American Handbook of Psychiatry

Basic Neuropharmacology

George K. Aghajanian

Basic Neuropharmacology

George K. Aghajanian

e-Book 2015 International Psychotherapy Institute

From *American Handbook of Psychiatry: Volume 6* edited by Silvano Arieti

Table of Contents

BASIC NEUROPHARMACOLOGY

In the past two decades, with the advent of the large scale use of drugs in psychiatric practice, the field of neuropharmacology has inevitably become closely linked to that of psychiatry. There has been an increasing involvement of psychiatrists as partners in basic as well as clinical neuro-pharmacological research. These developments are leading to a reversal of the previous trend toward an isolation of psychiatry from the biological sciences.

Basic neuropharmacology can be defined as the study of the actions and mechanisms of action of drugs on the nervous system. In a broad sense, efforts toward the elucidation of mechanisms of neurotropic drugs action depend for their success upon the growing sophistication of theory and methodology in neurobiology. At present, basic information about the action of drugs at multicellular, cellular, subcellular, microchemical, and molecular levels is approaching the point where we can soon expect a coherent and highly specific analysis of the mode of action of almost every major drug of interest to psychiatry. These promising developments hopefully will lead to a transition from a "cookbook" use of drags to a rational pharmacotherapy in the future.

A major emphasis of research in neuropharmacology has been upon presumptive transmitter substances and their vicissitudes. If the chemical transmission of impulses across synaptic junctions represents the common

coin of communication in the central nervous system, then the alteration of such transmission is likely to represent a key site for the action of drugs that alter neural function. The specificity of drug action would then depend upon which synapse or transmitter is affected and the direction of the change (i.e., facilitation or inhibition). Although superficially such a formulation seems quite simple, on a practical level the study of transmitter substances and synaptic transmission in the mammalian central nervous system poses formidable technical problems for the neurobiologist and pharmacologist. The amounts of the transmitters may be very low (e.g., 10^{-6} to 10^{-7} g/kg of brain) the neurons under study exceedingly small (ten to twenty microns in diameter) and the synapses difficult to isolate. It will therefore be illuminating to examine first some basic neural mechanisms and the methods employed in their study. The economy of this approach is that a few fundamental principles apply to many drugs. The second portion of this review will deal with current concepts of the mode of action of specific classes of therapeutic and nontherapeutic psychotropic drugs.

Mechanisms of Psychotropic Drug Action: Basic Approaches and Principles[1]

Biochemical

Presumably, since drugs are chemical agents, their primary site of action must be some kindred chemical site within the brain. Early on research

on the central effects of neurotropic drugs was largely concerned with processes such as energy metabolism, which were not peculiar to the brain. It was natural to apply to studies on the brain knowledge about general biochemical processes previously gained from research on non-neural tissues. However, this approach has gradually been superseded by studies on substances that are specific for the essential functions of the nervous system. There is a great deal of experimental support for the assumption that in the mammalian brain neurotransmission is mediated by chemical substances, liberated at the nerve endings of one neuron (the *presynaptic cell)* that impinge upon the soma or dendrites of another neuron (the *postsynaptic cell*). Thus, a great deal of attention is being given to the study of effects of psychoactive drugs upon putative transmitters in the brain. Substances in this category include acetylcholine, y-aminobutyric acid, and the monoamines, serotonin (5-hydroxytryptamine), dopamine, and norepinephrine. In general, in order to qualify as a neurotransmitter a substance should be synthesized and stored in the presynaptic neuron, be released upon firing of that neuron, and produce the same physiological action (inhibition or excitation) upon the postsynaptic neurons as activation of the presynaptic nerve. Also, some mechanism for terminating the action of the transmitter must be available. As one might expect, each of these steps in the life cycle of the various candidate central transmitters is undergoing careful scrutiny as a possible site of drug action. While biochemical approaches to each of these processes are

separately discussed, it is important not to lose sight of the fact that the ultimate importance of each step is in relation to its ability to modify synaptic transmission.

Synthesis is the initial stage at which a drug may effect the availability of a transmitter substance. It is generally assumed that when the synthesis of a transmitter is markedly inhibited, the transmission of impulses via this transmitter will be impaired. Similarly, if the synthesis of a transmitter substance is enhanced, then a facilitation of transmission may ensue. On this basis, a search has been underway in recent years for specific inhibitors or enhancers of neurotransmitter synthesis. Although none of the major drugs presently used therapeutically in psychiatry is believed to have as its primary action an alteration in synthesis (see below) there are a number of substances of this type whose actions are being explored in research studies in both animals and humans. One of these is parachlorophenylalanine, a selective depeletor of serotonin that acts by inhibiting tryptophan hydroxylase, the initial enzyme involved in the synthesis of serotonin from dietary tryptophan. The availability of this drug has prompted a multitude of research studies on the possible physiological function of serotonin. These have included the interesting hypothesis that serotonin serves to mediate sleep mechanisms in the brain. Another is alpha-methyl-p-tyrosine, a selective inhibitor of tyrosine hydroxylase, the limiting enzyme in the synthesis of catecholamines. This drug has been found to exacerbate some depressions in humans and to

produce a state resembling depression in monkeys. Conversely, L-3,4-dihydroxyphenylalanine (L-Dopa) which increases brain catecholamine synthesis, has been found to induce manic episodes in bipolar depressive patients. Such studies have implications for both the mechanism of action of psychotropic drugs and for theories about possible biological factors in these disease states. Moreover, this work underlines the potential influence of altering the rate of neurotransmitter synthesis. In the field of neurology, this strategy has led to the introduction of L-Dopa in the treatment of Parkinson's disease. Autopsy material from patients who died with this disease revealed a marked lowering of dopamine in portions of the extra-pyramidal system. On this basis it was reasoned that a deficiency in dopamine may account for the motor disturbance seen in this condition. Clinical trials with L-Dopa, the immediate precursor of dopamine, gave rise to dramatic therapeutic results that are now well known. A parallel instance in psychiatry (i.e., of a drug producing a clear-cut therapeutic effect by altering the synthesis of a neurotransmitter) remains a possibility for the future.

The *storage* of neurotransmitters is believed to occur largely within synaptic vesicles. The latter are small membrane-bound structures that are clustered at the presynaptic terminals. Only a very small percentage (much less than 1 percent) of the total store is released with each nerve impulse. However, depletion of stores can interfere with the effective release of transmitter by nerve impulses. None of the therapeutic or even

nontherapeutic drugs commonly used at this time acts primarily through this mechanism, but drugs that deplete stores of transmitter substances are nevertheless of considerable historical interest. In the mid 1950s, Brodie and his coworkers discovered that the drug reserpine, derived from the Indian plant *Rauwolfia serpentinia,* markedly reduced brain stores of serotonin. Soon afterwards, it was found that catecholamines in the brain were also depleted. Such a depletion of stores within the nerve terminals is sometimes referred to as "intraneuronal release," which is to be distinguished from "extraneuronal release" (i.e., release from the nerve endings onto a postsynaptic cell). Reserpine was used as a tranquilizer to a limited extent during that period (i.e., 1950s) but it never achieved the great success and acceptance that was accorded the phenothiazines, which were also introduced during the same period. Nevertheless, the demonstration that dramatic changes in brain monoamine levels were caused by reserpine provided a great impetus to the belief that the action of psychotropic drugs could be explained in terms of alterations in neurohumoral or neurotransmitter functions.

The next stage in the life cycle of a neurotransmitter comes with its *release* from the presynaptic terminals onto the postsynaptic cell, where it presumably interacts with a "receptor" site. It is presumed that a transitory transmitter-receptor complex forms and then triggers an alteration in ionic conductance within the postsynaptic cell membrane. Such conductance changes (e.g., to the entry of Na+ or Cl) are responsible for the altered

functional state of the postsynaptic cell (either depolarization or hyperpolarization). A drug that releases a transmitter substance can therefore produce quite profound effects upon neural functioning. There is much evidence, for example, that amphetamine and other stimulant drugs produce their effects by releasing catecholamines from nerve terminals onto postsynaptic sites (see below). Conversely, drugs that block the action of neurotransmitters at receptor sites may have powerful antagonistic actions within these same systems. The phenothiazines appear to block the central effects of the catecholamines, and thereby act in opposition to the amphetamines. In general, the influence of psychotropic drugs on the release and subsequent action at postsynaptic receptors of neurotransmitters represents a key site in the consideration of their mechanism of action.

At the next stage, a drug may interfere with *termination of the action* of a neurotransmitter. The classical example of this is where a drug inhibits enzymes responsible for the transformation of the active transmitter into inactive products or metabolites. As a consequence, the transmitter will persist in the vicinity of the postsynaptic receptor site and continue to produce its effects. It has long been known that drugs that inhibit cholinesterases, the enzymes that hydrolyze acetylcholine into its inactive substituents, acetate and choline, potentiate the activity of this neurotransmitter. Ultimately, if sufficient acetylcholine accumulates the postsynaptic membrane may fail to recover from such excessive activation

and a block in transmission can result. With the more commonly used psychotropic drugs, the monoamine oxidase inhibitors exemplify this paradigm of degradative enzyme inhibition. Monoamine oxidase is the principle route of destruction for serotonin and an important one for the catecholamines. Thus, monoamine oxidase inhibitors should promote the effects of these monoamines in the brain, and they have been used in the treatment of depressive illness. However, when monoamine oxidase is inhibited, "false" neurochemical transmitters may accumulate in nerve endings and, paradoxically, an impaired release of the normal transmitter can result. Moreover, when an important degradative pathway in the body is blocked, serious side effects may ensue from the accumulation of toxic substances that require this pathway for their destruction. This proved to be the case for the monoamine oxidase inhibitors, since large amounts of sympathomimetic amines can accumulate, particularly after the ingestion of cheese and other foods high in these substances. In some cases, severe cardiovascular damage occurred in depressed patients who were being treated with monoamine oxidase inhibitors. Therefore, a need for an alternate means of enhancing the activity of monoamines was created. An alternate mechanism came to light *ex post facto* when it was discovered that the tricyclic antidepressant drugs were powerful inhibitors of *reuptake* into presynaptic terminals. The concept has emerged that reuptake of monoamines released from monoaminergic neurons represents the major

mechanism for the termination of the action of these substances. By blocking uptake, the concentration of a transmitter at the synaptic junction should be elevated and its action thereby enhanced. However, since degradative enzymes are still intact, an excessive accumulation of toxic substances is avoided. Thus, blockage of uptake represents an important mechanism to consider in assessing the action of psychotropic drugs.

Finally, drugs may alter the number or sensitivity of the postsynaptic *receptor sites.* The "receptors" per se are essentially theoretical constructions and are inferred to exist because of functional changes in postsynaptic cells. They are presumably macromolecules with proteolipid and glycoprotein constituents that interact with transmitter substances or drugs in a lock-and-key fashion. Drug-induced changes in receptor sites are no doubt of great importance, particularly for long-term, adaptive changes such as may occur in states of tolerance or addiction. A phenomenon resembling denervation supersensitivity, which is commonly seen at peripheral neuro-effector junctions, has been found to occur in the striatum following chronic disruption of the nigrostriatal dopamine pathway. The effects of L-Dopa and apomorphine (a dopamine agonist) are greatly enhanced under these circumstances. Presumably, in response to post-lesion reduction in dopamine, there is a compensatory increase in the number of receptor sites upon the striatal cells. It seems safe to predict that many other instances of long-term, receptor changes of relevance to the effects of narcotics and other drugs will

be uncovered in the future.

Neurophysiological and Histochemical

To have physiological or behavioral meaning, the net effect of drugs interacting with neurotransmitters and receptors eventually must be expressed in terms of an altered rate of firing of neurons. On the simplest level, one can examine the effects of drugs on the firing of single neurons within homogenous populations. On a more complex level, the actions of drugs on systems of neurons within multisynaptic pathways can be investigated. Finally, an analysis of the read-out of such neuronal systems on a behavioral level is needed for a complete understanding of the "mechanism of action" of a psychotropic drug. Elsewhere in this volume the more complex indicators of neuronal function (e.g., EEG and behavior) will be discussed; this review will be limited primarily to drug actions at a cellular level.

During the past decade, techniques have been developed that permit not only the recording of action potentials (spikes or unit activity) from single neurons in the mammalian brain but also the application of minute amounts of drugs or transmitter substances through multi-barreled micropipettes during such recording. The latter technique, which is termed "micro-iontophoresis" or "electrophoresis," was originally developed by Curtis and Eccles. It provides a powerful tool for the analysis of drug action at a cellular

level. Only by directly applying drugs or putative transmitters to individual neurons by such micro-methods can it directly be established that a substance has a primary action upon a particular neuron under study. A second development during this same period has been the discovery of histochemical methods by which certain neurons within the brain can be identified according to their specific neurotransmitter content. Most prominently, this has been achieved for the monoamine-containing neurons in the brain. Heller and associates by means of selective brain lesions first provided evidence for the probable existence of monoamine neuronal pathways. These investigators found that this pathway traversed the medial forebrain bundle in the lateral hypothalamus. Dahlstrom, Fuxe, and their associates, utilizing the formaldehyde-condensation, histochemical-fluorescence method of Falck and Hillarp, directly determined and mapped the location of monoamine cell bodies and terminals in the brain. Three principal monoamine pathways were discovered: (1) a nigrostriatal dopamine system whose cells of origin are situated in the zona compacta of the substantia nigra and projections in the caudate nucleus, accumbens nucleus, and olfactory tubercules; (2) a “noradrenergic” pathway with cell bodies in the locus coeruleus and brainstem, reticular formation, and projections to various parts of the forebrain, including the hypothalamus, hippocampus, and molecular layer of the cerebral cortex; and (3) a “serotonergic” system with cell bodies in the raphe nuclei of the brainstem

and projections to the hypothalamus, amygdala, and other portions of the limbic system. The far-reaching implications of this discovery are currently permeating all aspects of research in neuropharmacology. It should be apparent that the identification of chemically specific neuronal systems sets the stage for integrating biochemical and neurophysiological knowledge on the mechanism of drug action. Specific examples of drug effects on histochemically characterized brain neurons will be given in some of the sections that follow.

Mechanism of Psychotropic Drug Action: Major Drug Classes

Antipsychotic Drugs

The principal drugs in this category are the phenothiazines and butyrophenones, as exemplified respectively by chlorpromazine and haloperidol. Chlorpromazine was first suggested for possible use in psychiatric patients in the early 1950s by Henri-Marie Laborit, a surgeon who had been testing a series of phenothiazine antihistamines as adjuncts to anesthesia. It is interesting to note that the denotation applied to these drugs has changed since their introduction and early years of use. They were originally most commonly called “tranquilizers” or “neuroleptics,” but partly as a result of the NIMH and VA hospital collaborative studies are now usually termed “antipsychotics.” This significant shift in terminology was based on

the conclusion that although these drugs may initially have some sedative actions, in the long run they do more than merely quiet patients or reduce their anxieties. On the whole, schizophrenic patients seemed to become less withdrawn and more involved in affairs of reality, and in that sense "primary" symptoms of schizophrenia were ameliorated. The significance of these clinical findings for the pharmacologist is that studies on the mechanism of action of these drugs may give some insight into the nature of brain systems that may relate to the brain systems primarily disturbed in schizophrenia.

On a biochemical level, the search for sites of action of chlorpromazine and other antipsychotics has in the past included investigations upon tissue respiration (electron transport and oxidative phosphoylation), phospholipids, and a variety of enzyme systems. In most such systems, some effect can be seen, but because rather high concentrations are usually necessary, the relevance of such changes to the behavioral actions of the drugs has been questioned. Of course, it is possible that the drugs may become concentrated at critical subcellular sites and thereby alter these basic biochemical systems. In any event, in recent years the main focus of work on the mechanism of action of these drugs has moved away from an examination of general metabolic systems. Instead, attention has focused upon putative neurotransmitters.

The occurrence of extrapyramidal side effects in patients who are being

treated with phenothiazines and butyrophenones is well known to every clinician. It has been suggested that there is a high correlation between the potency (on a milligram basis) of the various antipsychotic compounds and their tendency to produce extrapyramidal side effects. Thioridazine appears to be a partial exception to this pattern in that the incidence of extrapyramidal side effects is relatively low at clinically effective doses. In any event, evidence has accumulated that the antipsychotic drugs may be powerful blockers of the putative transmitter dopamine. The resulting reduction in dopamine activity is believed to be responsible for the extrapyramidal side effects seen with these drugs. Associated with this apparent receptor blockage is a marked acceleration in the synthesis of dopamine, which may represent a compensatory feedback mechanism. Consistent with this notion is the fact that when the synthesis of catecholamines is inhibited by alpha-methyl-p-tyrosine, the behavioral effects of antipsychotic drugs in animals is potentiated. Horn and Snyder have recently determined, on the basis of calculations utilizing X-ray crystallography measurements, that the active phenothiazines are similar to dopamine in structural conformation. Since there are several dopamine tracts outside the extrapyramidal system (e.g., to nucleus accumbens and olfactory tubercules) Horn and Snyder have suggested that these may be involved in the antischizophrenic activity of the phenothiazines and butyrophenones. These investigators also point out that the “similarity of the phenothiazine

conformation to that of dopamine would also apply to norepinephrine."

As in the periphery, certain actions of norepinephrine in the brain may be mediated by the "secondary transmitter," cyclic AMP (3',5'-adenosine monophosphate). Norepinephrine stimulates the production of cyclic AMP in brain slices, and the effects of norepinephrine on Purkinje cells appear to be mediated by cyclic AMP. Phenothiazines have been found to block the norepinephrine-induced increase in cyclic AMP in a manner that correlates with relative antipsychotic potencies. Phenothiazines may also block the release of norepinephrine from nerve terminals. Single-unit recordings from norepinephrine-containing neurons of the locus coeruleus and dopamine-containing cells of the substantia nigra have shown that the antipsychotic drugs are potent antagonists of the effects of amphetamine upon the firing of these cells. Interestingly, amphetamine, a drug that enhances dopamine actions, regularly induces a paranoid psychosis in volunteer subjects. Clinical effects of amphetamine can readily be reversed by the antipsychotic drugs. However, this situation is complicated by the fact that under certain circumstances the phenothiazines, but not the butyrophenones, tend to retard the rate at which amphetamine is metabolized and therefore prolong its stay in the body. In any case, on both a cellular and behavioral level the antipsychotic drugs and amphetamines appear to have opposing actions. It would appear that the blocking of dopamine and perhaps also norepinephrine by the antipsychotic drugs can account for both their

extrapyramidal side effects and amphetamine antagonism.

In addition to their importance in the treatment of schizophrenia, the antipsychotic drugs in high doses have been of value in highly active stages of manic-depressive psychosis. However, lithium carbonate appears to be more effective in long-term treatment of this condition. There is little information on the basic mechanism of the action of lithium. Since lithium can displace sodium ions, it presumably may effect neuronal membrane potential, transport mechanisms and other sodium-dependent processes. In brain slices, lithium has been found to impair the release of putative transmitters such as serotonin and norepinephrine. The relationship between these pharmacological findings and possible biochemical factors in naturally occurring psychoses such as mania and schizophrenia remains to be determined. Nevertheless, the discovery that the antipsychotic drugs have pronounced interaction with the catecholamine systems in the brain represents an exciting new and fruitful development in our attempts to understand the mechanism of action of this important class of drugs.

Antidepressant Drugs

Of the many chemical agents that have been tested in the treatment of depressive illness, the so-called “tricyclic” compounds have emerged as the most useful clinically. An inherent difficulty in the evaluation of the efficacy of

antidepressant drugs is the self-limiting nature of most illnesses categorized as “depressive.” Another difficulty is the fact that clinical response to these drugs tends to be delayed. Nevertheless, there is fairly wide agreement on the superiority of the tricyclic compounds as compared with placebo. The monoamine oxidase inhibitors are felt to be less effective than the tricyclic compounds, and their use has been limited by the occurrence of serious cardiovascular side effects. In any case, interest in understanding the basic mechanisms of action of the various drugs in this category has been given its main impetus by the clinical finding of antidepressant efficacy.

Imipramine, a close structural analogue of chlorpromazine, was the first of the antidepressant tricyclics to be tested. It was presumed to be just another “tranquilizer” and its antidepressant properties were discovered serendipitously during a routine clinical trial of phenothiazine-related compounds. Imipramine differs in chemical structure from chlorpromazine only in the substitution of an ethylene for a sulfide bridge in the middle ring and the absence of the 2-chloro substituent. Despite these similarities in chemical structure, the clinical and neuropharmacological actions of the tricyclic drugs are in most ways entirely distinguishable from that of antipsychotic phenothiazines. On a clinical level, although the tricyclic compounds have some sedative effects, they may aggravate rather than dampen psychotic symptomatology. On a pharmacological level, effects upon the brain-dopamine system that are so characteristic of the phenothiazines

and butyrophenones are lacking among the tricyclic drugs.

The first significant clue as to the mechanism of action of the tricyclic drugs was derived from the basic observations of Axelrod and his coworkers, that peripheral adrenergic nerves avidly accumulate radioactively-labeled catecholamines. This work was extended into the central nervous system with the finding that tricyclic drugs, but not chlorpromazine, blocked the uptake of exogenous norepinephrine injected into the cerebral ventricles. When the blood-brain barrier is circumvented by the latter route of administration, norepinephrine will enter the brain parenchyma and be taken up into catecholamine-containing neutrons. Presumably, if imipramine or other tricyclic compounds block the uptake of exogenous norepinephrine, then endogenous norepinephrine, released by central noradrenergic nerves, would also be blocked. Since reuptake probably represents the primary mechanism for terminating the action of norepinephrine upon postsynaptic receptors, the tricyclic compounds may produce their behavioral effects by this means.

New data now require some modification and extension of what might be called the “catecholamine hypothesis” of the mechanism of action of the tricyclic drugs as presented above. It has been found that some of the tricyclic compounds are much more potent blockers of serotonin than of norepinephrine uptake.' The differential activity of the various tricyclic

compounds on uptake seems to depend on the degree of methylation of the side-chain amine moiety. Those tricyclic drugs which have their side-chain nitrogen in the *tertiary* form (e.g., imipramine, amitriptyline, chlorimipramine) primarily block the uptake of serotonin. On the other hand, the demethylated analogues of these compounds, in which the side-chain nitrogen in *secondary* form (e.g., desmethylimipramine and protriptyline) are more active in blocking norepinephrine uptake. On this basis, Carlsson has suggested that these two subgroups within the general category of tricyclic drugs could have differing clinical actions. For example, he suggests the tertiary amine forms may have their greatest effect on "mood," whereas the secondary amines might primarily influence "drive." The validity of this concept of differential uptake and clinical action remains to be tested. It is important to note that blockage of monoamine uptake may not be a necessary attribute of all tricyclic antidepressants. Iprindole, a tricyclic compound containing a ring indole moiety, has been reported to be an effective antidepressant, yet it appears to lack any effect on amine uptake. Nevertheless, the studies on tricyclic antidepressants and amine biochemistry represent an excellent illustration of the mutuality among basic neuropharmacology and clinical psychopharmacology and therapeutics.

Stimulant Drugs

From the point of view of behavior, the principal drugs of interest in this

category are the various isomers and analogues of amphetamine and methylphenidate. The therapeutic uses of these drugs are becoming progressively narrower as concern over their abuse potential increases. In psychiatry at the present time, their use is now almost entirely limited to the treatment of hyperkinetic children. It has long been known from case histories and field observations that the ingestion of large amounts of amphetamines is associated with a paranoid psychosis that is often difficult to distinguish from paranoid schizophrenia. When unaccompanied by the use of barbiturates or other drugs, the person with the psychosis is free of the usual signs of confusion or disorientation classically associated with 'organic" mental states. However, until the study of Griffiths and coworkers it was not established that amphetamine, if given in sufficient amounts, would induce a psychosis in volunteer subjects under controlled conditions. In the latter study almost all subjects developed a paranoid psychosis within one to five days with cumulative doses of dextroamphetamine ranging from one hundred to seven hundred and fifty mg. Contrary to expectation, subjects appeared depressed rather than elated as the psychosis developed. Since it appears that a paranoid state can be induced in a regular fashion by amphetamine in most or all subjects at high-dose levels, this drug can be regarded as producing a true "model psychosis." These clinical observations have therefore stimulated much interest in the basic mechanisms of action of this class of drugs.

On an electrophysiological level it had been observed that d-

amphetamine causes a decrease in the threshold required for producing EEG arousal by electrical stimulation of the reticular formation. However, it is unclear by which neurochemical mechanism such effects are mediated. Of course, the amphetamines are structural analogues of the catecholamines and fall into the general category of sympathomimetic agents. However, it was not until the introduction of alpha-methyltyrosine, a selective inhibitor of catecholamine synthesis, that the means were available for testing the hypothesis that the amphetamines may produce their central effects through a catecholamine mechanism. It has been found that pretreatment with alpha-methyltyrosine blocked most of the behavioral effects of d-amphetamine. For example, the disruption of the conditioned avoidance response and excitatory responses produced by amphetamine in animals can all be blocked by alpha-methyltyrosine. These studies appear to establish a direct requirement for the ongoing synthesis of brain catecholamines to sustain the actions of amphetamine, since the block by alpha-methyltyrosine occurs prior to any significant depletion of the amine stores.

The foregoing behavioral studies strongly suggest that the central actions of the amphetamines are mediated through the catecholamines. Biochemical and histochemical studies give support to this view. Indirect evidence suggests that the amphetamines can both release catecholamines from central catecholamine neurons and block their reuptake. The fact that amphetamines have this dual action on catecholamines would seem to

provide an explanation for the potent behavioral effects of these drugs, since extraneuronal release would result in enhanced catecholamine activity at postsynaptic receptor sites and the block in reuptake would prevent the removal of the catecholamines from such sites. The action of excessive amounts of catecholamines at postsynaptic sites may be expected to produce a compensatory feedback inhibition of the firing of the catecholamine neurons, and this has been demonstrated by direct, single unit recordings from catecholamine-containing neurons in the *locus coeruleus* and *substantia nigra*.

Although much evidence now points to a direct mediation by brain catecholamines of the effects of amphetamine, the question still remains, which of the catecholamines—norepinephrine or dopamine—is primarily involved in the production of the paranoid psychosis in man? Since amphetamine produces several types of behavioral effects in animals, many studies have been carried out in an attempt to parcel out the relative contributions of the two catecholamines. The so-called stereotypic behaviors (e.g., compulsive gnawing) that may be most analogous to the amphetamine psychosis in man seem to be closely associated with dopamine and the dopamine tracts in the brain. On the other hand, the increased locomotor activity induced by amphetamine may involve norepinephrine as well as dopamine in the brain, Taylor and Snyder have studied this question by taking advantage of the fact that d-amphetamine is much more potent than 1-

amphetamine in blocking the neuronal uptake of norepinephrine, but that the two stereoisomers are essentially equipotent in blocking the uptake of dopamine by neuronal terminal in the corpus striatum. They have found that d-amphetamine is ten times more effective than 1-amphetamine in enhancing locomotor activity, but that the two have approximately the same potency with respect to compulsive gnawing behavior. If it is assumed that behavioral potency is a function of the degree to which uptake is blocked, then these results again suggest that norepinephrine is most important for mediating the activation and dopamine for the stereotyped behaviors induced by amphetamine. Taken together, these various results again underline the great importance dopamine and norepinephrine neuronal systems in the brain may have for abnormal behavioral patterns and their possible relevance to both amphetamine-induced and naturally occurring psychoses.

Psychotomimetic Drugs

A great many chemical substances, if ingested in large enough quantity, can alter fundamental metabolic processes and thereby produce a psychosis characterized by a generalized disturbance in perceptual, cognitive, affective, or vegetative functions. However, from a pharmacological standpoint the drugs of greatest interest are those which have selective actions and produce a well-defined "psychotic" state. The paranoid psychosis induced by amphetamine, discussed in the last section, is one example of this. Other well-

defined drug psychoses include: (1) the delirium states produced by the anticholinergic drugs; and (2) the "psychedelic" state associated with D-lysergic acid diethylamide (LSD), mescaline, and related drugs. There has been much controversy over whether any of these drugs accurately mimic schizophrenia or other nondrug induced psychoses. Bowers and Freedman have reported that some acute psychoses begin with a psychedelic state, but that this may represent only a transient phase in the overall illness. Thus, in some cases a psychotomimetic drug may be seen as mimicking phases or aspects of naturally occurring psychoses rather than the whole picture of an illness in a longitudinal sense. In any event, the significance of the psychotomimetic drugs for purposes of basic research is the fact that they can serve as tracers in the identification of chemical and neuronal systems in the brain that are of importance for the maintenance of normal mental or behavioral functions.

A specific hypothesis concerning chemical site of action was developed for LSD shortly after its introduction into pharmacological research in the early 1950s. Gaddum and Woolley and Shaw introduced the notion that LSD may produce its effects by interfering with the action of serotonin in the brain. It was found that LSD antagonized the effects of serotonin on certain smooth muscle preparations (e.g., isolated rat uterus). Moreover, LSD resembles serotonin structurally (i.e., both contain an indole nucleus) and serotonin is present in the brain. The hypothesis that LSD acts in the brain by

antagonizing serotonin was soon questioned as a result of the finding that 2-brom LSD was as potent as LSD in antagonizing serotonin in peripheral systems, but had little behavioral effect. Studies in man with a wide range of LSD congeners have confirmed this lack of relationship between peripheral anti-serotonin potency and psychotomimetic effect. However, it has also been found that LSD, particularly at low concentrations, could have a serotonin-like action in various smooth systems. 82,97,108 gut was apparent that studies with peripheral tissues could not settle the question of what, if any, interaction occurs between LSD and serotonin in the brain itself.

Freedman and Giarman, in a logical development from this earlier work dealing with LSD-serotonin interactions in the periphery, began to investigate the influence of LSD on the metabolism of serotonin in the brain. They found that LSD produced a small (60-100 nanograms) but reproducible increase in the concentration of serotonin in the brain. The LSD-induced increase in serotonin could be interpreted as resulting from either increased synthesis or decreased breakdown.

However, the isolated measurement of serotonin concentration gave little clue as to which general mechanism may be involved. It has more recently been found that the concentration of 5-hydroxyindoleacetic acid (5-HIAA), the principal metabolite of serotonin in the brain, is decreased after the administration of LSD and other indoleamine type psychotomimetics.

Furthermore, the rate of synthesis of serotonin from labeled precursor (L-tryptophan) is also decreased. These results point to the possibility that LSD acts to retard the turnover of brain serotonin.

Based on the dual observations that LSD reduced the turnover of brain serotonin and that electrical stimulation of the serotonin-containing neurons of the midbrain raphe nuclei increased turnover, it was suggested that LSD might depress the firing of raphe neurons. A similar suggestion was based on the fact that LSD slowed the rate of depletion of serotonin that occurs after inhibition of synthesis. By means of direct microelectrode recording from single raphe neurons in rats, it has been demonstrated that extremely small doses of LSD (10 μg/kg, i.v.) produced a total but reversible inhibition of firing. This is an invariable finding and occurs both in anesthetized and unanesthetized animals. This inhibitory effect of LSD was exceedingly selective and the firing of units outside the raphe nucleus was either unaffected or increased. The nonpsychotomimetic analogue of LSD, 2-brom-LSD, which is even more potent than LSD in blocking the actions of serotonin in smooth muscle preparations, was found to have less than 1 percent of the activity of LSD in depressing raphe neurons. Taken together these results reinforce the original hypothesis that LSD might act in the brain by interacting somehow with serotonin. There are a number of possible mechanisms that might account for the observed inhibition by LSD of serotonin-containing (i.e., raphe) neurons. First, LSD might have a direct

inhibitory action. In support of this possibility it has been found that raphe, but not other nearby neurons, were inhibited by direct, microiontophoretic administration of LSD. However, the fact that raphe neurons may be inhibited directly by LSD does not exclude the interesting possibility that the drug also acts at postsynaptic sites.

The above studies represent only beginning efforts toward clarifying the interrelationship between the effects of LSD and the functional state of the serotonin-containing neurons of the raphe system. Although LSD has been the most thoroughly studied of the psychedelic drugs in this respect, other members of this class probably act through similar mechanisms. Indoleamines such as N,N-dimethyl-tryptamine and psilocybin, which are structurally related to LSD, as well as certain substituted phenethylamines (e.g., mescaline) and amphetamines (e.g., 2,5-methoxy-4-methylamphetamine) resemble LSD in many though not all behavioral effects and biochemical or neurophysiological actions. In addition, mescaline and LSD show cross-tolerance toward one another in man. On the other hand, marijuana or its active principle, Δ^9-tetrahydrocannabinol, although it may be classified as a psychedelic drug, does not exhibit cross-tolerance with LSD in man, suggesting that it acts through a different mechanism. In any event, the elucidation of the mechanism of action of the psychedelic drugs will require more than simply isolated observations on their effects on serotonin-containing or other individual neurons. Ultimately, it will be necessary to

integrate data from the unit level with knowledge about the interconnections and physiological role of the neuronal systems within which these units function.

Conclusions

Neuropharmacology: Future Prospects

From the foregoing illustrations it can be seen that information about chemical and cellular sites of drug action is being elaborated on a wide front. Undoubtedly, trends that now seem promising will be discarded and other approaches that are not presently in vogue will supercede them. All drugs have multiple actions and it is possible that the currently known effects of certain drugs may not be the crucial ones in terms of behavior. However, there is every expectation that, in a relatively few years, given the current level of sophistication in methodology and approach, substantial progress will be made in the accurate characterization of the relevant mechanisms of action of most psychotropic drugs. We are closer to this goal in some areas than in others. The examples discussed in detail (i.e., antipsychotic, antidepressant, stimulant, and psychotomimetic drugs) seem to most clearly illustrate the current creative ferment in the field. In each case, a plausible and coherent basic mechanism of action has been proposed and is supported by a respectable amount of experimental work. On the other hand, in the case of

the narcotics and antianxiety drugs, progress toward ascertaining the mechanisms of action has been less rapid. However, because of public concern over drug abuse, which is leading to increased support for research in this area, we can expect a marked expansion in our knowledge of the basic neuropharmacology of these drugs as well. A decade ago, these goals seemed much further from reach than they do at the present time.

Implications for Psychiatry

These developments in neuropharmacology will have a continued impact upon psychiatry in many spheres. First, in the area of training, as knowledge both about basic brain mechanisms as well as drug action increases, it will appear more relevant in the future than it has in the past to include a significant body of neuropharmacology and neurobiology in the training programs of departments of psychiatry. This will become more than simply an academic exercise if we reach a stage where an understanding of the mechanisms of drug action forms the basis for the intelligent clinical administration of drugs. In the area of psychiatric research, the concepts and methods of basic neuropharmacology are already having a major influence. One of the best examples of this is in biological research on the affective disorders. Neuropharmacological theories of the mechanism of action of antidepressant drugs (e.g., catecholamine or indoleamine) have led to investigations upon the status of such systems in patients with disturbances

in affective states.[2] Finally, as our understanding of the mode of action of existing drugs increases, new drugs with improved efficacy or fewer unwanted effects can be developed. For example, if the antipsychotic drugs do, in fact, produce their therapeutic effects by blocking dopamine receptors, it would be useful to restrict this action to those dopamine pathways most directly concerned with the psychotic process. Since the dopamine pathway of the extrapyramidal motor system may not be directly involved in the therapeutic action of these drugs, it would be advantageous to have antipsychotic drugs that acted selectively upon dopamine receptors outside this system. Similar possibilities of increased specificity or efficacy exist for all of the presently used pharmacotherapeutic drugs. Through an understanding of their mode of action, rational procedures for improving known drugs or developing new drugs will thus be facilitated.

Bibliography

Aghajanian, G. K. and F. E. Bloom. "Electronmicroscopic Autoradiography of Rat Hypothalamus after Intraventricular H-norepinephrine," *Science,* 153 (1966), 308-310.

Aghajanian, G. K., W. E. Foote, and M. H. Sheard. "Lysergic Acid Diethylamide: Sensitive Neuronal Units in the Midbrain Raphe," *Science,* 161 (1968), 706-708.

----. "Action of Psychotogenic Drags on Single Midbrain Raphe Neurons," *J. Pharmacol. Exp. Ther.,* 171 (1970), 178-187. York: Academic, 1973.

Aghajanian, G. K., and D. X. Freedman. "Biochemical and Morphological Aspects of LSD Pharmacology," in D. H. Efron, ed.. *Psychopharmacology: A Review of Progress,* pp.

1185-1194. Washington: Government Printing Office, 1968.

Aghajanian, G. K. and H. J. Haigler. "Direct and Indirect Actions of LSD, Serotonin and Mescaline on Serotonin-Containing Neurons," in J. Barchas and E. Usdin, eds., *Serotonin and Behavior.* New York: Academic, 1973.

Ahlenius, S. and J. Engel. "Behavioral Effects of Haloperidol after Tyrosine Hydroxylase Inhibition," *Eur. J. Pharmacol.,* 15 (1971), 187-192.

Amin, A. H., T. B. B. Crawford, and J. H. Gaddum. "The Distribution of Substance P and 5-Hydroxytryptamine in the Central Nervous System of the Dog," *J. Physiol.* 126 (1954), 596-618.

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

Andén. N.-E., H. Corrodi, K. Fuxe et al. "Evidence for a Central 5-Hydroxytryptamine Receptor Stimulation by Lysergic Acid Diethylamide," *Br. J. Pharmacol.,* 34 (1968), 1-7.

Andén, N.-E., A. Dahlström, K. Fuxe et al. "Ascending Monoamine Neurons to the Telencephalon and Diencephalon," *Acta Physiol. Scand.,* 67 (1966), 313-326.

Andén, N.-E., A. Rubenson, T. Hökfelt. "Evidence for Dopamine Receptor Stimulation by Apomorphine," *J. Pharm. Pharmacol.,* 19 (1967), 627-629.

Axelrod, J., H. Weil-Malherbe, and R. Tomchick. "The Physiological Deposition of H-Epinephrine and its Metabolite Metanephrine," *J. Pharmacol. Exp. Ther.,* 127 (1959). 251-256.

Baldessarini, R. J. and I. J. Kopin. "The Effect of Drags on the Release of Norepinephrine-H from Central Nervous System Tissues by Electrical Stimulation *In Vitro," J. Pharmacol. Exp. Ther.,* 156 (1967), 31-38.

Bell, D. S. "Comparison of Amphetamine Psychosis and Schizophrenia," *Br. J. Psychiatry,* 111 (1965) 701-707.

Bertler, A., A. Carlsson, and E. Rosengren. "Release by Reserpine of Catecholamines from Rabbits'

Hearts," *Naturwissenschaften,* 43 (1956), 521.

Besson, M. J., A. Cheramy, P. Feltz et al. "Release of Newly Synthesized Dopamine from Dopamine-Containing Terminals in the Striata of the Rat," *Proc. Natl. Acad. Sci.* USA, 62 (1969), 741-745.

Borella, L., F. Herr, and A. Wojdan. "Prolongation of Certain Effects of Amphetamines by Chlorpromazine," *Can. J. Physiol. Pharmacol.,* 47 (1969), 7-13.

Bowers, M. B. and D. X. Freedman. "Psychedelic Experiences in Acute Psychoses," *Arch. Gen. Psychiatry,* 15 (1966), 240-248.

Bradley, C. "Benzedrine and Dexedrine in the Treatment of Children's Behavior Disorders," *Pediatrics,* 5 (1950), 24-36.

Bradley, P. B. and B. J. Key. "The Effect of Drugs on the Arousal Responses Produced by Electrical Stimulation of the Reticular Formation of the Brain," *Electroencephalogr. Clin. Neurophysiol.,* 10 (1958), 97-no.

Brodie, B. B., A. Pletscher, and P. A. Shore. "Evidence that Serotonin has a Role in Brain Function," *Science,* 122 (1965), 968.

Bunney, B. S. and G. K. Aghajanian. Unpublished data.

Bunney, B. S., J. R. Walters, R. H. Roth et al. "Dopaminergic Neurons: Effect of Antipsychotic Drugs and Amphetamine on Single Cell Activity," *J. Pharmacol. Exp. Ther.,* 185 (1973), 560-571.

Bunney, W. E., Jr., H. Brodie, H. Keith et al. "Studies of Alpha-methyl-para-tyrosine, L-Dopa, and L-Tryptophan in Depression and Mania," *Am. J. Psychiatry,* 127 (1971), 48-57-

Caffey, E. M., L. E. Hollister, C. J. Klett et al. "Veterans Administration (VA) Cooperative Studies in Psychiatry," in W. G. Clark and J. del Giudice, eds., *Principles of Psychopharmacology,* p. 429. New York: Academic, 1970.

Caldwell, A. E. "History of Psychopharmacology," in W. G. Clark and J. del Giudice, eds., *Principles*

of Psychopharmacology, p. 9. New York: Academic, 1970.

Carlsson, A. "Amphetamine and Brain Catecholamines," in E. Costa and S. Garattini, eds., *International Symposium on Amphetamines and Related Compounds,* p. 289. New York: Raven Press, 1970.

Carlsson, A., H. Corrodi, K. Fuxe et al. "Effects of Some Antidepressant Drugs on the Depletion of Intraneuronal Brain Catecholamine Stores Caused by 4, Alpha-Di-methyl-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. Lindqvist. "Effect of Chlorpromazine on Haloperidol on Formation of 3-Methoxytyramine and Normetanephrine in Mouse Brain," *Acta Pharmacol. Toxicol. (Kbh*), 20 (1963), 140-144.

Carr, L. A. and K. E. Moore. "Norepinephrine: Release from Brain by d-Amphetamine *In Vivo," Science,* 164 (1969), 322-32-3-

Cerletti, A. and E. Rothlin. "Role of 5-Hydroxytryptamine in Mental Diseases and Its Antagonism to Lysergic Acid Derivatives," *Nature,* 176 (1955), 785-786.

Cole, J. O. and D. Clyde. "Extrapyramidal Side Effects and Clinical Response to the Phenothiazines," *Rev. Can. Biol.,* 20 (1961), 565-574.

Cole, J. O., S. C. Goldberg, and J. M. Davis. "Drugs in the Treatment of Psychosis: Controlled Studies," in P. Solomon, ed., *Psychiatric Drugs,* pp. 153-180. New York: Grune & Stratton, 1966.

Connell, P. H. "Amphetamine Psychosis," *Maudsley Monographs,* No. 5, p. 62. London: Chapman and Hall, 1958.

Cooper, J. R., F. E. Bloom, and R. H. Roth. *The Biochemical Basis of Neuropharmacology.* New York: Oxford University Press, 1970.

Costa, E. “Effects of Hallucinogenic and Tranquilizing Drugs on Serotonin Evoked Uterine Contractions,” *Proc. Soc. Exp. Biol, Med.,* 91 (1956), 39-41.

Cotzias, G. C., P. S. Papavasilion, and R. Gellene. “Modification of Parkinsonism— Chronic Treatment with L-Dopa,” *N. Engl. J. Med.,* 280 (1969), 337-345.

Curtis, D. R. and R. M. Eccles. “The Excitation of Renshaw Cells by Pharmacological Agents Applied Electrophoretically,” *J. Physiol.,* 141 (1958), 435-445.

Dahlstrom, A. and K. Fuxe. “Evidence for the Existence of Monoamine-Containing Neurons in the Central Nervous System. I. Demonstration of Monoamines in the Cell Bodies on Brain Stem Neurons,” *Acta Physiol. Scand.,* 62 (1965), Suppl. 232, 1-55.

Daprada, M. and A. Pletscher. “Acceleration of the Cerebral Dopamine Turnover by Chlorpromazine,” *Experientia,* 22 (1966), 465-469.

Davies, B. E. “Tranylcypromine and Cheese,” *Lancet,* 2 (1963), 691-692.

Eccles, J. C. *The Physiology of Synapses.* New York: Springer-Verlag, 1964.

Ellinwood, E. H. “Amphetamine Psychoses: I. Description of the Individuals and Process,” *J. Nerv. Ment. Dis.,* 144 (1967), 273-283.

Ernst, A. “Mode of Action of Apomorphine and Dexamphetamine on Gnawing Compulsion in Rats,” *Psychopharmacologia,* 10 (1967), 316-323.

Espelin, D. E. and A. K. Done. “Amphetamine Poisoning: Effectiveness of Chlorpromazine,” *N. Engl. J. Med.,* 278 (1968), 1361-1365.

Falck, B., N.-A. Hillarp, G. Thieme et al. “Fluorescence of Catecholamines and Related Compounds Condensed with Formaldehyde,” *J. Histochem. Cytochem.,* (1962), 348-354.

Fann, W. E., J. M. Davis, D. S. Janowsky et al. “Effect of Iprindole on Amine Uptake in Man,” *Arch. Gen. Psychiatry,* 26 (1972), 158-162.

Fog, R. L., A. Randrup, and H. Pakkenburg. “Aminergic Mechanisms in Corpus Striatum and

Amphetamine-induced Stereotyped Behavior," *Psychopharmacologia,* (1967), 179-183.

Freedman, D. X. "Effects of LSD-25 Brain Serotonin," *J. Pharmacol. Exp. Ther.,* 134. (1961), 160-166.

Freedman, D. X. and N. J. Giarman. "LSD-25 and the Status and Level of Brain Serotonin," *Ann. N.Y. Acad. Sci.,* 96 (1961), 98-106.

Freedman, D. X., R. Gottlieb, and R. A. Lovell. "Psychotomimetic Drugs and Brain 5-Hydroxytryptamine Metabolism," *Biochem. Pharmacol.,* 19 (1970), 1181-1188.

Fuxe, K. "Evidence for the Existence of Monoamine Neurons in the Central Nervous System. IV. Distribution of Monoamine Nerve Terminals in the Central Nervous System," *Acta Physiol. Scand.,* 64 (1965). Suppl. 247, 41-85.

Fuxe, K. and U. Ungerstedt. "Localization of Catecholamine Uptake after Intra-ventricular Injection," *Life Sci.,* 5 (1966), 1817-1824.

Gaddum, J. H. "Antagonism between Lysergic Acid Diethylamide and 5-Hydroxytryptamine," *J. Physiol.,* 121 (1953), 15.

Gaddum, J. H. and K. A. Hameed. "Drugs which Antagonize 5-Hydroxytrypamine," *Br. J. Pharmacol.,* 9 (1954), 240-248.

Glowinski, J. and J. Axelrod. "Effects of Drugs on the Deposition of H-Norepinephrine in the Rat Brain," *Pharmacol. Rev.,* 18 (1966), 775-785.

Goldberg, S. C. "Brief Resume of the National Institute of Mental Health Study in Acute Schizophrenia," in W. G. Clark and J. del Giudice, eds., *Principles of Psycho-pharmacology,* p. 443. New York: Academic, 1970.

Graham, A. W. and G. K. Aghajanian. "Effects of Amphetamine on Single Cell Activity in a Catecholamine Nucleus, the Locus Coeruleus," *Nature,* 234 (1971), 100-102.

Griffith, J. D., J. Cavenaugh, J. Held et al. "Dextroamphetamine: Evaluation of Psychotomimetic

Properties in Man," *Arch. Gen. Psychiatry,* 26 (1972), 97-100.

Hanson, L. C. F. "Evidence that the Central Action of Amphetamine is Mediated Via Catecholamines," *Psychopharmacologia,* 10 (1967), 289-297.

Heller, A., J. A. Harvey, and R. Y. Moore. "A Demonstration of a Fall in Brain Serotonin Following Central Nervous System Lesions in the Rat," *Biochem. Pharmacol.,* 11 (1962), 859-866.

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

Herman, M. and S. H. Nagler. "Psychoses Due to Amphetamine," *J. Nerv. Ment. Dis.,* 120 (1954), 268-272.

Holzbaur, M. and M. Vogt. "Depression by Reserpine of the Noradrenaline Concentration in the Hypothalamus of the Cat," *J. Neurochem.,* 1 (1956), 8-11.

Horn, A. S. and S. H. Snyder. "Chlorpromazine and Dopamine: Conformational Similarities that Correlate with the Antischizophrenic Activity of Phenothiazine Drugs," *Proc. Natl. Acad. Sci.* USA, 68 (1971), 2325-2328.

Hornykiewicz, O. "Dopamine (3-Hydroxy-tryptamine) and Brain Function," *Pharmacol. Rev.,* 18 (1966), 925-964.

Isbell, H. and D. R. Janiski. "A Comparison of LSD-25 with (--)-Δ^9-Trans-Tetra-hydrocannabinol (THC) and Attempted Cross Tolerance Between LSD and THC," *Psychopharmacolgia,* 14 (1969), 115-123.

Isbell, H., E. J. Miner, and C. R. Logan. "Relationships of Psychotomimetic to Anti-Serotonin Potencies of Congeners of Lysergic Acid Diethylamide (LSD-25)," *Psychopharmacologia,* 1 (1959), 20-28.

Jequier, E., W. Lovenberg, and A. Sjoerdsma. "Tryptophan Hydroxylase Inhibition: The Mechanism by which p-Chloro-phenylalanine Depletes Rat Brain Serotonin," *Mol. Pharmacol.,* 3 (1967), 274-278.

Jouvet, M. “Biogenic Amines and the States of Sleep,” *Science,* 163, (1969), 32-41.

Kakiughi, S. and T. W. Rall. “The Influence of Chemical Agents on the Accumulation of Adenosine 3',-5'-Phosphate in Slices of Rabbit Cerebellum,” *Mol. Pharmacol.,* 4 (1968), 367-378.

Katz, R. I., T. N. Chase, and R. J. Kopin. “Evoked Release of Norepinephrine and Serotonin from Brain Slices: Inhibition by Lithium,” *Science,* 162 (1968), 466-467.

Kety, S. S. “Current Biochemical Approaches to Schizophrenia,” *N. Engl. J. Med.,* 276 (1967), 325-331.

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

Klerman, G. L. and J. O. Cole. “Clinical Pharmacology of Imipramine and Related Antidepressant Compounds,” *Pharmacol. Rev.,* 17 (1965), 101-141.

Koe, B. K. and A. Weissman. “p-Chloro-phenylalanine: A Specific Depletor of Brain Serotonin,” *J. Pharmacol. Exp. Ther.,* 154 (1966), 499-516.

Kopin, I. J., J. E. Fischer, J. Musacchio et al. “Evidence for a False Neurochemical Transmitter as a Mechanism for the Hypotensive Effect of Monoamine Oxidase Inhibitors.” *Proc. Natl. Acad. Sci.* USA, 52 (1964), 716-721.

Kuhn, R. “The Treatment of Depressive States with G-22355 (Imipramine Hydrochloride),” *Am. J. Psychiatry,* 115 (1958), 459-464.

Lemberger, L., E. D. Witt, J. M. Davis et al. “The Effects of Haloperidol and Chlorpromazine on Amphetamine Metabolism and Amphetamine Stereotype Behavior in the Rat,” *J. Pharmacol. Exp. Ther.,* 174 (1970), 428-433.

Lin, R. C., S. H. Ngai, and E. Costa. “Lysergic Acid Diethylamide: Role in Conversion of Plasma Tryptophan to Brain Serotonin (5-Hydroxytryptamine),” *Science,* 166 (1969), 237-239.

Mansour, T. E. "The Effect of Lysergic Acid Diethylamide, 5-Hydroxytryptamine, and Related Compounds on the Liver Fluke. Fasciola Hepatica," *Br. J. Pharmacol.,* 12 (1957), 406-409.

McIlwain, H. *Biochemistry of the Central Nervous System.* London: J. & A. Churchill, 1966.

Murphy, D. L., H. K. Brodie, F. K. Goodwin et al. "Regular Induction of Hypomania by L-Dopa in 'Bipolar' Manic-Depressive Patients," *Nature,* 229 (1971), 135-136.

Nyback, H. and G. Sedvall. "Effect of Chlorpromazine on Accumulation and Disappearance of Catecholamines Formed from Trysoine-C^{14} in Brain," *J. Pharmacol. Exp. Ther.,* 162 (1968), 294-301.

Palmer, G. C., G. A. Robeson, A. A. Manian et al. "Modification by Psychotropic Drugs of the Cyclic AMP Response to Norepinephrine in the Rat Brain *In Vitro," Eur. J. Pharmacol.,* (1972), in press.

Prien, R. F., E. M. Caffey, and C. V. Klett. "Comparison of Lithium Carbonate and Chlorpromazine on the Treatment of Mania," *Arch. Gen. Psychiatry,* 26 (1972), 146-153.

Quastel, J. J. "Metabolic Effects of Some Psychopharmacological Agents in Brain *In Vitro,"* in W. G. Clark and J. del Giudice, eds., *Principles of Psychopharmacology,* p. 142. New York: Academic, 1970.

Randrup, A. and I. Munkrad. "Role of Catecholamines in the Amphetamine Excitatory Response," *Nature,* 211 (1966), 540.

Rech, R. H., L. A. Carr, and R. E. Moore. "Behavioral Effects of Alpha-Methyltyrosine after Prior Depletion of Brain Catecholamines," *J. Pharmacol. Exp. Ther.,* 160 (1968), 326-335.

Redmond, D. E., Jr., J. W. Maas, A. Kling et al. "Social Behavior of Monkeys Selectively Depleted of Monoamines," *Science,* 174 (1971), 428-431.

Robeson, G. A., R. W. Butcher, and E. W. Sutherland. "On the Relation of Hormone Receptors to Adenyl Cyclase," in J. F. Danielli, J. F. Moran, and D. J. Truggle, eds., *Fundamental Concepts in Drug-Receptor Interactions,* p. 59. London: Academic, 1969.

Rosecrans, J. A., R. A. Lovell, and D. X. Freedman. "Effects of Lysergic Acid Diethylamide on the Metabolism of Brain 5-Hydroxytryptamine," *Biochem. Pharmacol.,* 16 (1967), 2011-2021.

Ross, S. B. and A. L. Renyi. "Inhibition of the Uptake of Tritiated 5-Hydroxytryptamine on Brain Tissue," *Eur. J. Pharmacol.,* 7 (1969). 270-277.

Schou, M. "Special Review: Lithium in Psychiatric Therapy and Prophylaxis," *J. Psychiatr. Res.,* 6 (1969), 67-95.

Shaskin, E. G. and S. H. Snyder. "Kinetics of Serotonin Accumulation into Slices from Rat Brain: Relationship to Catecholamine Uptake," *J. Pharmacol. Exp. Ther.,* 175 (1970), 404-418.

Shaw, E. and D. W. Woolley. "Some Serotonin Activities of Lysergic Acid Diethylamide," *Science,* 124 (1956), 121-122.

Siggins, G. R., B. J. Hoffer, and F. E. Bloom. "Cyclic Adenosine Monosphosphate: Possible Mediator for Norepinephrine Effects on Cerebellar Purkinje Cells," *Science,* 165 (1969), 1018-1020.

Spector, S., A. Sjoerdsma, and S. Udenfriend. "Blockade of Endogenous Norepinephrine Synthesis by Alpha-Methyl-Tyrosine, an Inhibitor of Tyrosine Hydroxylase," *J. Pharmacol. Exp. Ther.,* 147 (1965), 86-95.

Sulser, F., M. Owens, M. Norvich et al. "The Relative Role of Storage and Synthesis of Brain Norepinephrine in the Psychomotor Stimulation Evoked by Amphetamine or by Desiprimine and Tetrabenzine," *Psychopharmacologia,* 12 (1968), 322-331.

Taylor, K. M. and S. H. Snyder. "Amphetamine: Differentiation by *d* and *l* Isomers of Behavior Involving Brain Nore-epinephrine or Dopamine," *Science,* 168 (1970), 1487-1489.

Twarog, B. M. and I. H. Page. "Serotonin Content of Some Mammalian Tissues and Urine and a Method for Its Determinations," *Am. J. Physiol,* 175 (1953), 157-161.

Udenfriend, S., P. Zaltzman-Nirenberg, R. Gordon et al. "Evaluation of the Biochemical Effects

Produced *In Vivo* by Inhibitors of the Three Enzymes Involved in Norepinephrine Biosynthesis," *Mol. Pharmacol.,* 2 (1966), 95-105.

Ungerstedt, U. "Postsynaptic Supersensitivity after 6-Hydroxydopamine Induced Degeneration of the Nigro-Striatal Dopamine System," *Acta Physiol. Scand., Suppl.* 367 (1971), 69-93.

Uzunov, P. and B. Weiss. "Effects of Phenothiazine Tranquilizers on the Cyclic 3', 5'-Adenosine Monophosphate System of Rat Brain," *Neuropharmacology,* 10 (1971), 697-708.

Weissman, A. "Behavioral Pharmacology of PCPA," in J. Barchas and E. Usdin, eds., *Serotonin and Behavior,* New York: Academic, 1973.

Weissman, A., B. S. Koe, and S. S. Tenen. "Amphetamine Effects Following Inhibition of Tyrosine Hydroxylase," *J. Pharmacol. Exp. Ther.,* 151 (1966), 339-352.

Welsh, J. H. "Serotonin as a Possible Neurohumoral Agent: Evidence Obtained in Lower Animals," *Ann. N.Y. Acad. Sci.* USA, 66 (1957), 618-630.

Wolbach, A. B., H. Isbell, and E. J. Miner. "Cross Tolerance Between Mescaline and LSD-25 with a Comparison of the Mescaline and LSD Reactions," *Psychopharmacologia,* 3 (1962), 1-14.

Woolley, D. W. and E. Shaw. "A Biochemical Pharmacological Suggestion about Certain Mental Disorders," *Proc. Natl. Acad, Sci.* USA, 40 (1954), 228-231.

Woolley, D. W. and E. N. Shaw. "Evidence for the Participation of Serotonin in Mental Processes," *Ann. N.Y. Acad. Sci. USA*, 66 (1957), 649-665.

Zirkle, C. L., and C. Kaiser. "Antipsychotic Agents," in A. Burger, ed., *Medicinal Chemistry,* p. 1410. New York: Wiley-Interscience, 1970.

Notes

1 For more extensive coverage of this area consult the recent excellent and succinct textbook by Cooper, Bloom, and Roth.

2 Developments in this and similar areas are described in some other chapters of this volume.