DRUGS & BEHAVIOR

Second Edition

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California State University
Hayward

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Series Preface

This series of books is addressed to behavioral scientists interested in the nature of human personality. Its scope should prove pertinent to personality theorists and researchers as well as to clinicians concerned with applying an understanding of personality processes to the amelioration of emotional difficulties in living. To this end, the series provides a scholarly integration of theoretical formulations, empirical data, and practical recommendations.

Six major aspects of studying and learning about human personality can be designated: personality theory, personality structure and dynamics, personality development, personality assessment, personality change, and personality adjustments. In exploring these aspects of personality, the books in the series discuss a number of distinct but related subject areas: the nature and implications of various theories of personality; personality characteristics that account for consistencies and variations in human behavior; the emergence of personality processes in children and adolescents; the use of interviewing and testing procedures to evaluate individual differences in personality; efforts to modify personality styles through psychotherapy, counseling, behavior therapy, and other methods of influence; and patterns of abnormal personality functioning that impair individual competence.

IRVING B. WEINER

University of Denver
Denver, Colorado

Preface

Writing a book has been compared with fathering a child, but the writer has the advantage of opportunity to revise unsatisfactory offspring. (On the other hand, the process of fathering is a lot more fun.) Although the first edition of *Drugs and Behavior* was generally well-received, there are several areas where I welcomed the chance to revise. The main one derives from a conversion to the view that overprescription of psychoactive drugs constitutes a major health problem in the United States. There is something amiss in a society that encourages use of drugs for falling asleep, waking up, being able to stagger to the bathroom (and to do something upon arrival there), for crossing the street without fear of cars, and for experiencing pleasure in the event of being hit by one. It seems bizarre that such a society invokes severe penalties for recreational use of certain drugs.

I declined one suggested revision, which was to organize the book by drug rather than behavior. In the first place, the market life of most drugs is short, so that a book dealing with a few specific drugs would rapidly become dated. Secondly, organization by behavior is more efficient. For example, research on drugs and creativity is plagued by several methodological difficulties. With a separate chapter on creativity, the issues are discussed as a unit. Had the book been organized by drug, it would have been necessary to reintroduce the problems as they arose for each new drug.

I wish to express my annoyance with Herb Reich, editor at Wiley-Interscience, for denying me fulfillment of a fantasy. I had dreamed of valiantly holding forth for artistic integrity while some editor, concerned only with commercial success, crudely slashed my manuscript. Instead, I found myself in total agreement with virtually all of Herb's suggestions. Fantasy denied, but the book is a lot better as a result.

I dedicate the book to the same fearsome foursome who helped me through the first edition. Diane, Jessica, Melanie, Mom, I love you. Also to Tom, Mimi, Eileen, Dave, and Adrienne; to Judy, Irv, Etta, Dave and Bess. A very belated, but strongly felt thanks to Steve. To Martin and Denise, with whom I spent many pleasurable hours investigating drugs; and to Art, who proves that even nonusers can be crazy.

FRED LEAVITT

Hayward, California
January 1982

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Introduction

WHAT IS PSYCHOPHARMACOLOGY?

Psychopharmacology is the science which deals with the effects of drugs on behavior. A drug is any chemical agent which has an effect on living protoplasm. Behavior has been variously defined; a definition adequate for most purposes is that it is any observable response of an organism. Such a definition is sufficiently broad so as to encompass drug-induced changes in perception, mood, thinking, and so forth.

WHY STUDY PSYCHOPHARMACOLOGY?

Works of fiction, and some literature not labeled fiction, abound in descriptions of fascinating drug effects. Travelers through Hades sipped from the river Lethe and became oblivious to all which went before. *Time* Magazine reported in 1966 that we might someday have memory pills which would enable us to instantaneously assimilate large bodies of knowledge. Ponce de Leon was unsuccessful in his attempts to find a fountain of youth, although he did discover Florida; but Brown-Sequard, a French physician and modern-day Ponce de Leon, reported self-rejuvenation at the age of 72 after he injected himself with a special extract of dog testes. (For an explanation of the Brown-Sequard effect see chapter 13.) Kindly Dr. Jekyll swallowed a blood-red potion and became transmogrified into the evil Mr. Hyde. The inhabitants of *Brave New World* used soma, and were content. Rosemary drank a special brew and her baby grew strong.

Humans do not yet have at their disposal drugs that will produce blissful oblivion or instant knowledge. The fountain of youth still awaits discovery. Many substances are capable of reducing our inhibitions, but none transform man to beast. Soma-like drugs are available, but none are completely free of annoying side effects. And, although many people believe that certain drugs exist primarily to provide nourishment for the devil, the claim is disputed. Nevertheless, drugs may someday be available which will accomplish most of the above-named ends. And that is the lure of psychopharmacology.

There are at least three general reasons for studying psychopharmacology. The first is that the understanding of a phenomenon—in this case, all aspects of human behavior—is usually greatly facilitated by the development of reliable means for producing the phenomenon. Drugs can be powerful tools to this end. For example, the physiological mechanisms underlying sleep and dreaming have been clarified by investigations with drugs that promote or reduce the need for sleep (see chapter 15).

Second, drugs can be used to elicit or suppress various behaviors. The phenothiazines are highly effective in suppressing psychotic agitation; marijuana is used, outside the doctor's office, for its euphoric properties. One aspect of the psychopharmacologist's job is to find drugs which are of value in modifying behavior; equally important is work toward the development of congeners (any drugs related to one another) that produce even more powerful effects than the original compound, yet have fewer undesirable side effects.

The third reason is that human beings are drug-taking animals. Anthropologists have reported the use of various drugs in virtually every culture studied. The ancient Sumerians of 4000 B.C. had a name for the poppy: joy plant. In America, physicians and unsavory characters on dimly lit streetcorners are not the only sources of substances that affect behavior. Any supermarket will do. Caffeine, nicotine, and many vitamins and spices have powerful mind-altering effects. Only through well controlled experimentation will these effects become sufficiently well understood so that users will be able to derive maximum benefit from them. For example, most coffee drinkers probably know that caffeine may produce insomnia, so they take their last cup of the day well before bedtime. But probably few people who eat citrus fruits are aware of the postulated effects of vitamin C, which is found in great abundance in citrus fruits, on mood and affect.

GOALS OF THE BOOK

I have attempted to give a methodologically oriented, comprehensive, but concise introduction to the very exciting field of psychopharmacology. My aim has been to make the book suitable for study at home as well as in the classroom. Therefore I have assumed no prior knowledge of actions of drugs or of psychological principles. Instructors of psychopharmacology may find this a useful text for a one-semester course. It may also be helpful as a supplementary text for courses in physiological psychology, sociology, experimental design and methodology, and pharmacology.

CHAPTER 1

Classification of Drugs

No two drugs are identical in all respects, but many have qualitatively similar actions on a great many physiological and psychological systems. For example, all of the more than 2500 barbiturates are central nervous system depressants; virtually all are capable of inhibiting convulsions; all depress the respiratory system; and all have characteristic effects on the liver, kidneys, gastrointestinal tract, and cardiovascular system. To say that a drug is a barbiturate conveys a great deal of information about the drug. Placebos, another class of drugs, may differ among themselves in many ways—color, size, shape, frequency of dosage, and even in effectiveness—yet to know that a particular drug is a placebo is to know a great deal about the drug.

The purpose of any classification system is to provide a convenient framework around which to organize information and thinking. Hence, the particular system chosen should reflect the interests of the users; there is no single best system. The purposes of lawyers might best be served simply by classifying drugs as licit or illicit (or, for sophisticated lawyers, the illicit drugs may be further subdivided into those punishable as misdemeanor or as felony). Some drug users make do with a simple two-factor system: uppers and downers. Those with an aristocratic bent use a different two-factor system: cocaine and everything else.

For serious scientists more descriptive categories are needed. Most pharmacologists classify drugs according to molecular structure, which enables them to best understand the relationships between structure of a molecule and its pharmacological effects. Chemists do the same, so that they can most efficiently direct research aimed at synthesizing new drugs. However, classification according to molecular structure is not always satisfactory for researchers who are interested in behavior; it results, for example, in the placement of LSD, one of the strongest of all drugs that affect the central nervous system (CNS), with 2-bromo-LSD, which has weak CNS actions (8). Still, drugs of the same family do tend to have similar actions. The difference between LSD and 2-bromo-LSD is explained by the failure of the latter to reach the brain after ingestion. Attention to chemical structure can lead to valuable ideas about directions for research. For example, when a clinically useful drug has some undesirable properties, a program for synthesizing structurally similar compounds can be instituted. This strategy probably maximizes the probability of finding a

new drug with a greater margin of safety.

Because classification systems are useful but arbitrary, several different ones are described below. No attempt has been made to single one out as superior to the rest. Before describing the various systems, two points must be emphasized. First, all drugs have many actions. For example, chlorpromazine (brand name Thorazine) may be classified as an antipsychotic drug, but it also has many important effects on the autonomic nervous system. It modifies dreaming, learning, and motor activity; increases proneness to seizures; and affects the heart, kidneys, and endocrine system. It also inhibits vomiting, so is often used to treat motion sickness.

The second crucial point is that drugs do not act in vacuo. Their effects depend on the resultant of their interactions with the four sets of variables (organismic, drug, environmental, and task) listed in chapter 2. A drug that activates behavior under some circumstances may depress it under others. Here is one brief example, illustrating the all-important effect of expectations. Tart (39) reported that 75% of American respondents answered that they enjoyed food more and ate increased amounts after smoking marijuana; by contrast, Rubin and Comitas (33) noted that 60% of users in Jamaica reported that marijuana reduces hunger. In fact, it is often used there by field workers and fishermen to prevent hunger.

A BROAD CLASSIFICATION OF CNS DRUGS

Franz (16) developed a simple system for classifying CNS drugs. There are only three categories.

1. *General (nonselective) CNS depressants.* These drugs depress excitable tissue throughout the CNS. Included are anesthetic gases and vapors, alcohols, barbiturates, and related sedative-hypnotic drugs.
2. *General (nonselective) CNS stimulants.* These also act throughout the CNS, by either of two mechanisms. The first, exemplified by strychnine, is to block inhibitory impulses; the second, exemplified by pentylenetetrazol, involves direct excitation of neuronal structures. Caffeine, theophylline (from tea), and theobromine (from cocoa) are examples of weak nonselective stimulants.
3. *Drugs that selectively modify CNS function.* These agents may exhibit either depressant or excitatory effects, sometimes both simultaneously on different systems. Included in this category are anticonvulsants, antiparkinsonism drugs, narcotic-analgesics, analgesic-antipyretics (fever reducing), and all of the psychopharmacological drugs.

CLASSIFICATION ACCORDING TO CLINICAL USE

Domino (13) developed a system in which drugs within a given category of clinical usefulness are further divided according to chemical structure. For example, the antianxiety agents chlordiazepoxide, diazepam, and oxazepam

are grouped together because they are all benzodiazepine derivatives. In the list which follows, common brand names of the drugs are in parentheses.

ANTIANXIETY AGENTS. These reduce pathological anxiety, tension, and agitation without greatly affecting the autonomic nervous system. They often lead to dependency if taken in high doses for prolonged periods of time.

benzodiazepines: chlordiazepoxide (Librium), diazepam (Valium), oxazepam (Serax)

propanediols: meprobamate (Miltown), tybamate (Solacen)

diphenylmethanes: hydroxyzine (Atarax), diphenhydramine (Benadryl)

ANTIDEPRESSANTS. These are used for treating psychiatric depressive states.

tricyclics: imipramine (Tofranil), desipramine (Pertofrane), amitriptyline (Elavil), nortriptyline (Avantyl), doxepin (Sinequan).

monoamine oxidase inhibitors: isocarboxazid (Marplan), phenelzine (Nardil), nialamide (Niamid), tranylcypromine (Parnate)

ANTIPSYCHOTICS. These are used to treat psychoses and other types of psychiatric disorders.

phenothiazines: chlorpromazine (Thorazine), trifluoperazine (Stelazine), fluphenazine (Prolixin), thioridazine (Mellaril), piperacetaxine (Quide)

thioxanthines: chlorprothixene (Taractan), thiothixene (Navane)

butyrophenones: haloperiodol (Haldol), droperidol (Inapsine)

ANTIMANIC DRUGS. These are used in the treatment of mania and recurrent manic-depressive episodes.

lithium carbonate: (Eskalith, Lithane, Lithonate)

PSYCHOMOTOR STIMULANTS. These increase level of alertness and decrease drowsiness.

amphetamines: *d*-amphetamine (Dexedrine), methamphetamine (Methedrine, Desoxyn)

miscellaneous: methylphenidate (Ritalin), pipradol (Meratran), phenmetrazine (Preludin)

PSYCHOTOMIMETICS. These produce distortions in cognition and perception. Although they are called psychotomimetic, they poorly mimic the primary symptoms of schizophrenia. (On the other hand, prolonged use of high doses of amphetamine does generate a fairly accurate schizophrenic state.)

phenethylamines: mescaline, 4-methyl-2, 5 dimethoxy amphetamine (with two nicknames: STP and DOM).

indoles: LSD-25, psilocybin, dimethyltryptamine (shortened to DMT)

arylcyclohexylamines: phencyclidine, better known as PCP (Sernyl)

piperidyl benzilate esters: ditran

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NARCOTIC ANALGESIC AGONISTS AND ANTAGONISTS. These are used for both their analgesic and antianxiety effects in patients with acute or chronic pain.

pure agonists (for definitions of agonist and antagonist, see page 25-26): morphine, codeine, heroin, meperedine (Demerol), methadone (Dolophine), propoxyphene (Darvon), levorphanol (Levo-Dromoran), phenazocine (Prinadol)

mixed agonist-antagonists: nalorphine (Nalline), levallorphan (Lorphan), cyclazocine

pure antagonists: naloxone (Narcan), naltrexone, diprenorphene (M5050)

SOCIAL DRUGS. These are used primarily in individual and social settings.

methylated xanthines: caffeine, theophylline, theobromine

cholinergic agonists: nicotine, arecoline

marijuana

ethyl alcohol

A problem with multiple classification systems is that different writers use different systems. Consequently, students who intend to keep up with the psychopharmacology literature must familiarize themselves with several sets of five-syllable words. Antianxiety drugs are also called anxiolytics and minor tranquilizers. Antipsychotics are neuroleptics and major tranquilizers. Psychotomimetics masquerade as psychodysleptics, hallucinogens, and psychedelics. Three suffixes are frequently used in labeling drugs. It is worth memorizing their meanings.

1. *-ergic, from the Greek work.* Cholinergic fibers are fibers which release acetylcholine, histaminergic fibers release histamine, and tryptaminergic fibers release tryptamine. Drugs that act to release acetylcholine from cholinergic fibers are called cholinergic drugs.
2. *-lytic, from the Greek unfastening, breaking up.* An anxiolytic drug reduces anxiety; a parasympatholytic reduces activity in the parasympathetic division of the autonomic nervous system.
3. *-mimetic, from the Greek imitative.* Psychotomimetic drugs are supposed to cause the user to act psychotic. Sympathomimetics mimic the action of stimulation of the sympathetic division of the autonomic nervous system.

CLASSIFICATION OF DRUGS ACCORDING TO THEIR ACTIONS ON NEUROTRANSMISSION

The functional unit of the CNS is the nerve cell, or neuron. Although they vary greatly in size and shape, all neurons have three principal parts (see Fig. 1.1). In common with all cells, each neuron has a cell body; there are one or more

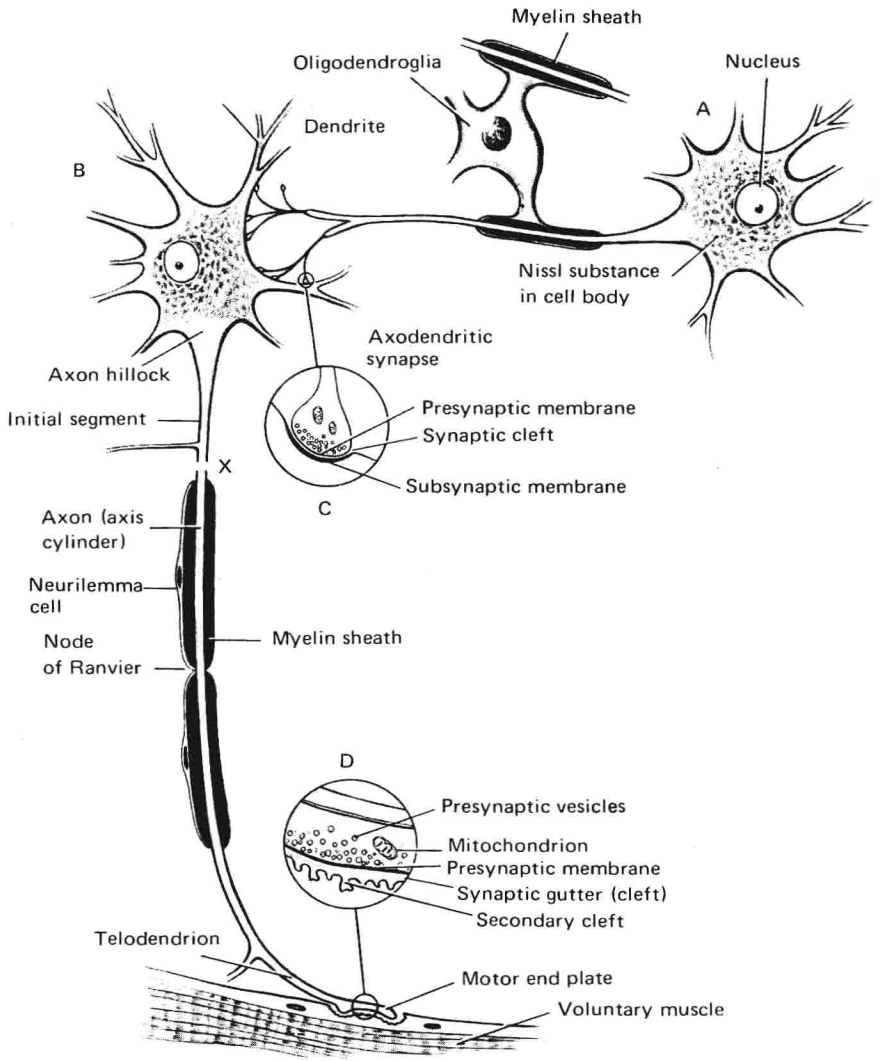

Figure 1.1. Diagram of (A) a neuron located within the CNS and (B) a lower motor neuron located in both the ventral and peripheral nervous systems. The latter synapses with a voluntary muscle cell to form a motor end-plate. Note the similarities, as reconstructed from electron micrographs, between a synapse between two neurons (C) and a motor end-plate (D). The hiatus in the nerve (X) represents the border between the CNS (above the X) and the peripheral nervous system (below the X). (From Noback, C. & Demarest, R. The Nervous System: Introduction and Review. New York: McGraw-Hill, 1972.)

slender dendrites, which generally carry nerve impulses into the cell body; and one relatively thick axon which carries impulses away from the cell body.

Neurons transmit information to each other at junctions called synapses. Electrical transmission has been described, but virtually all mammalian synapses are chemical in nature. Because transmission between neurons is so rapid, it was once thought the process must be electrical. But in 1921 Otto Loewi, in an elegant series of experiments, conclusively demonstrated the chemical nature of the process. Loewi bathed the isolated heart of a frog in a special medium in which it could be kept beating. When the vagus nerve leading to the heart was stimulated, heart rate was reduced just as in intact animals. The fluid in which the heart was bathed was allowed to flow into a second vessel where a second isolated heart was beating. The second heart then slowed. This showed that a substance released by the stimulated vagus nerve causes slowing of the heart. The substance was later isolated and identified as acetylcholine. In a similar experiment the accelerans nerve, which in intact animals speeds up the heart, was stimulated. A second isolated heart, bathed in fluid released from the stimulated one, also speeded up. The second substance was later identified as norepinephrine.

Acetylcholine and norepinephrine are two of a class of compounds called neurohumoral transmitters or neurotransmitters (NTs). Whenever an adequate stimulus is applied to a presynaptic neuron, the neuron releases an NT. The NT diffuses across the synaptic cleft (the space between the neurons) and may then either increase or decrease the likelihood that the postsynaptic neuron will fire. Most drugs that act on the CNS and that affect behavior act by influencing some aspect of neurotransmission. The various points of attack are listed below.

1. Synthesis of transmitter.
2. Release of transmitter.
3. Production of false transmitter. (A drug may replace the normal NT in a neuron, to be released later on nerve stimulation or by other drugs. The effects may or may not be similar to those of the normal transmitters.)
4. Selective neurotoxic agents.
5. Action on postsynaptic receptor. (When a drug combines with a receptor it may elicit the same effect as the normal NT or it may have no direct action, but by combining with the receptor may prevent the action of the normal transmitter.)
6. Destruction of transmitter.
7. Uptake inhibition. (Most NTs are inactivated primarily by being taken back up into the neurons or into extraneuronal sites. Many drugs act on one or both reuptake mechanisms.)
8. Changes in receptor sensitivity.

A few examples are in order. Botulinus toxin, an often deadly poison found in meats that have been improperly canned, acts by preventing the release of

acetylcholine. Reserpine, a drug that was once widely used as an antipsychotic and that is still popular in the treatment of hypertension, causes a slow, prolonged depletion of several NTs. Amphetamine promotes release of the same transmitters, but does so rapidly and briefly, so has very different effects from reserpine. L-DOPA is needed for the synthesis of dopamine and so is given to victims of Parkinson's disease, a condition that is associated with a dopamine deficit. (Dopamine itself is not administered because it does not get into the brain.) LSD is an antagonist of the NT serotonin. Many antidepressant drugs interfere with destruction of norepinephrine. Cocaine blocks the reuptake of norepinephrine.

Although many substances have been proposed as NTs, conclusive evidence is generally lacking. Several criteria must be satisfied, and the enterprise is enormously difficult. Hebb (21) suggested the following criteria.

1. The enzymes necessary for synthesis of the substance should be present within the neuron.
2. Direct application of the substance to the postsynaptic neuron should be equivalent in effect to stimulation of the presynaptic neuron.
3. Drugs that interfere with synthesis of the substance, or its reaction with the postsynaptic membrane, should block the effects of neuronal stimulation.
4. Drugs that block the enzyme which normally inactivates the substance should lead to a prolongation of its effects and of the effects of neuronal stimulation.

Two goals of brain researchers are to identify NTs at different synapses and to determine which NTs modulate particular behaviors. As noted above, evidence for establishing a particular substance as an NT is hard to come by. The second goal is equally hard to achieve, but researchers regularly speculate about which transmitters affect which behaviors. Such speculation is fine—it helps to organize data and leads to further research—but readers should be aware that almost all such speculation, given our present state of knowledge, is likely to be gross oversimplification. Several reasons are given below for exercising caution. Then, throwing caution to the winds, a listing is given of the various substances which have been proposed as transmitters, with brief speculations about their functions.

DIFFICULTIES INVOLVED IN ASSIGNING SPECIFIC FUNCTIONS TO NEUROTRANSMITTERS

Researchers have in the past administered drugs with (presumed) known effects on transmitter function. If the drug had effects on a particular behavior, the transmitter was assumed to play a role in the normal control of that behavior. Mandell et al. (30) showed the limitations of that approach. They

tested the effects of 25 amino acids on sleep and arousal in young chickens. The amino acids are normally found in the brain. Only eight of them were without effect. Six were behaviorally activating and 11 produced depression. Had the investigators merely tested one activating and one depressing amino acid, as in the model followed by many researchers, there would have been a temptation to conclude that they had found the crucial transmitters.

NTs act in combination with other NTs. Also, changes in the concentration of one transmitter may elicit compensatory changes in others.

Mandell (29) presented data which indicate widespread regulation of NT concentration throughout the CNS. Thus, if a drug blocks a receptor, more transmitter is subsequently synthesized and released. If the reuptake mechanism is blocked, synthesis and release slow down. Both norepinephrine and dopamine inhibit an enzyme which is required for their synthesis; thus, if either of the transmitters is present in high concentration, its rate of synthesis will be slowed; if supply of either transmitter is depleted, the inhibition is removed and synthesis speeds up. Since there are so many ways in which a drug may act on neurotransmission, it is unlikely that any drug impairs all mechanisms simultaneously. When some are impaired, others carry through with compensation and the transmitter-receptor interaction tends to return to a baseline state. It is worth mentioning that Mandell entitled his paper "Neurobiological barriers to euphoria." He believes that the existence of compensatory mechanisms assures that no drug will ever provide other than transient states of euphoria.

An additional reason for hesitation in assigning specific transmitter functions is the sheer complexity of the human CNS. There are many billions of neurons, and some of them synapse with as many as 10,000 other neurons. Neurochemistry is a vast field and new brain substances seem to be discovered almost daily. Therefore it is highly unlikely that many complex behaviors will be explained by the actions of a single NT on a single group of cells.

PROVED AND PROBABLE NEUROTRANSMITTERS OF THE HUMAN CNS

Several groups of scientists have mapped brain areas of greatest concentration, and NT circuits, for several NTs. (For descriptions of procedures used in mapping the circuits, see 9, 10, 14, 17, 25, 40 and 42.) The maps have served at least two useful functions. First, they show that NTs are unevenly distributed throughout the brain. Second, they suggest a method which has been widely used in brain research: stimulate (electrically or chemically) or lesion brain areas particularly rich in an NT, and study the resulting behavioral changes; the NT is presumed to be involved in the normal control of those behaviors most affected by the experimental manipulation.

Acetylcholine

Acetylcholine (ACh) excites postsynaptic neurons in some areas and is inhibitory in others. ACh has been implicated as a possible NT for such diverse behaviors as food and water intake, sleep and arousal, learning and memory, and motor activity. Several hallucinatory drugs have strong inhibitory actions on ACh, that is, they are anticholinergic. ACh has a much more rapid onset and duration of action than the catecholamine NTs (norepinephrine, epinephrine, and dopamine).

Catecholamines

Catecholamines are organic compounds that contain a catechol nucleus and an amine group (see the appendix for further details). Three different catecholamines are almost certainly NTs: dopamine, epinephrine, and norepinephrine.

Dopamine is important for the control of motor activity. Victims of Parkinson's disease, a severe motor disorder, have lowered levels of dopamine in the basal ganglia. Evidence is presented in chapter 8 for a linkage between dopamine excess and symptoms of schizophrenia.

Epinephrine is found in the hypothalamus and is probably involved in control of the autonomic nervous system.

Norepinephrine, like ACh, excites some cells and inhibits others. Norepinephrine, and the other catecholamines, have been implicated in the control of sleep and arousal, body temperature regulation, and food and water intake. There is a catecholamine theory of depression (see chapter 8).

5-Hydroxytryptamine (Serotonin)

5-hydroxytryptamine (5-HT) has also been implicated in the control of sleep and arousal and of mood. Tryptophan is an important precursor of 5-HT, that is, tryptophan is required for the synthesis of 5-HT. Tryptophan is an amino acid, the least abundant amino acid in dietary protein, and one which cannot be synthesized by mammalian cells. These facts were utilized by Hartmann (20) in developing a program of treating insomniacs without drugs. The subjects were placed on a high tryptophan diet, which has the effect of increasing brain levels of 5-HT, and they reported considerable relief from their insomnia.

Gamma-Aminobutyric Acid (GABA)

GABA is an amino acid that is inhibitory in most areas of the mammalian CNS. It may be the major inhibitory NT of the cerebral cortex. Recent evidence suggests that antianxiety drugs exert their effects via actions on GABA neurons. Mushrooms of the genus *Amanita*, which are hallucinogenic, contain the GABA agonist muscimol; muscimol may be one of the causative agents of the hallucinations.

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