps the most compelling argument that the principal systems involved in the depressive disorders are of the noradrenergic type.

Given the above reasoning, the next question is: Is it possible that a particular central, noradrenergic system is involved in the genesis of depression? The data relative to this point are very soft and nonspecific, but a few comments can be made. In general, the studies of changes in histochemical fluorescence of NE systems, as induced by pharmacological manipulations, do not indicate that the tricyclic amines of the secondary type are exerting their effects on any one of the specific NE systems. This, of course, may be a function of the investigative use of a drug that generally blocks the NE neuronal pump mechanism.

In summary, it is suggested that specific brain NE systems are intimately related to the genesis of depression. Studies of the regulation of behavior (including depressive mood and psychomotor activity) by specific NE systems can be expected to emerge in the next few years and this new information will undoubtedly be of major value, whatever the demonstrated relationship of NE systems to depression may ultimately be.

Aminergic Brain Systems and Schizophrenia

The data as to the specificity of action of neuroleptics on aminergic brain systems are somewhat less clear than are those for the tricyclic

antidepressant drugs, but in some areas there has been remarkable agreement. We feel that there is heuristic value in suggesting that specific aminergic systems may be involved in the production of psychotic states, particularly schizophrenia. Neuroleptics that are clinically effective, whatever their chemical structure, block central DA receptors and increase the turnover of this amine in dopaminergic systems. This increase in DA turnover, as a consequence of neuroleptic drug treatment, has been demonstrated by studies that have measured metabolite accumulation, changes in amine level following enzyme inhibition, alterations in histochemical fluorescence in dopaminergic systems, formation of DA from labeled precursors, or the rate of the disappearance of labeled DA from the brain. The data from function-type studies are generally consistent and can be reasonably interpreted as indicating that many of the potent neuroleptics block central DA receptors. The mechanism by which DA receptor blockage is linked to increased DA turnover per se needs further investigation. In the aggregate the available data clearly indicate that neuroleptic drugs have marked effects upon brain DA systems.

The neuroleptic agents may also affect noradrenergic systems, but it would seem that this action is not crucial to the drugs' clinical effectiveness. There is disagreement as to the neuroleptic's ability to produce increased NE turnover. Some investigators find no effects, whereas others do. In those cases where changes in NE turnover have occurred as a consequence of

treatment with the neuroleptics, the magnitude of the effect has been modest, inconsistent, and frequently occurred only at higher doses. The Swedish group of investigators, who in general have produced the affirmative data as to increased NE turnover after neuroleptics, have also produced data indicating that some potent neuroleptics are without effect on NE turnover. Function-type studies indicate that while some neuroleptics block both DA and NE receptors, viz., chlorpromazine, others block principally or only DA receptors, viz., fluphenazine, spiroperidol, pimozide. Most importantly, those drugs which chiefly block DA receptors are among the more potent, at least in terms of dosage, of the neuroleptics. Phrased differently, the effectiveness of the neuroleptic drugs seems to be more related to their effects upon DA than to noradrenergic systems.

In the aggregate then, it is felt that a good case can be made for the hypothesis that dopaminergic systems, and not noradrenergic systems, are involved in the genesis of psychotic behavior that can be effectively treated with the neuroleptic drugs.

The neuroleptic drugs alter brain 5-HT systems, but this area has been less extensively studied; and the interpretation of the available data is made difficult by variations in results as a function of dose, and questions as to mechanisms by which the drugs produce their effects.

Finally, the question arises as to the possibility that a *specific* dopaminergic system may be involved in the production of psychotic states. As before, sufficient data to even modestly approach this question is unavailable. Histochemical-fluorescent techniques do not indicate a differential action of the neuroleptics on the meso-limbic or nigro-striatal brain DA systems. The future development of drugs that block DA receptors, but are without extrapyramidal side effects, may help with this issue, in that the retention or loss of the antipsychotic properties may allow one to differentiate between the neuroleptic activity being mediated via nigro-striatal versus meso-limbic DA systems. In this respect it is of interest that Bobon et al. reported that pimozide produces a low incidence of Parkinsonism-like side effects, but caution is needed, in that in experimental animals this drug clearly blocks DA receptors in the striatum and is concentrated in the caudate nucleus.

Bibliography

Aghajanian, G. and F. Bloom. "Electron Microscopic Localization of Tritiated NE in Rat Brain: Effect of Drugs," *J. Pharmacol. Exp. Ther.,* 156 (1967), 407-416.

Aghajanian, G., F. Bloom, and M. Sheard. "Electron Microscopy of Degeneration Within the Serotonin Pathway of Rat Brain," *Brain Res.,* 13 (1969), 26673.

Ahlskog, J. and B. Hoebel. "Hyperphagia Resulting From Selective Destruction of an Ascending Adrenergic Pathway in the Rat Brain," *Fed. Abstr.,* 1002 (1972), 397. Also personal communication.

Alpers, H. S. and H. Himwich. “An In Vitro Study of the Effects of Tricyclic Antidepressant Drugs on the Accumulation of C-5HT by Rabbit Brain,” *Biol. Psychiatry,* 1 (1969), 81-85.

Anden, N., S. Butcher, H. Corrodi et al. “Receptor Activity and Turnover of Dopamine and Noradrenaline after Neuroleptics,” *Eur. J. Pharmacol.,* 11 (1970), 303-314.

Anden, N., H. Corrodi, K. Fuxe et al. “Increased Impulse Flow in Bulbospinal NA Neurons Produced by CA Receptors Blocking Agents,” *Eur. J. Pharmacol., 2 (1967)*, 59-64.

Anden, N., H. Corrodi, K. Fuxe et al. “Evidence for a Central NE Receptor Stimulation by Clonidine,” *Life Sci.,* 9 (1970), 513-523.

Anden, N., A. Dahlstrom, K. Fuxe et al. “The Effect of Haloperidol and Chlorpromazine on the Amine Levels of Central Monoamine Neurons,” *Acta Physiol. Scand.,* 68 (1966), 419-420.

Anden, N., A. Dahlstrom, K. Fuxe et al. “Further Evidence for the Presence of Nigro-Neostriatal DA Neurons in the Rat,” *Am. J. Anat.,* 116 (1965), 329-333.

----. “Mapping Out CA and 5-HT Neurons Innervating the Telencephalon and Diencephalon,” *Life Sci.,* 4 (1965), 1275-1291.

----. “Functional Role of the Nigro-Neostriatal Dopamine Neurons,” *Acta Pharmacol. Toxicol.,* 24 (1966), 263-274.

Anden, N., A. Dahlstrom, K. Fuxe et al. “Ascending Monoamine Neurons to the Telencephalon and Diencephalon,” *Acta Physiol. Scand.,* 67 (1966), 313-326.

Anden, N. E., B. E. Roos, and B. Werdinius. “Effects of Chlorpromazine, Haloperidol and Reserpine on the Levels of Phenolic Acids in Rabbit Corpus Striatum,” *Life Sci.,* 3 (1964), 149.

Arnfred, T. and A. Randrup. “Cholinergic Mechanisms in Brain Inhibiting Amphetamine Induced Stereotyped Behavior,” *Acta Pharmacol. Toxicol.,* 26 (1968), 384-394.

Bickel, M. H. “Metabolism and Structure-Activity Relationships of Thymoleptic Drugs,” in S. Garattini and M. N. G. Dukes, eds., *Antidepressant Drugs*, pp. 3-9 Milan: Excerp. Med.

Found., 1966.

Bickel, M. H. and B. B. Brodie. "Structure and Antidepressant Activity of Imipramine Analogues," *Int. J. Neuropharmacol,* 3 (1964), 611-621.

Bjarklund, A., B. Ehinger, and B. Falck. "A Method for Differentiating DA from NE in Tissue Sections by Microspectroluorometry," *J. Histochem. Cytochem.,* 16 (1968), 263-270.

Blackburn, K. T., D. C. Funch, and R. J. Merrills. "5-HT Uptake by Rat Brain In Vitro," *Life Sci.,* 6 (1967), 1653-1663.

Bobon, J., J. Collard, A. Pinchard et al. "Neuroleptiques a longue durée d'action Etude pilote du pimozide (R6238)," *Acta Neurol. Belg.,* 68 (1968), 137-153.

Brodie, B. B., E. Costa, A. Groppetti et al. "Interaction Between Desipramine, Tyramine, and Amphetamine at Adrenergic Neurones," *Br. J. Pharmacol.,* 34 (1968), 648-658.

Bunney, W. E., Jr. and J. M. Davis. "Norepinephrine in Depressive Reactions," *Arch. Gen. Psychiatry,* 13 (1965), 483-494.

Burkard, W. P., K. F. Gey, and A. Pletscher. "Activation of Tyrosine Hydroxylation in Rat Brain In Vivo by Chlorpromazine," *Nature,* 213 (1967), 732.

Carlsson, A. "Structural Specificity for Inhibition of" [C]-5-hydroxytryptamine Uptake by Cerebral Slices," *J. Pharm. Pharmacol.,* 22 (1970), 729-732.

Carlsson, A., H. Corrodi, K. Fuxe et al. "Effect of Antidepressant Drugs on the Depletion of Intraneuronal Brain 5-hydroxytryptamine Stores Caused by 4-Methyl-a-Ethyl-Meta-Tyramine," *Euro J. Pharmacol.,* 5 (1969), 357-366.

----. "Effects of Some Antidepressant Drugs on the Depletion of Intraneuronal Brain Catecholamine Stores Caused by 4,a-Dimethyl-Meta-Tyramine," *Eur. J. Pharmacol,* 5 (1969), 367-373.

Carlsson, A., K. Fuxe, B. Hamberger et al. "Biochemical and Histochemical Studies on the Effects of Imipramine-Like Drugs and (+)—Amphetamine on Central and Peripheral

Catecholamine Neurons," *Acta Physiol. Scand.,* 67 (1966), 481-497.

Carlsson, A. and M. Lindquist. "Effect of CPZ on Haloperidol on Formation of 3-Methoxytyramine and Normetanephrine in Mouse Brain," *Acta Pharmacol. Toxicol.,* 20 (1963), 140-144.

Cools, A. and J. Van Rossum. "Caudal Dopamine and Stereotype Behavior of Cats," *Arch. Int. Pharmacodyn.,* 187 (1970), 163-173.

Corrodi, H. "Decreased Turnover in Central 5-HT Nerve Terminals Induced by Antidepressant Drugs of the Imipramine Type," *Eur. J. Pharmacol.,* 7 (1969), 56-59.

Corrodi, H. and K. Fuxe. "The Effect of Imipramine on Central Monoamine Neurons, *J. Pharm. Pharmacol,* 20 (1968), 230-231.

Corrodi, H., K. Fuxe, and T. Hokfelt. "The Effect of Neuroleptics on the Activity of Central Catecholamine Neurons," *Life Sci.,* 6 (1972), 767-774.

Crow, T. "A Map of the Rat Mesericephalon for Electrical Self-Stimulation," *Brain Bes.,* 36 (1972), 265-273.

Crow, T., P. Spear, and G. Arbuthnotl. "Intracranial Self-Stimulation With Electrodes in the Region of the Locus Coeruleus," *Brain Res.,* 36 (1972), 275-287.

Dahlstrom, A. and K. Fuxe. "Evidence for the Existence of Monoamine Containing Neurons in the CNS: I. Demonstration of Monoamines in the Cell Bodies of Brain Stem Neurons," *Acta Physiol. Scand.,* Suppl., 232 (1965), i-55-

Da Prada, M. and A. Pletscher. "Acceleration of the Cerebral Dopamine Turnover by Chlorpromazine," *Experientia,* 22 (1966), 465-466.

Dingell, J. V., Sulser, F., and J. R. Gillette. "Species Differences in the Metabolism of Imipramine and Desmethy-limipramine (DMI)," *J. Pharmacol. Exp. Ther.,* 143 (1964), 14-22.

Domino, E. and M. Olds. "Cholinergic Inhibition of Self-Stimulation Behavior," *J. Pharmacol. Exp. Ther.,* 211 (1968), 164-202.

Falck, B. “Observations on the Possibilities of the Cellular Localization of Monoamines by a Fluorescence Method,” *Acta Physiol Scand.,* Suppl. 197, (1962), 1-25.

Fog, R., A. Randrup, and H. Pakkenburg. “Neuroleptic Action of Quarternary Chlorpromazine and Related Drugs Injected into Various Brain Areas in Rats,” *Psychopharmacologia,* 12 (1968), 428-432.

Fuxe, K. “The Distribution of Monoamine Terminals in the CNS,” *Acta Physiol. Scancl.,* Suppl. 247, (1965), 38-86.

Fuxe, K. and T. Hokfelt. “Catecholamines in the Hypothalamus and the Pituitary Gland,” in W. Ganong and L. Martini, eds., *Frontiers in Neuroendocrinology,* pp. 47- New York: Oxford University Press, 1969.

Fuxe, K., T. Hokfelt, and U. Ungerstedt. “Localization of Indolealkylamines in the CNS,” *Adv. Pharmacol.,* 6 (1968), 235-251.

----. “Central Monoaminergic Tracts,” *Princ. Psychopharmacol*., 6 (1970), 87-96.

----. “Morphological and Functional Aspects of Central Monoamine Neurons,” *Int. Rev. Neurobiol.,* 13 (1970), 93-126.

Fuxe, K. and U. Ungerstedt. “Histochemical Studies of the Effect of (+) — Amphetamine, Drugs of the Imipramine Group, and Tryptamine on Central Catecholamine and 5-HT Neurons After Intraventricular Injection of Catecholamines and 5-HT,” *Eur. J. Pharmacol.,* 4 (1968), 135-144.

Gey, K. F. and A. Pletscher. “Influence of Chlorpromazine and Chlorprothixene on the Cerebral Metabolism of 5-Hydroxy-tryptamine, Norepinephrine and Dopamine,” *J. Pharmacol. Exp. Ther.,* 133 (1961), 18-24.

----. “Alteration of Turnover of C-Catecholamines in Rat Brain by Chlorpromazine,” *Experientia,* 24 (1968), 335-336.

Giacalone, E. and W. Kostowski. “5-Hydroxytryptamine and 5-Hydroxyindole-acetic Acid in Rat Brain: Effect of Some Psychotropic Drugs and Electrical Stimulation of Various

Forebrain Areas," *Br. J. Pharmacol.,* 34 (1968), 662-663.

Gillette, J. R., J. V. Dingell, and G. P. Quinn. "Physiological Distribution and Metabolism of Imipramine (Tofranil)," *Fed. Proc.,* Part I, 19 (1960), 137.

Gillette, J. R., J. V. Dingell, F. Sulser et al. "Isolation from Rat Brain of a Metabolic Product, Desmethylimipramine, that Mediates the Antidepressant Activity of Imipramine (Tofranil)," *Experientia,* 17 (1961), 417-418.

Glowinski, J. "Release of Monoamines In Central Nervous Systems," in H. J. Schumann and G. Kroneberg, eds., *New Aspects of Storage and Release Mechanisms of CA,* p. 301. Berlin: Springer-Verlag, 1970.

Glowinski, J. and J. Axelrod. "Inhibition of Uptake of Tritiated-Noradrenaline in the Intact Rat Brain by Imipramine and Structurally Related Compounds," *Nature,* 204 (1964),.1318-1319.

Glowinski, J., J. Axelrod, and L. L. Iverson. "Regional Studies of Catecholamines in the Rat Brain. IV. Effects of Drugs on the Disposition and Metabolism of H-NE and H-Dopamine," *J. Pharmacol. Exp. Ther.,* 153 (1966), 30-41.

Guldberg, H. C. and C. Yates. "Effects of Chlorpromazine on the Metabolism of Catecholamines in Dog Brain," *Br. J. Pharmacol,* 36 (1969), 535-548.

Gumulka, W., R. Samanin, and L. Valzelli. "Effect of Chlorpromazine on 5-Hydroxytryptamine Metabolism in Hippocampal Stimulated Rats," *Eur. J. Pharmacol,* 12 (1970), 276-279.

Häggendal, T. and B. Hamberger. "Quantitative In Vivo Studies on Noradrenaline Uptake and Its Inhibition by Amphetamines, Desimipramine and Chlorpromazine," *Acta Physiol. Scand.,* 70 (1967), 277-280.

Heller, A. and R. Moore. "Effect of CNS Lesions on Brain Monoamines in the Rat," *J. Pharmacol. Exp. Ther.,* 150 (1965), 1-9.

Herrmann, B. and R. Pulver. "Der Stoffwechsel Des Psychopharmakons Tofranifl," *Arch. Int.*

Pharmacodyn, 126 (1960), 454-468.

Himwich, W., J. Davis, K. Leiner et al. "Biochemical Effects of Haloperidol in Different Species," *Biol. Psychiatry,* 2 (1970), 315-319.

Igic, R., P. Stern, and E. Basagic. "Changes in Emotional Behavior After Application of Cholinesterase Inhibitor in the Septal and Amygdala Region," *Neuropharmacology,* 9 (1970), 73-75.

Janowsky, D., J. Davis, M. El-Yousef et al. "Physostigmine Reversal of Methyl Phenidate Induced Stereotyped Behavior." Submitted for publication, 1972.

Janowsky, D., M. El-Yousef, and J. Davis. "Cholinergic Adrenergic Balance and Affective Disorders," Annu. Meet. Am. Psychiatr. Assoc., Dallas, Texas, 1972.

Janowsky, D., M. El-Yousef, J. Davis et al. "Cholinergic Reversal of Manic Symptoms, *Lancet,* 1 (1972), 1236-1237.

Janssen, P. A. J., C. J. E. Niemegeers, K. H. L. Schellekens et al. "Pimozide, a Chemically Novel Highly Potent and Orally Long-Acting Neuroleptic Drug. Parts I, II, and III," *Arzneim. Forsch.,* 18, (1968), 261-287.

Janssen, P. A. J., C. J. E. Niemegeers, K. H. L. Schellekens et al. "Is it Possible to Predict the Clinical Effects of Neuroleptic Drugs (Major Tranquillizers) From Animal Data?" *Arzneim. Forsch.,* 17 (1967), 841-854.

Jonsson, G. The Formaldehyde Fluorescence Method for the Histochemical Demonstration of Biogenic Monamines, pp. 1-50. Stockholm: Ivar Haeggstroms Tryckeri AB, 1967.

Jouvet, M. "Neurophysiology of the States of Sleep," *Physiol. Rev.,* 47, (1967), 117-177.

----. "Neuropharmacology of Sleep," in Efron, ed., *Psychopharmacology*, *a Review of Progress 1957-1967,* pp. 523-540. Washington: U.S. Govt. Print. Off., 1968.

Jung, O. and E. Boyd. "Effects of Cholinergic Drugs on Self-Stimulation Response Rates in Rats." *Am. J. Physiol.,* 210, (1966), 432-434.

Klein, D. F. and J. M. Davis. *Diagnosis and Drug Treatment of Psychiatric Disorders*, p. 480. Baltimore: Williams & Wilkins, 1969.

Koelle, G. and J. Friedenwald. "A Histochemical Method for Localizing Cholinesterase Activity," *Proc. Soc. Exp. Biol. Med.,* 70 (1949), 617-622.

Kostowski, W. and E. Giacalone. "Stimulation of Various Forebrain Structures and Brain 5HT, 5HIAA and Behavior in Rats," *Eur. J. Pharmacol.,* 7 (1969), 176-179.

Kostowski, W., E. Giacalone, S. Garattini et al. "Studies on Behavioral and Biochemical Changes in Rats After Lesion of Midbrain Raphe," *Eur. J. Pharmacol.,* 4 (1968), 371-376.

----. "Electrical Stimulation of Midbrain Raphe: Biochemical, Behavioral, and Bioelectric Effects," *Eur. J. Pharmacol.,* 7 (1969), 170-175.

Kuhur, M., R. Roth, and G. Aghajanian. "Selective Reduction of Tryptophan Hydroxylase Activity in Rat Forebrain After Midbrain Raphe Lesions," *Brain Res.,* 35 (1971), 167-176.

Laverty, R. and D. F. Sharman. "Modification by Drugs in the Metabolism of 3, Dehydroxyphenylethylamine, Noradrenaline, and 5-Hydroxytryptamine in the Brain," *Br. J. Pharmacol.,* 24 (1965), 759-772.

Leitz, F. H. "Mechanisms by Which Amphetamine and Desipramine Inhibit the Metaraminol-Induced Release of Norepinephrine From Sympathetic Nerve Endings in Rat Heart," *J. Pharmacol. Exp. Ther.,* 173 (1970), 152-157.

Lewis, P. and C. Shute. "The Cholinergic Limbic System," *Brain,* 90 (1967), 521-540.

Mandell, A. J., D. S. Segal, T. Kuczenski et al. "Some Macromolecular Mechanisms in CNS Neurotransmitter Pharmacology and Their Psychobiological Organizations," in J. McGough ed., *Brain Mechanisms and Behavior.* New York: Plenum, forthcoming.

Margules, D. "Localization of the Anti-Punishment Actions of NE and Atropine in Amygdala and Entopeduncular Nucleus of Rats," *Brain Res.,* 35 (1971), 177-184.

Margules, D. and L. Stein. "Cholinergic Synapses of a Periventricular Punishment System in the

Medial Hypothalamus," *Am. J. Physiol*., 17 (1969), 475-480.

----. "Cholinergic Synapses in the Ventromedial Hypothalamus for the Suppression of Operant Behavior by Punishment and Satiety," *J. Comp. Physiol. Psychol.,* 67 (1969), 327-335.

Maxwell, R. A., E. Chaplin, S. B. Eckhardt et al. "Conformational Similarities Between Molecular Models of Phenethylamine and of Potent Inhibitors of the Uptake of Tritiated Norepinephrine by Adrenergic Nerves in Rabbit Aorta," *J. Pharmacol. Exp. Ther.,* 173 (1970), 158-165.

Maxwell, R. A., S. B. Eckhardt, and G. Hite. "Kinetic and Thermodynamic Considerations Regarding the Inhibition by Tricyclic Antidepressants of the Uptake of Tritiated Norepinephrine by the Adrenergic Nerves in Rabbit Aortic Strips," *J. Pharmacol. Exp. Ther.,* 171 (1970), 62-69.

Maxwell, R. A., P. D. Keenan, E. Chaplin et al. "Molecular Features Affecting the Potency of Tricyclic Antidepressants and Structurally Related Compounds as Inhibitors of the Uptake of Tritiated Norepinephrine by Rabbit Aortic Strips. *J. Pharmacol. Exp. Ther.,* 166 (1969), 320-329.

McMahon, R. E., F. J. Marshall, H. W. Culp, et al. "The Metabolism of Nortriptyline-N-Methyl-C in Rats," *Biochem. Pharmacol.,* 12, (1963), 1207-1217.

Meek, J. and B. Werdinius. "Hydroxytryptamine Turnover Decreased by the Antidepressant Drug Chlorimipramine," *J. Pharm. Pharmacol*., 22, (1970), 141-143.

Moore, R., R. Bhatnagar, and A. Heller. "Anatomical and Chemical Studies of a Nigro-Neostriatal Projection in the Cat," 100. *Brain Res*., 30, (1971), 119-135.

Moore, R., A. Bjorklund, and U. Stenevi. "Plastic Changes in the Adrenergic Innervation of the Rat Septal Area in Response to Denervation," *Brain Res*., 33, (1971), 13-35.

Neff, N. H. and E. Costa. "Effect of Tricyclic Antidepressants and Chlorpromazine on Brain Catecholamine Synthesis," in S. Garattini and M. N. G. Dukes, eds., *Antidepressant Drugs.* Milan: Excerp. Med. Found., 1966.

Nyback, H., Z. Borgecki, and G. Sedvall. “Accumulation and Disappearance of Catecholamines Formed From Tyrosine C in Mouse Brain; Effect of Some Psychotropic Drugs,” *Eur. J. Pharmacol.,* 4, (1968), 395-403.

Nyback, H. and G. Sedvall. “Effect of Chlorpromazine on Accumulation and Disappearance of Catecholamines Formed 104. From C-Tyrosine in Brain,” *J. Pharmacol. Exp. Ther.,* 162 (1968), 294-301.

----. “Further Studies on the Accumulation and Disappearance of Catecholamines Formed From Tyrosine C in Mouse Brain. Effect of Some Phenothiazine Analogues,” *Eur. J. Pharmacol.,* 10, (1970), 193-205.

Nyback, H., G. Sedvall, and I. J. Kopin. “Accelerated Synthesis of Dopamine-C From Tyrosine-C in Rat Brain After Chlorpromazine,” *Life Sci.,* 6 (1967), 2307-2312.

Olds, M. and J. Olds. “Approach-Avoidance Analysis of Rat Diencephalon,” *J. Comp. Neurol.,* 120 (1963), 259-295.

Palaic, D., I. Page, and P. Khairallah. “Uptake and Metabolism of [C] Serotonin in Rat Brain,” *J. Neurochem.,* 14 (1967), 63-69.

Poirier, L., E. McGeer, L. Larochelle et al. “The Effect of Brain Stem Lesions on Tyrosine and Tryptophan Hydroxylases in Various Structures of the Telencephalon of the Cat,” *Brain Res.,* 14 (1969), 147-155.

Pradham, S. and S. Dutta. “Central Cholinergic Mechanism and Behavior,” *Int. Rev. Neurobiol.,* 14 (1971), 173-231.

Randrup, A., I. Munkvard, and P. Udsen. “Adrenergic Mechanisms and Amphetamine Induced Abnormal Behaviors,” *Acta Pharmacol. Toxicol.,* 20 (1963), 145-157.

Ross, S. B. and A. L. Renyi. “Inhibition of the Uptake of Tritiated Catecholamines by Antidepressant and Related Agent,” *Eur. J. Pharmacol.,* 2 (1967), 181-186.

----. “Inhibition of the Uptake of Tritiated 5-Hydroxytryptamine in Brain Tissue,” *Eur. J. Pharmacol.,* 7 (1969), 270-277.

Salama, A. I., J. R. Insalaco, and R. A. Maxwell. "Concerning the Molecular Requirements for the Inhibition of the Uptake of Racemic H-Norepinephrine into Rat Cerebral Cortex Slices by Tricyclic Antidepressants and Related Compounds," *J. Pharmacol. Exp. Ther.,* 173 (1971), 474-481.

Schanberg, S. M., J. J. Schildkraut, and I. J. Kopin. "The Effects of Psychoactive Drugs 011 Norepinephrine H Metabolism in Brain," *Biochem, Pharmacol.,* 16 (1967), 393-399.

Schildkraut, J. J. "The Catecholamine Hypothesis of Affective Disorders: A Review of Supporting Evidence," *Am, J. Psychiatry,* 122 (1965), 509-522.

----. "Changes in Norepinephrine-H (NE-H) Metabolism in Rat Brain After Acute and Chronic Administration of Tricyclic Antidepressants," *Fed. Proc.,* 28 (1969), 795.

Schildkraut, J. J. and S. S. Kety. "Biogenic Amines and Emotion, *Science,* 156 (1967), 21-30.

Schildkraut, J. S. Schanberg, G. Breese et al. "Effects of Psychoactive Drugs on the Metabolism of Intracisternally Administered Serotonin in Rat Brain," *Biochem. Pharmacol,* 18 (1969), 1971-1978.

Schildkraut, J., A. Winokur, and C. Applegate. "Norepinephrine Turnover and Metabolism in Rat Brain After Long-Term Administration of Imipramine," *Science,* 168 (1970), 867-869.

Schildkraut, J., A. Winokur, P. R. Draskoczy et al. "Changes in NE Turnover in Rat Brain During Chronic Administration of Imipramine and Protryptyline: A Possible Explanation for the Delay in Onset of Clinical Antidepressant Effects," *Am. J. Psychiat.,* 127 (1971), 1032-1039.

Schubert, J., H. Nyback, and G. Sedvall. "Effect of Antidepressant Drugs on Accumulation and Disappearance of Monoamines Formed In Vivo From Labelled Precursors in Mouse Brain," *J. Pharm. Pharmacol.,* 22 (1970), 136-138.

Shute, C. and P. Lewis. "The Ascending Cholinergic Reticular System," *Brain,* 90 (1967). 497-520.

Sladek, J. R., Jr. "Differences in the Distribution of Catecholamine Varicosities in Cat and Rat

Reticular Formation," *Science,* 174 (1971), 410-412.

Smith, D., M. King, and B. Hoebel. "Lateral Hypothalamic Control of Killing: Evidence for a Cholinoceptive Mechanism," *Science,* 167 (1970), goo-901.

Snyder, S. H., K. M. Taylor, J. T. Coyle et al. "The Role of Brain Dopamine in Behavioral Regulation and the Actions of Psychotropic Drugs", *Am. J. Psychiat.,* 127 (1970), 199-207.

Stark, P. and E. Boyd. "Effects of Cholinergic Drags on Hypothalamic Self-Stimulation Response Rates in Dogs", *Am J. Psychiat.,* 205, (1963), 745-748.

Steinberg, M. I. and C. B. Smith. "Effects of Desmethylimipramine and Cocaine on the Uptake, Retention and Metabolism of H-Tyramine in Rat Brain Slices," *J. Pharmacol. Exp. Ther.,* 173 (1970), 176-192.

Sulser, F., M. L. Owens, S. J. Strada et al. "Modification by Desipramine (DMI) of the Availability of Norepinephrine Released by Reserpine in the Hypothalamus of the Rat In Vivo," *J. Pharmacol. Exp. Ther.,* 168 (1969), 272-286.

Tagliamonte, A., P. Tagliamonte, and G. L. Gessa. "Reserpine-Like Action of Chlorpromazine on Rabbit Basal Ganglia," *J. Neurochem.,* 17 (1970), 733-738.

Ungerstedt, U. "Stereotaxic Mapping of the Monoamine Pathways in the Rat Brain," *Acta Physiol. Scand.,* Suppl. 367 (1971), 1-48.

----. "Striated DA Release After Amphetamine or Nerve Degeneration Revealed by Rotational Behavior," *Acta Physiol. Scand.,* Suppl. 367, (1971), 49-68.

----. "Adipsia and Aphagia After OH-DA Induced Degeneration of the Nigro-Striatal DA System," *Acta Physiol. Scand.,* Suppl. 367 (1971), 95-122.

Ungerstedt, U., L. Butcher, S. Butcher et al. "Direct Chemical Stimulation of Dopaminergic Mechanisms in the Neostriatum of the Rat," *Brain Res.,* 14 (1969), 467-471.

Wise, C. and L. Stein. "Facilitation of Brain Self-Stimulation by Central Administration of NE," *Science,* 163 (1969), 299-301.

Notes

1 Abbreviations used in this chapter are: DA, dopamine; NE, norepinephrine; 5-HT, serotonin; ACh, acetylcholine; NM, normetanephrine; HVA, homovanillic acid; Dopa, dihydroxyphenylalanine; 5-HIAA, 5-hydroxyindoleacetic acid.

2 ACh—a quaternary ammonium compound, not strictly classified as an amine, is commonly included among the monoamine neurotransmitters.

3 They may, however, be quite helpful in decreasing the anxiety that is an integral part of some depressive states and, in fact, many clinicians prefer to give these drugs in combination with an antidepressant when anxiety is an important component of the clinical picture.

4 With apologies to George Beadle and E. L. Tatum.

5 There are, of course, many other studies that indicate that the functional amounts of brain amines, particularly NE, are involved in the affective disorders, and these have been well summarized elsewhere.104' The focus in this chapter, however, is on the possibility that specific amine systems are involved in the genesis of depression. Hence cited references and speculations are directed toward this issue of specificity.