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Hallucinogens: Neurochemical, Behavioral, and Clinical Perspectives

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TO DIANE

Preface

Humans have been self-administering hallucinogenic drugs for many hundreds of years, and apparently in a few societies, for thousands of years. Historically, the use of these drugs was almost exclusively for religious and/or mystical purposes. More recently, however, especially within the past 60 or 70 years, the recreational use of hallucinogens has increased substantially. This trend peaked in the middle 1960s, when the use of hallucinogenic drugs reached what some have described as epidemic proportions. Coincident with this rising recreational use and possibly spurred by it, there has been a growing interest in the biologic bases or mechanisms of action of hallucinogenic drugs. Many answers to these questions have been elucidated as a result of recent technical advances in the fields of pharmacology and neuroscience.

In retrospect, two discoveries can be singled out as being seminal for advancing our understanding of the biologic bases of hallucinogenic drugs. First, in the early to middle 1950s, the monoamines norepinephrine, dopamine, and serotonin were found within the mammalian central nervous system and shown to be differentially concentrated in various brain regions. Based on this, it was proposed that these compounds might act as chemical neurotransmitters in the central nervous system. A second important advance was made about 10 years later. A group of Swedish investigators, utilizing fluorescence histochemistry, produced a detailed map of the localization of the cell bodies, efferent pathways, and axon terminal distribution of these monoamine-containing neurons. This "wiring diagram" provided other investigators with the basic information that allowed them to study or manipulate these neurochemically identifiable groups of neurons. This pioneering research in these two related areas set the stage for much of what is described in the experimental chapters in this book.

On the basis of their own research as well as that of others, most authors in this volume have concluded that of all the brain neurotransmitters studied to date, none plays as crucial a role in drug-induced hallucinogenesis as serotonin.

The major focus of the present volume is to provide an up-to-date account of current research on the mechanisms of action of hallucinogenic drugs. The approach is a multidisciplinary one that, hopefully, avoids many of the pitfalls inherent in a dependency on any single experimental methodology.

The book begins with introductory chapters on the natural history of hallucinogens and on the effects of these drugs in humans, followed by two chapters on the behavioral effects of hallucinogens in animals, with one focusing on unconditioned, and the other on conditioned effects. The next section deals with neurochemical studies of hallucinogenic drug action in which structure–activity relationships and receptor binding are examined. This is followed by

two chapters in which the neurophysiologic aspects of the action of these drugs is examined at the single unit level, *in vitro* and in anesthetized rats, and in freely moving cats. The book concludes with an overview and speculations about future research in this field.

This book will be of interest to students and professionals in the fields of neuroscience, psychology, physiology, pharmacology, and psychiatry.

B. L. Jacobs

Acknowledgments

When Sam Enna, the series editor, wrote and asked me to edit a book on hallucinogenic drugs, I told him I would do it if one critical condition was met: I would have to obtain the agreement of the leading scientists in this field to contribute chapters. If even as few as two or three refused to undertake writing yet another chapter, the project, at least with me as editor, would be dropped. I am happy to say, and as the reader can plainly see from the list of contributing authors to this volume, that most of the scientists that I contacted agreed.

Many outstanding investigators who have made important contributions to the study of hallucinogenic drugs are not included among the authors in this volume for two reasons: First, this volume represents the field from my own scientific interest and perspective. Thus all research areas may not be represented. Second, in several of the content areas covered in this volume, there are considerably more than one or two excellent researchers. Space limitations and danger of overlapping subject coverage forced us to confine ourselves to nine chapters.

Two unique aspects of this book are worthy of mention. First, the reader will note that three of the chapters have authors from two different institutions. It was an expediency that saved me from having to choose between excellent scientists, and, more important, it fostered and encouraged a give-and-take dialogue between the coauthors. Second, this volume is not simply nine individually contributed chapters. In initial conversations and letters with many of the authors before they began their writing, we attempted both to cover the specific fields comprehensively and to insure that there would be little overlap between chapters. The attainment of these objectives was bolstered by having each author send me an initial draft of the chapter, which was then edited and sent back for revision. Much of this was time-consuming and I would like to thank both Sam Enna and Raven Press for their patience with me and confidence in this project.

I would also like to thank the Psychology Department at Princeton University and the National Institute of Mental Health for various forms of support which made this project feasible. I owe a special debt of gratitude to Ms. Arlene Kronewitter for her good humor and outstanding secretarial skills.

B. L. Jacobs

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The Natural History of Hallucinogens

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Wandering about in the planetary garden, botanists have encountered more than 700,000 species of plants. Many plants provide sources of food; others provide materials for clothing and shelter; still others yield medicines and poisons. Among this latter group, 91 species have been identified as hallucinogenic plants. These plants are unique: sometimes "magic," "mystical," or "religious." They are actually complex chemical factories that produce compounds capable of inducing hallucinations. These compounds are referred to as hallucinogens.

Experiences with hallucinogens have puzzled and intrigued man for centuries. They have given him "sights" to see, "voices" to hear, "thoughts" to ponder, and "altered states of consciousness" to explore. They have generated conditions that can only be described by such global terms as ecstacy or madness. It is not surprising that man has given these drugs numerous descriptions varying widely in precision. A study of these historic descriptions adds greatly to a definition of hallucinogens. In the following section, the definitions used in early historic works are examined in an effort to explain the conceptual grouping of some drugs as hallucinogens.

The history of the drugs that are defined as hallucinogens is explored through the natural history of their development among the flora and fauna of the planetary garden. From early uses by primitive peoples to later experimentation, hallucinogens followed a natural path dictated by certain chemical properties and behavioral possibilities. First, the common botanical origins of these plant drugs are discussed in terms of the production of alkaloids which had unusual consequences for browsing animal life. These accidental encounters were observed by early man, who quickly discovered the unique properties of the hallucinogenic plants. The story of primitive experimentation with five representative groups of hallucinogenic plants is then told. Such experimental use appeared to be chiefly concerned with perceptual changes, and the history of the experimental analysis of these phenomena is briefly described. The discussion is then concluded by an outline of theoretical speculations and future developments in this natural history.

DEFINITIONS AND HISTORIC WORKS ON HALLUCINOGENS

Succinctly defined, the word hallucinogen refers to substances capable of producing hallucinations. Hallucinations, in turn, comes from the Latin *alucinatio,* meaning a wandering in mind, idle talk, prating. To the extent that substances produce a wandering in mind or attention, most psychoactive drugs might qualify as hallucinogens. However, hallucinations have more commonly referred to visions and apparitions. The first use of the word in the English language was by Lavater (1572), who used the term to refer to "ghostes and spirites walking by nyght" (32). Accordingly, hallucinogens become substances that produce false sensory perceptions in the absence of an actual external stimulus. These false perceptions can occur in any of the senses.

The definition remains far from precise. While the 91 plant hallucinogens, and a greater number of synthetic hallucinogens, are capable of producing hallucinations, other drugs may also produce these false perceptions, particularly when taken in toxic or lethal dosages. Conversely, the classic plant hallucinogens often produce nonhallucinatory effects as well as experiences lacking in false perceptions. In order to circumvent this difficulty, Hoffer and Osmond (15) offer the following broad and generally accepted definition:

> Hallucinogens are then chemicals which in nontoxic doses produce changes in perception, in thought, and in mood, but which seldom produce mental confusion, memory loss, or disorientation for person, place, and time.

This contemporary definition is reminiscent of the description offered by French psychiatrist Jacques Moreau (23) in the first book on hallucinogens in 1845. Although Humphrey Davy (5) had published a 600-page book on nitrous oxide and its hallucinatory effects in 1800, Moreau's work was the first to include other hallucinogens. Moreau claimed that one could study mental illness by provoking it artificially through the ingestion of hashish (*Cannabis*), which possessed the characteristics of plunging one into an hallucinatory state while preserving the ability to observe and report events. Moreau described hallucinations as being similar to dreams wherein imagined visual, auditory, and tactile stimuli appear to be part of reality. He noted that the psychologic phenomena of hallucinations were basically the same whether induced by nitrous oxide, *Datura stramonium, Atropa belladonna, Hyoscyamus niger,* or a variety of other hallucinogens. With uncanny insight into what future neurophysiologic research would reveal, Moreau believed that the hallucinatory state resulted from excitation of the brain, which enabled imagined thoughts and memories to become transformed into the sensory impressions of visions and sounds:[1]

> . . . the hallucinating person hears his own thoughts as he sees, hears the creations of his imagination as he is moved by his memories . . . and, what is even more extraordinary, certain combinations of thought are transformed into sensory impressions—that is to say, are endowed with the property of acting physically upon our senses in the manner of exterior stimuli.

[1] Translated from the original by R. K. Siegel.

After experimenting on both himself and his patients, Moreau tried to persuade his colleagues at the Hôpital de Bicetre to try hashish for themselves. His medical friends were hesitant to accept Moreau's notion of "objective experimentation" with a hallucinogen, but the Bohemian artists and writers of 19th century Paris were more receptive. Among them were several writers who formed the Club des Haschichins. Its members included Theophile Gautier, Honore de Balzac, Charles Baudelaire, Alexander Dumas, and Victor Hugo. Their writings emphasized various aspects of the hashish-induced hallucinatory experience, including an overwhelming joy.

The second book on hallucinogens, *Die narkotischen Genussmittel und der Mensch* by Ernst Freiherr von Bibra (37) in 1855, referred to the hallucinogenic plants as *Genussmittel,* meaning "medium of enjoyment." In the same year, James Johnston, in his two-volume masterpiece *The Chemistry of Common Life* (19), referred to these plants as "narcotics." Johnston wrote that man uses narcotics to "multiply his enjoyments, intellectual and animal, and for the time to exalt them" (vol. II, p. 7). Included in his extensive discussion of narcotics were *Cannabis, Datura,* and *Amanita.* Here, as in later books on hallucinogens, the word narcotic was used in its broadest sense, meaning to benumb or to stupefy. Thus a narcotic was viewed as any substance which, when taken into the body, induced drowsiness, sleep, stupefaction, or insensibility. Certain stages of intoxication resulting from hallucinogens, such as *Cannabis,* and even stimulants, such as coca, were seen as depressive enough to qualify for the classification of narcotic.

The next book on hallucinogens, *The Seven Sisters of Sleep* by British mycologist M. C. Cooke (4), continued the narcotic labeling but suggested that the hallucinations and stimulating effects of drugs, such as *Cannabis,* make them qualitatively different from opium and the other "sisters of sleep." Several texts were subsequently published in both Europe and the United States, and these retained either the narcotic or *Genussmittel* classifications. Among these, Hartwich's 1911 opus *Die Menschlichen Genussmittel* (14) is noteworthy in that it added new drugs to the list of those capable of producing hallucinations. In 1907, De Veze (6) made the daring attempt to separate psychoactive substances into narcotic plants (opium) and magical plants (*Cannabis* and other hallucinogens), but his classification system was not adopted widely.

The definitions did not change substantially until the publication of Louis Lewin's *Phantastica* (22) in 1924. An influential German toxicologist and early psychopharmacologist, Lewin classified narcotic and stimulating drugs into five subgroups: euphorica, phantastica, inebriantia, hypnotica, and excitantia. His definition of phantastica is a definition of hallucinogens:

> Phantastica; hallucinating substances. This series comprises a number of substances of vegetable origin, varying greatly in their chemical constitution, and to these belongs in its proper sense the name Phantastica, or Drugs of Illusion. The representatives of this group, such as mescal buttons (*Anhalonium lewinii*), Indian hemp (*Cannabis indica*), and the plants which contain tropines, bring about evident cerebral excitation in the form of hallucinations, illusions, and visions. These

phenomena may be accompanied or followed by unconsciousness or other symptoms of altered cerebral functioning.

While Lewin's term phantastica did not survive in the literature, his separate classification of hallucinating substances did. Various alternative labels have been applied to these drugs, including deliriants, delusionogens, eidetics, hallucinogens, misperceptinogens, mysticomimetics, phanerothymes, phantasticants, psychedelics, psycotics, psychoticants, psychogens, psychosomimetics, psychodysleptics, psychotaraxics, psychotogens, psychotomimetics, and schizogens. Of these terms, three have persisted in the contemporary literature. Several texts (e.g., ref. 7) use the term psychotomimetic, which Hollister (16) defines with five criteria:

(a) In proportion to other effects, changes in thought, perception and mood should predominate; (b) intellectual or memory impairment should be minimal with doses producing the above mental effects; with large doses these may occur; (c) stupor, narcosis or excessive stimulation should not be an integral part of the action; (d) autonomic nervous system side-effects should be neither disabling nor severely disconcerting; (e) addictive craving should be minimal.

Objections to the use of psychotomimetics have been raised on the grounds that the term is pejorative, limiting, and misleading. For example, Grinspoon and Bakalar (12) note that the symptoms of the drug reaction at times resemble the symptoms of functional psychoses, but most investigators agree they are not the same. Alternatively, these authors adopt the popular term psychedelic, a term coined by psychiatrist Humphrey Osmond in a correspondence with novelist Aldous Huxley in 1956, meaning "mind manifesting" or "mind revealing." The term psychedelic has acquired numerous value-laden cultural meanings, however, which compromise its utility in academic or scientific discourse.

The third term in current use, hallucinogens, is the one Osmond himself selected after discarding psychedelic for scientific writings (15). The term hallucinogen perhaps overemphasizes the perceptual effects, but its continuing use as the classification of choice in science has served to deemphasize perceptual effects and give balanced attention to changes in thought and mood. It is also the term adopted by anthropologists (e.g., ref. 11), botanists, and chemists (e.g., ref. 26), as well as psychiatric workers studying drug-induced hallucinations (e.g., ref. 9). As these scientists are fond of noting, from their botanical origins, it was precisely the overemphasized perceptual effects that led to the discovery, identification, and use of hallucinogenic plants.

BOTANICAL ORIGINS

Hallucinogenic species occur among the highest evolved flowering plants (angiosperms) and in one division (fungi) of the simpler plants. As a general rule, these plants are rich in bitter-tasting alkaloids that act as extremely effective feeding deterents. Alkaloids also have a wide range of physiologic activity, including psychologic, teratogenic, and toxic effects. Indeed, it has been argued

that many of the naturally occurring hallucinogenic plants are evolutionarily justified in terms of the maladaptive effects that they could have on herbivores (29). The initial effects of such plant browsing—bitterness, nausea, emesis, and dizziness—give animals clear warnings to avoid continued feeding. Interestingly, most of the angiosperm hallucinogens evolved at roughly the same time the giant dinosaurs began to disappear. Swain (36) has noted that these reptiles, unlike the birds and mammals that followed, failed to evolve effective mechanisms with which to detect and/or detoxify these alkaloids. Subsequently, changes occurred in the thickness of dinosaur egg shells; there was an increase in the size of their hypothalamus; and their fossils have been found in contorted positions suggestive of alkaloid poisoning. It may be speculated that alkaloid poisoning contributed to the ultimate demise of at least some dinosaurs.

Today, perhaps 65 million years later, veterinarians are well acquainted with the contorted bodies of grazing horses, cattle, and other animals that have accidentally ingested lethal amounts of highly toxic hallucinogenic plants, such as *Datura* (33). Similar accidents have occurred in man. For example, a group of soldiers, sent to Jamestown in 1676 to quell Bacon's Rebellion, ate the young shoots of *Datura* as a pot green and became severely intoxicated for several days. *Datura* (containing scopolamine, atropine, and hyoscyamine) has since been known as "Jamestown" or jimson weed. Anthony's legion had a similar *Datura* accident during a retreat in 38–37 B.C.

Periodic ingestions of the fungus *Claviceps purpurea,* which attacks rye and other small grains or forage plants, caused the convulsive or gangrenous death of many grazing animals. This fungal disease is known as ergot, meaning "spur," and refers to the sclerotium or fruiting body of the fungus which parasitically replaces the grain kernel. The pharmacologically active constituents of ergot include ergoline alkaloids, mainly derivatives of lysergic acid. When the fungus-infected rye kernels were milled into flour, periodic outbreaks of ergotism occurred, resulting from eating the poisoned bread. Epidemics occurred in France as far back as 857 A.D. and as recently as 1951. In 944 A.D., 40,000 people died of the disorder. In many such cases, the death of dogs and other animals fed on the rye fungus was equally unavoidable and dramatic.

There are two types of ergotism: gangrenous and convulsive. Gangrenous ergotism was known by a number of names, including *ignis sacer,* the holy fire, or St. Anthony's fire, in reference to the feverish hallucinations of fires and devils. This condition is usually characterized by dry gangrene of the extremities, followed by the falling away of the affected portions of the body. Convulsive ergotism is characterized by symptoms including crawling sensations in the skin, tingling in the fingers, vertigo, tinnitus aurium, headaches, disturbances in sensation, hallucinations, painful muscular contractions leading to epileptiform convulsions, vomiting, and diarrhea. Muscle fibers are involuntarily contracted, and mental disturbances, including mania, melancholia, psychosis, and delirium, occur.

Symptoms of convulsive ergotism were conspicuous in the Salem witchcraft records of the 17th century. The sudden onset of the condition was considered

symptomatic of demonic possession rather than disease. In her 1976 study of the Salem witch trials, Caporael (3) notes that "the content of hallucinations and other perceptual disturbances would have been greatly influenced by the state of mind, mood, and expectations of the individual." Accordingly, victims who experienced visions of undulating objects and lights tended to interpret them as specters of accused witches or agents of the devil in animal form. Spanos and Gottlieb (35), however, have argued that hallucinations, such as are to be expected from ergot, were conspicuously absent from these reports.

In his account of the 1951 ergotism epidemic in France, Fuller (10) describes the presence of classic drug-induced hallucinations among the victims:

> A common vision among the sick was that of fireballs coming toward them, then receding and coming back again. *Zoopsie,* hallucinatory visions of animals, was rampant among the victims . . . patients talked of the astonishing, brilliant, vivid, intense, and unbelievable colors—orange, red, brilliant white, moving in spirals, glowing from objects—that encompassed all their surrounding. Others described the conviction that they had been in a vast room, where the ceiling descended and the walls closed in on them, ready to crush them to death. Or there were those who described the feeling that their arms were pulling into their bodies, their knees telescoping up into their shoulders and chests. Auditory hallucinations—the noise of a clock, music, voices—were rare but noted by some. Three of the victims were absolutely sure they were witnessing their own funerals and actually invited the fatigued volunteers to take part in the obsequies. Nearly always the same hallucinations returned to each individual, varying little from the one that struck the victim at the beginning. Some patients were in helpless confusion, knowing neither time nor space. Some were not even able to perceive heat when they were so tested. Often the tetanuslike convulsions would seize the patients and throw them into uncontrolled paroxysms, usually at the times the hallucinations began again.

Ingestion of hallucinogenic plant alkaloids and allied compounds does not always result in death. Many grazing animals display paresis, ataxia, dullness, and a tendency to isolate themselves from the herd. Some animals appear to act bizarre. Observations of such animal-plant interactions could have provided man with much information about hallucinogens.

Even when ingestion of plant hallucinogens did not result in death or even intoxication of the animals, it did contribute to the dispersal of these plants throughout the world. For example, horses and cattle constantly swallow spores of hallucinogenic fungi (e.g., *Psilocybe* spp.) in the grass they eat and pass them in a germinating condition. Other plants ingested and dispersed by animals throughout the world include: *Cannabis* (insects, birds, rodents), *Datura* (goats, cattle, horses, ants), *Atropa belladonna* (birds, pigs), *Claviceps purpurea* (flies), and *Amanita muscaria* (deer, rodents, insects).

DISCOVERY OF HALLUCINOGENS BY OBSERVATIONS ON ANIMALS

Not all man's encounters with naturally occurring hallucinogens were accidental. Ritual, magic, religious, or medicinal uses of these drugs date back into

the early history of both Old and New World peoples. Anthropologists have traced the use of hallucinogens as far back as paleolithic Europe and neolithic Asia Minor. Archaeologically, hallucinogen use has been dated to 8500 B.C. in the New World. Throughout recorded history, there are abundant instances of such plant use being surprisingly discriminative and efficacious. Early man learned much of this basic psychopharmacology from observations on animal-plant interactions.

Folklore and mythology are replete with examples of man's discovery of these hallucinogenic plants through observations on animals (27). For example, *Tabernanthe iboga,* a tropical West African shrub containing the hallucinogen ibogaine, was reportedly discovered by boars, porcupines, and gorillas. According to one anthropologist: "Several accounts mention that the natives saw boars dig up and eat the roots of the plant, only to go into a wild frenzy, jumping around and perhaps fleeing from frightening visions" (29). In Eastern Europe, a folktale tells that the avidity with which grasshoppers and leafhoppers jump about the *Cannabis* plant suggested its properties as a strong and stimulating plant. The story is probably related to the Polish custom of dancing or jumping to promote the growth of the plant. The hemp dance, as it is called, is modeled after movements of these creatures and is marked by high jumps with much excitement and enjoyment. Even the ancient Greeks and Scythians were reported to have adopted the habit of eating seeds from the *Cannabis* plant after watching finches pick at them with a remarkable passion. The Greek physician Galen (130–200 A.D.) wrote that it was customary to give hemp seeds to the guests at banquets as a promoter of hilarity, enjoyment, and passion.

The names given by early man to hallucinogenic plants also reveal much about their observed effects on animals. The etymology of such terms provides us with an instructive lesson in the natural history of animal use of these drugs. Many plants were named for their apparent aversive properties. Henbane (*Hyoscyamus niger,* containing atropine and scopolamine) seems to have derived its name from the baneful effects its seeds have upon poultry. When eaten by man, henbane produced sleepy and drowsy behavior and thus acquired the alternative name "insana." Fly-agaric (*Amanita muscaria*) killed the flies that landed on it. Wormwood (*Absinthium* spp., containing thujone, which is similar to tetrahydrocannabinol found in *Cannabis*) drove away insects and insect larvae. Flea bane (marigolds, including the hallucinogenic *Tagetes lucida*) repulsed fleas and other insects. Other plants were identified by the attraction that animals displayed toward them. Catnip (*Nepeta cataria,* containing the hallucinogen nepetalactone) attracted cats that eagerly ingested it. Pigeon candy was an early vernacular name for *Cannabis* seeds because of its stimulating effects on pigeons.

EARLY EXPERIMENTATION BY MAN

Despite the benefit of animal observation, early man developed experience with hallucinogenic plants far beyond that obtained by animals. Cultural uses of hallucinogens established efficient methods for harnessing the specific psy-

choactive properties of these plants. Experimentation with *Amanita* resulted in patterns of recycling active ingredients that passed into the urine. Controlled usage of the deadly ergot alkaloids from *Claviceps* and other plant sources contributed greatly to religious ecstasy among both ancient Greeks and Aztecs. *Cannabis* was found to be effective via inhalation of the burning plant. Resin from the bark of *Virola* trees and beans from *Anadenanthera peregrina* trees were found by South American Indians to be effective hallucinogens when administered intranasally as snuffs. Peyote (*Lophophora williamsii*) was employed by Indians in Mexico who discovered it to be an effective medicine and ceremonial hallucinogen when orally ingested or administered as an enema. Several members of the Nightshade family of plants (mainly *Hyoscyamus niger, Atropa belladonna,* and *Mandragora officinarum*) were employed by medieval witches who experimented with topical applications and discovered the broom as an effective vaginal applicator for their hallucinatory ointments.

Amanita

Fly-agaric, or *Amanita muscaria,* a mushroom native to Europe, Africa, Asia, and America, is perhaps man's oldest hallucinogen. The initial discovery may have been prompted by animal use. The native peoples of the Asian forest and tundra regions in Siberia, who employ fly-agaric in shamanistic practices, have observed their reindeer browsing the mushrooms. This browsing results in the reindeer becoming unmanageable and suffering "profound mental disturbances" (38). The natives may have copied this behavior only to discover the hallucinatory effects they later employed in their shamanism. The most expressive account of *Amanita* intoxication is given by anthropologist Waldemar Jochelson who traveled among the Koryaks in Siberia (38):

> Like certain other vegetable poisons, as opium and hashish, the alkaloid of fly-agaric produces intoxication, hallucinations, and delirium. Light forms of intoxication are accompanied by a certain degree of animation and some spontaneity of movements. Many shamans, previous to their seances, eat fly-agaric in order to get into ecstatic states. . . . Under strong intoxication, the senses become deranged; surrounding objects appear either very large or very small, hallucinations set in, spontaneous movements, and convulsions. So far as I could observe, attacks of great animation alternate with moments of deep depression. The person intoxicated by fly-agaric sits quietly rocking from side to side, even taking part in the conversation with his family. Suddenly his eyes dilate, he begins to gesticulate convulsively, converses with persons whom he imagines he sees, sings, and dances. Then an interval of rest sets in again.

The Koryaks were also urine drinkers. They rapidly discovered that the active principles of fly-agaric are excreted unchanged in the urine and practiced saving their postmushroom urine for additional intoxications. Ceremonial urine drinking is also mentioned in the Rig-Veda, a 3,500-year-old collection of hymns celebrating Soma, the god-narcotic of ancient India. Called soma, this most ancient of all hallucinogens has now been identified as *Amanita.* It has also been suggested that *Amanita* may have been the original Tree of Knowledge in the Garden of Eden (25).

As early settlers crossed the Bering Strait into the Americas, remnants of the fly-agaric shamanism followed. Consequently, it is not surprising that religious use of this mushroom has been found among the native Indians in northwestern Canada and on Lake Superior in Michigan. Use has also been suspected among the Maya of highland Guatemala, who refer to its sacred power as "evil or diabolical mushroom" (25). This early experimental use of fly-agaric, involving drying the mushrooms and recycling the urine, appears to have a firm pharmacologic basis. Ibotenic acid and the alkaloid muscimole have been isolated from the mushroom. Initially, the drying of the mushroom induces the transformation, through decarboxylation, to the more active muscimole. Both ibotenic acid and muscimole are found in human urine within 1 hr after ingestion of *Amanita.* Thus the early experimentation by man led to the highly efficacious use of this ancient hallucinogen.

Ergot Alkaloids

Despite the mass poisonings and hallucinatory attacks that accompanied accidental ergot use in medieval Europe, midwives found that ergot could help labor pains. They were not the only ones who discovered uses for the ergot alkaloids, however. Religious, magic, and medical uses were employed by numerous cultural groups of early man. After the conquest of Mexico, for example, the Spanish chronicler Hernandez, who was physician to the King of Spain, reported in 1651 that *ololiuqui* and *tlitliltzin* were important divinatory hallucinogens among the Aztecs. Since that time, *ololiuqui* has been identified as the seeds of *Rivea* or *Turbina corymbosa,* and *tlitliltzin* consisted of the seeds of *Ipomoea violacea.* These seeds contain ergine (*d*-lysergic acid diethylamide) and *iso*-ergine and other related bases, including chanoclavine, elymoclavine, and lysergol. *Ololiuqui* was used to produce hallucinations for religious practices: "When the priests wanted to commune with their gods and receive messages from them, they ate this plant to induce a delirium. A thousand visions and satanic hallucinations appeared to them" (11).

Deliberate ingestion of ergot alkaloids for the purpose of religious hallucinations also took place in ancient Greece during the Mysteries of Eleusis (39). There, for almost 2,000 years, initiates entered the portals of Eleusis to celebrate the divine gift of grain. They emerged the next day reporting trembling in the limbs, vertigo, nausea, sweating, and a sense of awe and wonder at an indescribable vision (39):

> Then there came the vision, a sight amidst an aura of brilliant light that suddenly flickered through the darkened chamber. Eyes had never before seen the like, and apart from the formal prohibition against telling of what had happened, the experience itself was incommunicable, for there are no words adequate to the task. Even a poet could only say that he had seen the beginning and the end of life and known that they were one, something given by god. The division between earth and sky melted into a pillar of light.

The hallucinogen ingested in these ceremonies was *Claviceps paspali* that grew on the various cereal grasses native to Greece. This fungus, like *C. purpurea,* contains substantial amounts of ergonovine together with the hallucinogenic alkaloids of the ergotamine and ergotoxine group. The ecstatic visions at Eleusis may have been the only deliberate hallucinogenic use of *Claviceps* by man. However, there has been recent speculation about the intentional use of ergot by a small school of medieval Flemish artists, including Hieronymus Bosch.

Cannabis

Early experimentation with the genus of plants known as *Cannabis,* a Greek word meaning hemp-like, led man to a wide variety of medical and nonmedical uses. Originally an Old World plant that originated in the desert region in Central Asia, *Cannabis* was probably unknown in the Western Hemisphere before the 16th century. Archaeologic specimens have been found in both Asia and Europe, indicating that knowledge of its use by man goes back more than 6,000 years. Coarse hemp fabrics have been excavated from some of the oldest sites of human habitation in Europe, showing that most if not all early uses were for fiber. Medical and pharmacologic uses may have begun in 2737 B.C. with the publication of the Chinese emperor Shen-Nung's pharmacopeia, which urged the use of *Cannabis* for a variety of medicinal properties. Since that time, the folk medicine of many peoples have included *Cannabis* preparations.

Anthropologists have speculated that use of *Cannabis* may be far older than these findings indicate. Early man, searching for edible plants, could have been led by the powerful odor of the ripened tips of the weeds and discovered the edible seeds. The female *Cannabis* plants bear the fruit, which is a single seed tightly covered by the hardened wall of the ovary. This seed is enclosed within a hairy bract sheathing with abundant resin glands, which secrete the psychoactive chemicals. While searching for the seeds, early man could have simply rubbed against the plant, causing the sticky resin to adhere to his naked skin. Licking or grooming the skin would have introduced him to the more euphoriant and hallucinatory properties of this plant. Indeed, in Nepal, the resins were once collected by having naked men run through *Cannabis* fields and then scraping off the sticky substance that adhered to their skin.

Other accidents could have introduced early cultures to the hallucinatory effects. While harvesting the plant for seeds (for oil) or fiber, accidental fires could have produced a resinous smoke, which was then inhaled. The smoke would have also appealed to the magicoreligious practices of native shamans (30). The smoke itself is inherently evocative of visions and mystery—a natural medium for shamanism: It contained a property that could induce a form of trance; it was readily consumed by the cleansing power of fire; its smoke rose to the abode of the gods; and it allowed dreams to be materialized.

These hallucinogenic properties were recognized when *Cannabis* was administered in a variety of ways. The Scythians threw hemp seeds on hot rocks

and inhaled the resulting vapors. One account relates how they danced, sang, and howled with joy after such vapor baths. The ravings of the priestess Pythia at Delphi may have been the consequences of inhaling hemp seed vapors together with carbon dioxide vented from the ground beneath the oracle. The Greeks drank *Cannabis* with wine and myrrh to produce visions or ate hemp cakes to produce intoxications. In ancient India, various mixtures of leaves, resins, and flowering tops of *Cannabis* were employed as candies, teas, or smoking mixtures for religious and visionary quests. In Assyria, it was used as an inebriating incense. In Persia, a tincture of hashish was used to produce religious visions. According to Marco Polo, the secret cult of Hashishins ingested the resin in order to experience visions of the afterlife. In ancient African rites, tribal participants inhaled fumes from piles of smoldering *Cannabis* before employing reed tubes and pipes with which to induce religious visions.

In most of these practices, the hallucinations were one of the most salient features of the intoxications. A glimpse at the nature of these experiences is provided by William James (18), who cited the following account from a friend who ingested hashish:

> Directly I lay down upon a sofa there appeared before my eyes several rows of human hands, which oscillated for a moment, revolved and then changed to spoons. The same motions were repeated, the objects changing to wheels, tin soldiers, lamp-posts, brooms, and countless other absurdities. . . . I saw at least a thousand different objects. These whirling images did not appear like the realities of life, but had the character of the secondary images seen in the eye after looking at some brightly-illuminated object. . . . I became aware of the fact that my pulse was beating rapidly. . . . I could feel each pulsation through my whole system. . . . There were moments of apparent lucidity, when it seemed as if I could see within myself, and watch the pumping of my heart. A strange fear came over me, a certainty that I should never recover from the effects. . . . Suddenly there was a roar and a blast of sound and the word "Ismaral". . . . I thought of a fox, and instantly I was transformed into that animal. I could distinctly feel myself a fox, could see my long ears and bushy tail, and by a sort of introversion felt that my complete anatomy was that of a fox. Suddenly, the point of vision changed. My eyes seemed to be located at the back of my mouth; I looked out between the parted lips, saw the two rows of pointed teeth, and, closing my mouth with a snap, saw—nothing . . . the whirling images appeared again. . . . It was an image of a double-faced doll, with a cylindrical body, running down to a point like a peg-top. It was always the same, having a sort of crown on its head, and painted in two colors, green and brown, on a background of blue.

Hallucinogenic Snuffs

The earliest archaeological evidence for the use of hallucinogenic snuffs dates to 1500 B.C. in Mesoamerica. Use of tobacco snuffs, from which such use was modeled, however, may date to 5000 B.C. There are probably no animal examples of intranasal self-administration that served as original models for this behavior, although the iconography of snuffing pipes and other paraphernalia is replete with animal symbolism (11). Bird bones were commonly used as early snuffing

tubes, although other tubes and nose pipes were made from fired clay, wood, and bamboo.

The most important hallucinogenic snuff is *Anadenanthera* (*peregrina* and *colubrina*), which is primarily used in the Orinoco basin of Colombia and Venezuela but has been found in shamanistic use in northern Argentina, Brazil, and even the West Indies. The Indians of the Orinoco have developed an elaborate recipe for preparation of the *Anadenanthera* seeds, which are abundant in tryptamine derivatives, including bufotenine and dimethyltryptamine. The seeds are usually toasted and pulverized and sometimes mixed with alkaline substances, such as lime from snails or ashes. Enormous amounts of the resultant powder are then blown forcefully into the nostrils through long tubes. The snuff is sometimes taken as a daily stimulant but most often is used to induce hallucinatory trances wherein the user communicates with supernatural beings. The snuff is believed to protect against sickness and to make hunters and their dogs more alert. (It is interesting to note that *Anadenanthera* enemas were employed by the Incas for their hallucinogenic effects.)

Another important snuff is prepared from several species of *Virola* in the upper Orinoco and western part of the Amazon. Once again, native Indians developed a complex recipe for the snuff powder, used in annual 2- or 3-day ceremonies involving large dosages. Their native empiricism illustrates a sophisticated sense of psychopharmacology. The inner bark of most species of *Virola* contains a red resin, which is scraped, boiled down to a thick syrup, dried, pulverized into a fine dust-like powder, and sometimes mixed with other ingredients. The boiling is thought to deactivate enzymes which can destroy the alkaloids, while some of the ingredients, such as the highly aromatic leaves of *Justicia pectoralis,* are hallucinogenic as well. *Virola* snuff contains approximately 11% 5-methoxy-N,N-dimethyltryptamine as well as related tryptamines. While these tryptamines are generally not active orally, the presence of β-carbolines, acting as monoamine oxidase inhibitors, may be the key ingredient in allowing the natives to experience profound hallucinatory effects from intranasal use. Schultes (24) reports that within minutes after a large dose of *Virola* is blown into the nostrils, the characteristic effects are:

> Numbness and tingling of the limbs, twitching of the facial muscles, inability to coordinate muscular activity, nausea, visual hallucinations, and a deep stupor are characteristic. Macroscopia is frequent, entering into Waika belief about the spirits that dwell within the plant. Levitation, or a sensation of floating in air or flying, is reported.

Peyote

Peyote is a common term for two species of cactus, *Lophophora williamsii* and *L. diffusa,* native to Mexico and Texas. Archaeological specimens suggest that peyote has been used ceremonially for perhaps as many as 8,000 years. Known to the Aztecs as *peyotl,* the ritual use of this cactus has persisted among

contemporary Mexican groups. Peyote contains more than 50 alkaloids, the most important of which is mescaline.

Most ritual use has involved ingestion of the raw peyote by itself or in cold water "soups" prepared with dried powdered cactus buttons and fresh green cactus tops. The Huichol Indians in the western Sierra Madre in Mexico have also employed peyote enemas using a syringe of deer femur and a bulb of deer bladder. Informants claim that the enema infusion bypasses the traditional nausea and vomiting associated with oral ingestion and is favored by shamans with weak stomachs (11).

The main purpose of peyote use is to induce visions that put the user into contact with the spirit world. Ellis (8) provided a detailed account of the classic peyote vision:

> The appearance of vision with closed eyes was very gradual. At first there was merely a vague play of light and shade which suggested pictures, but never made them. Then the pictures became more definite, but too confused and crowded to be described, beyond saying that they were of the same character as the images of the kaleidoscope, symmetrical groupings of spiked objects. Then, in the course of the evening, they became distinct, but still indescribable—mostly a vast field of golden jewels, studded with red and green stones, ever changing. . . . On the whole, I should say that the images were most usually what might be called living arabesques . . . all sorts of odd and grotesque images passed in succession through my mind during part of the first night. They might have been the dreams of a Baudelaire or of an Aubrey Beardsley. I would see figures with prodigious limbs, or strangely dwarfed and curtailed, or impossible combinations such as five or six fish, the color of canaries, floating about in air in a gold wire cage. But these were purely mental images, like the visions seen in a dream by a distempered brain.

An equally important native use for peyote was as a medicine and stimulant. Indeed, even in religious ceremonies, the use of peyote is clearly therapeutic. Peyote has been used to purge the body of sickness through vomiting, to alleviate alcoholic hangovers and intoxications, and to protect the user from sickness. Anderson (1) notes the range of application in modern peyote cult use:

> In fact, some Indians believe that peyote can cure nearly everything; they claim it to be effective as a cure for tuberculosis, pneumonia, rheumatism, scarlet fever, venereal disease, diabetes, influenza, colds, hemorrhages, intestinal ills, cramps, fainting spells, bites, cuts, bruises, wounds, snake bite, and toothache. A partly chewed "button" may even be used externally on bruises, wounds, or bites. In a sense, the Indian employs peyote like those of the white culture use aspirin—as a tonic to relieve pain and facilitate healing.

Not surprisingly, peyote enjoyed a brief period of use as a cardiac tonic. Recently, one of its alkaloids, hordenine, has been credited with antiseptic action against a wide spectrum of microorganisms.

Nightshade

The Nightshade family of plants includes three important hallucinogens: *Atropa belladonna* (belladonna), *Hyoscyamus niger* (henbane), and *Mandragora*

officinarun (mandrake). These plants contain the alkaloids hyoscyamine, atropine, and scopolamine throughout plant parts, but the highest concentrations are in the seeds and roots. The hallucinogenic effects are produced by the scopolamine, which allows for a narcosis in which hallucinations are experienced. The resultant state is substantially different from, and more toxic than, that produced by the more classic hallucinogens (25).

> Those experiencing intoxication with Henbane feel a pressure in the head, a sensation as if someone were closing the eyelids by force; sight becomes unclear, objects are distorted in shape, and the most unusual visual hallucinations are induced. Gustatory and olfactory hallucinations frequently accompany the intoxication. Eventually sleep, disturbed by dreams and hallucinations, ends the inebriation.

These plants have a long history of use as magic plants in sorcery and witchcraft. While used in ancient Egypt and Greece to mimic insanity and allow for divination of future events, it was during the Middle Ages in Europe that they attained their most sophisticated applications. An elegant analysis of primary sources from as early as 1470 by anthropologist Michael Harner (13) had revealed much about these early uses. The European witches rubbed their bodies with an ointment containing such plants as belladonna, mandrake, and henbane; the atropine and scopolamine from the plants was readily absorbable through the skin. The associated nakedness of the witches' meetings thus facilitated absorption, as did application of the ointment "under the arms and in other hairy places." The staff or broom also associated with witches served as an applicator for the hallucinogenic ointment to the sensitive vaginal membranes. Typically, the anointed witch would then straddle the broom to help provide the suggestion of riding on a steed, a common illusion of the witches' ride to the Sabbat. The Sabbat was actually an hallucinatory state in which the participants took an imaginary aerial journey to a rendezvous with spirits or demons. While in this state, they would sometimes experience the hallucination of being transformed into a wolf or other predatory animal (lycanthropy). This latter hallucination was facilitated by the wearing of a wolf skin or wolf skin girdle; the tactile suggestions of the wolf skin coupled with the drug-induced parasthesias strongly influenced the experience.

Numerous observers of these rituals have described the witches as appearing stuporous and almost catatonic after the ointment took effect. The lowered body temperature and lack of responsivity to stimulation prompted people to believe that the witches had "died" temporarily and were in communication with the devil:

> . . . the devil enters them and deprives them of sense and they fall as dead and cold. And he represents to their fancies that they go to other houses and places and do and see and say such and such things. But nothing of this is true, though they think it to be, and though they relate many things of what passes there. And while they are thus dead and cold they have no more feeling than a corpse and may be scourged and burnt; but after the time agreed upon with the devil he leaves them, their senses are liberated, they arise well and merry, related what they have done and bring news from other lands. (Ciruelo, 1628, in ref. 13, pp. 134–135.)

Direct reports of the experience from the witches themselves often consisted of sensations of flying, floating out of their bodies, and strange images, reports consistent with dissociative hallucinatory reactions. Experimental administration of a "flying ointment" prepared from a 17th century formula resulted in dreams of flying in spirals, wild rides, frenzied dancing, and other similar hallucinations (13).

EXPERIMENTAL ANALYSIS OF HALLUCINOGEN-INDUCED HALLUCINATIONS

Hallucinations have always been the most salient effect of hallucinogenic intoxications. The experimental analysis of these phenomena began with Moreau's studies on hashish (23). He listed several characteristics of the drug-induced hallucinatory state: general feelings of pleasure; increased excitement combined with a heightening of all senses; distortion of the dimension of space and time; improved sense of hearing combined with a great susceptibility to music; delusions and fixed ideas; disturbances of the emotions, especially an increase of already existing feeling; irresistable impulses; illusions; and hallucinations. The hallucinations themselves were described by Moreau as being similar to mental images projected outward.

When comparing these hashish hallucinations to those produced by opium and belladonna, other writers (2,34) noted that such hallucinations were more than simple projected images. As William James (18) wrote at the turn of the century:

> They are often talked of as mental images projected outwards by mistake. But where an hallucination is complete, it is more than a mental image. An hallucination is a strictly sensational form of consciousness, as good and true as if there were a real object there. The object happens not to be there, that is all.

James thus distinguished between true hallucinations, which appear objectively real and "fool" the perceiver, and pseudohallucinations, which lack the character of "objective reality." According to this terminology, the hallucinations produced by drugs were a mixture of true hallucinations, pseudohallucinations, and illusions (perceptual distortions).

In both Moreau's and James' accounts, there are striking similarities to the descriptions of these hallucinations. Concentrating on an analysis of the dramatic visual imagery, both observers remarked on the qualities of being vivid, minute, detailed, abrupt, and spontaneous. Surprisingly similar imagery was reported by other investigators for a wide variety of hallucinogenic plants and substances (for review, see ref. 31).

Despite the frequent reports of drug-induced visual imagery, it was not until the work of Heinrich Klüver in this century (20,21) that a precise analysis began. Klüver reported that following the ingestion of mescaline, visual imagery could be observed with either closed or opened eyes. This imagery consisted of four types of form-constants. One type was referred to by terms such as grating,

lattice, fretwork, honeycomb, or chessboard design; the second resembled cobweb figures; the third was described by terms such as tunnel, funnel, alley, cone, or vessel; and the fourth type consisted of spiral figures. The form-constants were further characterized by varied and saturated colors, intense brightness, and symmetrical configurations. The visions of these form-constants seemed to be localized at reading distance, varied greatly in apparent size, and, generally, could not be controlled volitionally.

The form-constants appear in the first of two stages of hallucinogen-induced imagery. The images of the second stage, which are more complex but can incorporate the simple constants, include landscapes, faces, and familiar objects and places. The complex images, which are perhaps the most dramatic aspect of the hallucinatory experience, probably are related to an activation of images already recorded in the memory. Siegel and Jarvik (31) found that the complex imagery is also surprisingly constant for most hallucinogenic experiences. Subjects often see similar scenes, colors, and movements, in addition to the form-constants. These investigators concluded that both simple and complex imagery of drug-induced hallucinations are related to states of excitation and arousal of the central nervous system, with some minor contribution of structures within the visual system itself.

DEVELOPMENT OF THEORETICAL SPECULATIONS

The remarkable constancies of hallucinogenic experiences lead naturally to an inquiry into universal theoretical explanations. Throughout the history of experimentation with hallucinogens, there has been abundant speculation on underlying mechanisms of action. Investigators have attempted to explain how hallucinogens induce their various effects, most notably the hallucinations, with models involving molecular, neurochemical, neurophysiologic, behavioral, imaginal, experiential, and cognitive systems.

Early man offered explanations based on religious, magic, or supernatural excitement that allowed one to enter into a trance or vision and communicate with the gods. Recent electrophysiologic research has confirmed Moreau's early speculations that the excitement induced by hallucinogens is directly related to states of excitation and arousal of the central nervous system, which are coupled with a functional disorganization of the part of the brain that regulates incoming stimuli. Behaviorally, the result is an impairment of discrimination normally based on external stimuli and a preoccupation with internal imagery (see ref. 28). Some investigators have described this hallucinatory process by such terms as "memory flashback" and "involuntary reminiscence." Some suggest that it is a result of a general regression to primitive or childlike thinking, coupled with the emergence of repressed information and memories. Students of "psychedelic" phenomena have postulated that hallucinogens release normally suppressed information and memories.

Perhaps the most integrated explanation has been provided by the perceptual-release theory of hallucinations (17). The theory assumes that normal memories

are suppressed by a mechanism that acts as a gate to the flow of information from the outside. An input of new information inhibits the emergence and awareness of previous perceptions and processed information. If the input is decreased or impaired while awareness remains, such perceptions are released and may be dynamically organized and experienced as hallucinations, dreams, or fantasies. Consider the following analogy to illustrate this process: A man is in his living room, standing at a closed window opposite his fireplace and looking out at the sunset. He is absorbed by the view of the outside world and does not visualize the interior of the room. As darkness falls outside, however, the images of the objects in the room behind him can be seen reflected dimly in the window. With the deepening of darkness the fire in the fireplace illuminates the room, and the man now sees a vivid reflection of the room, which appears to be outside the window. As the analogy is applied to the perceptual-release hypothesis, the daylight (sensory input) is reduced while the interior illumination (the general level of arousal of the central nervous system induced by hallucinogens) remains bright, so that images originating within the rooms of the brain may be perceived as though they came from outside the windows of the senses.

FUTURE DEVELOPMENTS

Through such past research and hypotheses, we now approach the present research and theory with renewed understanding. We have begun to understand the "magic" plant hallucinogens as simply substances with certain chemical properties and behavioral possibilities. We begin to view their "mystical" and "religious" hallucinations as stored images in the brain. Like a mirage that shows a magnificent city on a desolate expanse of ocean, the images of hallucinations are actually reflected images of real objects located elsewhere. The city is no less intriguing and no less worthy of study and visitation because it is not where we think it is. Future developments, like those that follow in this book, will help illuminate the path.

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Effects of Hallucinogens in Humans

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A variety of constraints during the past 15 years have virtually eliminated experimental work with hallucinogens in man. Most recent human experience occurred during social use. In this chapter, an attempt is made to use both sources of data to provide a current view of the effects of these drugs in man.

DEFINITION OF HALLUCINOGEN

As it is difficult to document clearly the presence of hallucinations in animals, the term hallucinogen and most others that relate to this class of drugs have largely been defined on the basis of human experience. The widely used term psychotomimetics is based on the belief that many of the symptoms evoked by these drugs resemble various kinds of human psychoses. The term psychedelics, coined more recently, alludes to their supposed "mind-revealing" aspects. Older terms that have been applied to this class of drugs are phantasticas, psychotogens, and dysleptics.

In general, criteria for classifying a drug in this class are also derived from human experience. They include the following: (a) in proportion to other effects, changes in thought, perception, and mood should predominate; (b) intellectual or memory impairment should be minimal with doses producing the above mental effects; with large doses these may occur; (c) stupor, narcosis, or excessive stimulation should not be an integral part of the action; (d) autonomic nervous system side effects should be neither disabling nor severely disconcerting; and (e) addictive craving should be minimal.

CLASSIFICATION OF HALLUCINOGENS

Seven groups of these drugs can be separated based on their various chemical structures: (a) lysergic acid derivatives, of which lysergide (LSD) is the prototype; (b) phenylethylamine derivatives, of which 3,4,5-trihydroxyphenylethylamine (mescaline) is the prototype; (c) indolealkylamines, such as 4-phosphorodimethyltryptamine (psilocybin); (d) other indolic derivatives, such as the harmine

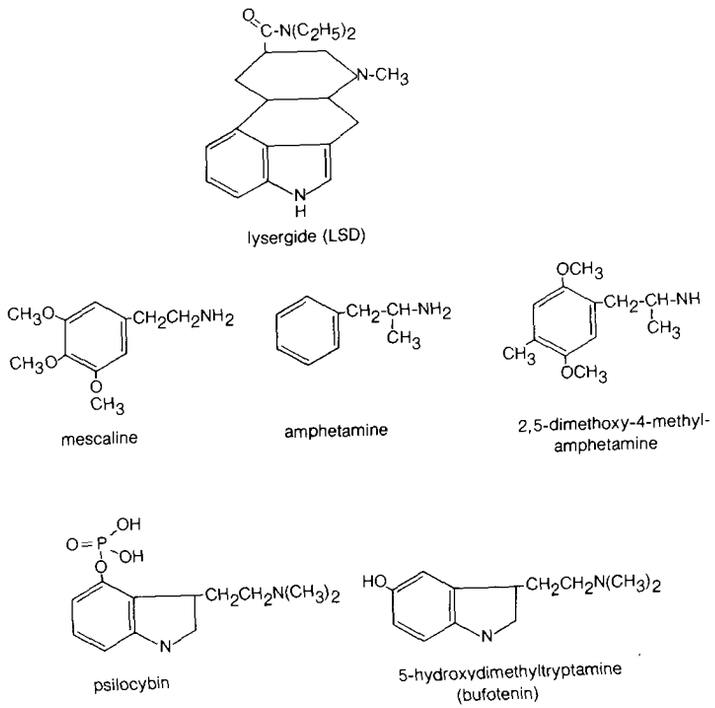

FIG. 1. Structural relationship between various hallucinogens of the LSD group.

alkaloids or ibogaine; (e) piperidyl benzilate esters, such as N-ethyl-3-piperidyl cyclopentylphenyl glycolate (JB-329 ditran); (f) 1-phenylcyclohexyl compounds, such as phenylcyclidine (PCP, Sernyl); and (g) a miscellaneous group of varying chemical structures.

Because the first three groups are virtually identical in their clinical effects, they are often lumped together as the LSD-mescaline-psilocybin group (25) (Fig. 1). Of the latter group, only LSD is widely available. The harmala alkaloids are rarely used, and the use of the piperidyl benzilates and other anticholinergics has never been great. Currently, the most important drugs, both in terms of degree of use and severity of consequences, are PCP and LSD.

EPIDEMIOLOGIC ASPECTS

The current frequency of use of hallucinogens is virtually impossible to determine. Epidemiologic studies of drug abuse are fraught with many difficulties. Data are largely anecdotal, and it is well known that what people say and what they do may be quite different. To compound the difficulty, even the most

honest and cooperative respondent labors under the burden of not really knowing what drug was taken. Mislabeling of street drugs is more common than accurate labeling. The only bases that drug users have for correcting for mislabeling are their past experience with similar drugs, the opinions of fellow drug users, or the reputation of their source of drugs. None of these factors is likely to resolve ambiguity about what was actually taken. Thus epidemiologic studies that lack any chemical verification of drugs (and these are virtually impossible to design) will only be crude indices of what drugs are being used.

Data about the use of hallucinogens in the United States indicate that total use has remained relatively constant over the past few years (1). According to one survey (29), the amount of regular use of hallucinogens among the younger age groups most likely to use such drugs was 2 per 1,000. LSD is no longer the favorite hallucinogen. On the other hand, increased use of PCP has made up the difference. Trends change with remarkable rapidity, however, and a sharp decrease in PCP use has been noted recently in some parts of the country.

THE LSD GROUP

Members

The most potent compound in this series, if not one of the most potent drugs or toxins known, is LSD. A number of clinical comparisons have been made between LSD and closely related lysergic acid derivatives. It appears that alterations in the basic structure of LSD may or may not materially change the quality of the clinical effects but generally tend to reduce potency.

Mescaline is scarcely ever available as such on the street. Most is LSD that has been mislabeled. The deception is easily carried off as the two drugs, except for dose, produce similar effects. A number of mescaline homologs have hallucinogenic activity. The amphetamine homolog trimethoxyamphetamine produces much the same effects as mescaline over a similar timespan. Other amphetamine homologs have become popular as street drugs. The most widely used has been 2,5-dimethoxy-4-methylamphetamine (DOM or STP). Our studies of the drug showed it to have properties similar to those of mescaline, although it was about 40 to 50 times as potent (26). 3,4-Methylenedioxyamphetamine (MDA) was found by self-experimentation to be a psychotomimetic resembling mescaline. It is more potent by three- to fourfold (46). Human studies of 3-methoxy-4,5-MDA (MMDA) are scanty, but such as exist suggest that it, too, resembles the other amphetamine homologs (40).

Psilocybin is never found on the streets. Drugs labeled as such are usually LSD. Once again, the deception is meaningless. A psilocybin homolog with highly potent hallucinogenic effects, N-N-dimethyltryptamine, no longer seems to be available. Some use has been made of endogenous *Psilocybe* mushrooms (22).

Clinical Effects

Three characteristic types of symptoms—somatic, perceptual, and psychic—have followed use of members of the LSD group of hallucinogens. In repeated laboratory experiments, subjects report a basic clinical syndrome that might be described as follows:

1. Somatic symptoms: dizziness, weakness, tremors, nausea, drowsiness, paresthesias, and blurred vision.
2. Perceptual symptoms: altered shapes and colors, difficulty in focusing on objects, a sharpened sense of hearing, and, rarely, synesthesias.
3. Psychic symptoms: alterations in mood (happy, sad, or irritable at varying times), tension, distorted time sense, difficulty in expressing thoughts, depersonalization, dreamlike feeling, and visual hallucinations.

Physiologic effects are relatively few. Dilated pupils, hyperreflexia, increased muscle tension, incoordination, and ataxia are common physical signs. Effects on pulse rate, respiration, and blood pressure are so variable that they probably represent varying levels of anxiety of subjects rather than true physiologic effects. Changes in appetite and salivation are inconstant, being increased in some subjects and decreased in others.

The clinical syndrome tends to follow a sequential pattern, with somatic symptoms presenting first, perceptual and mood changes next, and, finally, psychic changes, although there is considerable overlap between these phases (Table 1). Between the range of 1 to 16 μg/kg, the severity of psychophysiologic effects of LSD in a given subject are proportional to the dose (30). Specific types of reaction, such as paranoid ideation, are more likely a matter of personal predisposition than a function of dose.

The major difference between the principal members of this group of hallucinogens is their potency. In doses of 1 μg/kg, LSD is roughly equivalent to

TABLE 1. *Patterns of clinical effects for hallucinogens of the LSD group*

Time course	Clinical effect
0–30 min	Dizziness, nausea, weakness, twitches, anxiety
30–60 min	Blurred vision, increased contrasts, visual patterns with eyes closed; less discriminatory hearing; yawning; decreased concentration, feelings of unreality; incoordination, tremulous speech
60–120 min	Increased visual effects, wavelike motions; impaired distance perception; euphoria; slow passage of time
120–240 min	Waning of above effects
4–12 hr	Returning to normal but continued arousal
Late effects	Headache, fatigue, contemplative state

150 to 200 μg/kg psilocybin and 5 to 6 mg/kg mescaline. Thus equivalent doses of these drugs vary by several orders of magnitude. Otherwise, in terms of both principal clinical effects and duration of action, few differences can be found among the three drugs, despite their considerable chemical differences (25).

Pharmacokinetics

No modern studies of the human pharmacokinetics of LSD have been done, largely because human experimentation has virtually stopped. An older study that used a spectrofluorometric technique for measuring plasma concentrations of LSD was done in humans given doses of 2 μg/kg i.v. After equilibration had occurred in about 30 min, the plasma level was between 6 and 7 ng/ml. Subsequently, plasma levels gradually fell until only a small amount of LSD was present after 8 hr. The half-life of the drug in humans was calculated to be 175 min (2). Subsequent pharmacokinetic analysis of these data indicated that plasma concentrations of LSD were explained by a two-compartment open model. Performance scores were highly correlated with concentration in the tissue (outer) compartment, which was calculated at 11.5% of body weight. The new estimation of half-life for loss of LSD from plasma, based on this model, was 103 min (47).

Adverse Effects

The clinical manifestations of adverse psychiatric effects of LSD have been reviewed elsewhere (39). In general, not much new has been added over the years. The acute panic reaction is still most common, but of much greater concern has been the prolonged psychosis. The latter, fortunately, remains uncommon. Most people believe that such reactions indicate a psychosis precipitated in a particularly vulnerable person. Treatment with antipsychotic drugs may be required, but remission usually is prompt. The long-term outlook for such drug-induced psychosis is not especially good. Approximately one-half of 15 such patients did poorly; two committed suicide. This evidence also suggests an individual vulnerability in some patients (10).

Acute panic reactions to LSD, which are usually of only a few hours duration, may be handled in two ways. One may "talk the patient down," provided staff or friends are available, or one may simply sedate the patient and allow him to sleep off the effects of the drug. In the latter case, experience suggests that diazepam or a similar drug is preferable to the antipsychotics (9). The latter drugs produce such lasting and noxious side effects that the treatment may ultimately prove to be more disagreeable than the illness. Panic attacks, as well as episodes of depression, déjà vu, and visual changes, have occurred long after use of hallucinogens in the form of "flashbacks." Minor electroencephalographic abnormalities (slow waves and occasional sharp waves in the temporal areas)

have suggested a mechanism similar to epilepsy. Response to sedative-hypnotic drugs usually is good (28).

Flashbacks, or acute, unpredictable recurrences of phenomena experienced under LSD, have always been a mystery. Because they occur months later with completely lucid intervals, most of us have subscribed to a psychologic theory of causation. They may, of course, be triggered by other drugs that alter consciousness, such as marijuana or, in one unusual case, biperiden given to prevent phenothiazine-induced extrapyramidal reactions (44). Biperiden, a potent anticholinergic, especially when combined with phenothiazines, may itself be hallucinogenic. Although it is difficult to see why it should be effective, haloperidol eliminated flashbacks in four of eight patients treated over a 4-week period and reduced their frequency in the other four patients (34).

About 23% of regular users of hallucinogens report experiencing flashbacks. These have been classified as perceptual (visual effects), somatic (numbness), or emotional (reexperience of a disturbing emotion). Many theories about their causation remain unproved. Usually they fade with time, and no specific treatment is needed (49).

Homicides have been committed under the influence of LSD and other drugs of this type, although these agents are not intrinsically likely to unleash violent behavior. Rather, the disinhibiting effects may remove constraints or violence already present in an individual. I have encountered instances of persons accused of homicide who claimed that the crime was perpetrated under the influence of hallucinogens. Unfortunately, it is not possible to substantiate such claims. Some, however, strain one's credulity and suggest that this type of plea of diminished responsibility is often misused.

Self-injury, due to lapses in sound judgment, was a major danger with the use of these drugs, but is no longer as great a problem. Various speculations have been made about the cause of this change, such as more exact doses, more experienced users, and more frequent use in the company of an unintoxicated person, but no specific reason has been found for the diminution of this risk. Staring at the sun can cause macular burns with severe loss of vision (21). Other users have suffered falls or accidents due to their delusion of having supernatural powers.

The issue of chromosomal damage from LSD is no longer critical. A recent review by one of the investigators who first reported such damage stated that no conclusions could be drawn on the basis of existing evidence (17). A naturalistic study used Huichol Indians of northern Mexico as subjects. Fifty-seven subjects were chosen who not only had many exposures to peyote but whose forebears also were peyote cultists. Compared with 57 other Indians without such history, as well as 10 laboratory controls, no differences in abnormalities were observed in the lymphocyte chromosomes of the three groups. Thus even multigenerational use of peyote seems not to produce significant chromosome abnormalities (20).

Whether LSD causes dysmorphogenesis is also difficult to evaluate. A third case of multiple ocular abnormalities was reported in a premature infant of a mother who had used LSD sporadically, as well as other drugs, such as cocaine and heroin. No definite cause-effect relationship could be drawn (14).

Overdose

Deaths directly attributable to LSD have not been documented. A suspected case occurred in a 34-year-old man who had been known to act strangely on occasion and who was later found dead. Postmortem examination revealed no anatomic cause of death, but the liver showed extremely high concentrations of LSD (23). Hyperthermia, coma, and respiratory arrest were found among eight users who had snorted an unusually large amount of LSD; serum concentrations ranged from 2 to 26 ng/ml in these patients (3). These complications, as well as seizures, which have been reported in other cases of overdose, could produce death in an unattended subject.

Therapeutic Use

Although a vogue once existed for using LSD as a therapeutic agent, little work has been done during the past 15 years. Good results have been reported in facilitating psychotherapy, as well as in treating a variety of psychiatric conditions (obsessive-compulsive-phobic disorders, depressions, alcoholism, autistic children, and pain of terminal cancer). No evidence of real efficacy has been adduced for any of these indications, and they have not been supported by controlled evaluations (25). A recent report on use by psychiatric patients showed a typical result: All the patients thought the treatment was beneficial, but the staff could find no evidence of change, either for better or for worse (8).

PCP

History

PCP, initially thought to be useful for medical practice, was first studied in 1957 as a potential anesthetic agent, and ultimately was marketed under the name Sernyl (22). Although it lacked muscle relaxation, it produced a state of analgesia without full loss of consciousness and laryngeal reflexes. By 1959, however, it had become apparent that patients emerging from anesthesia with this drug experienced a mental state that in some ways resembled that of hallucinogenic drugs. As studies of its hallucinogenic effects grew, it became apparent that PCP had such properties, and that these were highly variable, depending on dose and route of administration (32). Furthermore, they were distinctly different from those of LSD. In the opinion of many investigators, the PCP-induced mental state was a better model for schizophrenia than was that produced

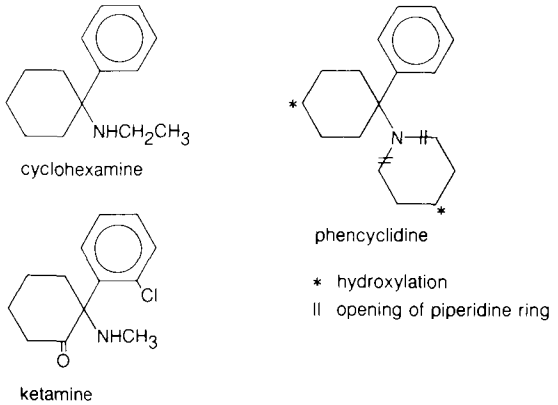

FIG. 2. Structural relationship of PCP-type hallucinogens.

by LSD. Verification of the hallucinogenic effects of the drug in man led to its withdrawal from the market as an anesthetic in 1965. Its hallucinogenic properties were of less consequence in animals; by 1967, therefore, it was reintroduced into the market as an anesthetic for veterinary use under the name Serylan. This use of the drug has remained to the present; it is considered to be quite valuable for anesthesia in primates.

The first street use of the drug occurred in 1967, during the "summer of love," when the drug culture erupted on the streets of San Francisco. The popularity of the drug was short-lived, as its unpredictable, unpleasant, and often startling effects gave it a bad reputation. During the next several years, PCP was hardly ever used knowingly by drug takers. By 1972, it had become a popular substance for being mislabeled as other drugs or as an adulterant of other drugs (24). By 1974, however, the pendulum swung completely back; PCP now became an acceptable drug, despite its vagaries. From that point, its use has grown to what is now called epidemic proportions. Because of the frequently dramatic consequence of its use, the actual rate of use may have been overestimated.

The drug is readily synthesized by illicit chemical laboratories; the evidence suggests that virtually all PCP on the streets comes from such sources (Fig. 2). Nonetheless, the panic created by its rising use has led to the proposal that tighter controls be placed on licit supplies of the drug, a paradoxic situation. Control of its chemical precursors is virtually impossible, as they are widely used in everyday commerce. Some PCP has been mislabeled as tetrahydrocannabinol (THC), but most is now sold as itself, following the new popularity of the drug.

Clinical Effects

The effects of the drug described in laboratory experiments have been more variable than those reported by street users but have been generally similar.

Distortion of body image, disorientation, detachment from surroundings, and vivid dreaming are some of the most common mental effects of PCP. Those who take it seem to lose the ability to integrate sensory input, especially for touch and proprioception (38). This effect may in turn lead to the analgesia and paresthesias that are experienced, as well as produce a cataleptic state in some individuals. Such effects are generally produced by 0.1 to 12 mg/kg single doses, regardless of the route of administration. Some persons develop mania or hostility, but these are generally considered to be side effects, more related to the personality of the subject than a direct effect of the drug. Although some similarities to the schizophrenic state are obvious, it is not clear that the mental state produced by PCP is an especially good model of that illness.

Physical symptoms include dizziness, dysarthria, ataxia, nystagmus, lid ptosis, tachycardia, sweating, and increased deep tendon reflexes. Most subjects show some degree of hypertension, associated with increased minute and tidal volumes of respiration, increased formation of urine, and increased muscle tone. The latter may lead to increased serum creatinine phosphokinase concentration. With very large doses, convulsions and respiratory arrest are the terminal events (11). The course of clinical symptoms and signs following various doses of PCP is shown in Table 2.

In most of the experiments with PCP done in the early 1960s, the drug was administered intravenously. On the street, however, the major method of administration is by inhalation (often smoked as a cigarette using parsley as the medium for smoking), "snorting," or by the oral route in a variety of formulations. The typical PCP user has a history of polydrug abuse. Among those in the 18- to 25-year age group, that period of life when hallucinogen use is highest, those with experience with PCP increased from 9.5 to 14% during the year 1976 to 1977. Possibly because experimental subjects are chosen with great care, violent behavior induced by the drug was less common in them than has been observed during street use. Some of this behavior may simply be uncovered by

TABLE 2. *Patterns of clinical effects from increasing oral doses of PCP*

Oral dose (mg)	Clinical effect
5–10	Ataxia, nystagmus, mood changes, hallucinations, vomiting, analgesia, paresthesias; onset 1–2 hr, duration 4–8 hr
10–20	Stupor, eyes open, random movements, resting nystagmus, hyperreflexia, hypertension; onset 30–60 min, duration 8–24 hr
>50	Deep coma, chills, nystagmus, eyes closed, hypertension, labored breathing, seizures; duration up to 4 days
>100	Lethal, 3 to 10 days; respiratory depression, hypertensive crisis, cerebral bleeding, loss of deep tendon reflexes, decreased renal function, decreased liver function

the disinhibiting effects of the drug rather than caused directly. Continued use tends to lead to tolerance. Even during periods of abstinence, users may complain of memory loss, fatigue, irritability, and depression (42).

Human Pharmacology

The effects of PCP in man seem to involve a number of systems. Sympathomimetic actions are apparent in the symptoms of overdose. Although the drug seems to have fairly strong anticholinergic actions in animal studies, these do not play a major role in clinical effects. The best explanation for the mental effects of the drug is that it acts by increasing dopaminergic activity, but this may be an oversimplification. Specific PCP binding sites have been described in the brains of animals, but the possible sources of artifact are so great that one must reserve judgment about these claims (41).

The drug is unique among hallucinogens in being self-administered by animals (7). This difference, as well as many clinical and pharmacologic differences from the LSD group of hallucinogens, has led some to suggest that PCP be considered as a separate class of drug, similar to the classification of cannabis. The definition of hallucinogen, however, is broad enough to include drugs other than the LSD group. With respect to use of the drug on the streets, it is clearly being used by hallucinogen fanciers. Animals can discriminate the drug from morphine, chlorpromazine, THC, ditran, and pentobarbital, again indicating its rather unique set of enteroceptive cues. In man, the effects are said to be similar to those seen in schizophrenic patients, but the closeness of this model psychosis to actual psychosis has not been studied carefully for many years. It again might be appropriate for doing so; if it proved to be a viable model, it might be a valuable tool for research into the nature of schizophrenia.

Pharmacokinetics

In man, PCP is generally considered to be a rather long-acting drug; yet its half-life in plasma is only about 11 hr, even after large overdoses (33). The high degree of lipid solubility causes it to move rapidly into the brain, so that concentrations in brain and in cerebrospinal fluid are more persistent. Thus the toxicity of the drug may be greatest when the plasma levels are lowest. Some of the drug is secreted from the blood into the stomach, where the acid content keeps the weakly basic drug ionized. As it enters the more alkaline medium of the upper intestine, it again becomes un-ionized and is reabsorbed. Thus a certain amount of gastroenteric recycling of the drug occurs. It is also likely that PCP produces active metabolites. Thus three factors—active metabolites, sequestration in fat, and recycling through the gastrointestinal tract—may account for its long duration of action, which is especially evident in cases of overdose.

Adverse Effects

In some areas, PCP may be a leading precipitant of psychiatric emergencies. Routine blood samples from 145 consecutive admissions to the Los Angeles County Hospital psychiatric emergency room during a 48-hr period in June, 1979 showed 63 samples positive for PCP. A wide variety of psychiatric clinical pictures were found in these patients, including mania, depression, and schizophrenia. Three patients also had symptoms of a toxic psychosis (50).

The psychoses produced by heavy doses of PCP have many similarities to schizophrenia: hostility, agitation, delusions of grandeur, and auditory hallucinations. On the other hand, the presence of hypertension, disorientation, nystagmus, ataxia, and other neurologic signs, as well as the drug history, facilitates the diagnostic distinction. Some acute psychoses lasted as long as 30 days, despite treatment with antipsychotics (3). Acute PCP-induced psychoses are best managed with diazepam or a similar drug, reserving antipsychotics for those cases in which agitation cannot be controlled or the psychosis persists. Some subjects show analgesia, as well as amnesia for the psychotic state (36). A rare subject has self-inflicted serious wounds during this analgesic-amnesic state. The long-term prognosis for most such patients is good, although some question has been raised about persistent organic impairment. Twelve abstinent PCP users were compared with 12 polydrug users who did not use PCP and with 12 controls, using neuropsychologic testing. Signs of organic mental impairment were found in six of the 12 PCP users and five of 12 polydrug users but in none of the controls (13).

The possibility of cerebrovascular action of PCP was raised by the development of focal seizures and hemiparesis in a 6-year-old boy who had ingested what was presumed to be PCP (18). Hypertensive encephalopathy with a blood pressure of 260/160 occurred in an 18-year-old woman who used PCP (43). These clinical findings are compatible with *in vitro* studies indicating that cerebral artery spasms can be produced by PCP as well as by LSD and mescaline (4). Whether such cerebrovascular actions are pertinent to the mental effects of these drugs is questionable.

During periods of acute psychosis, some patients exhibit so much muscular activity that they develop muscular destruction with the muscle product myoglobin in urine, which produces acute renal failure (16). Some muscle destruction may be due to involuntary muscle activity induced by the drug, while some may be due to the struggles of the agitated patient. In the latter case, the use of restraints may worsen the situation.

People who take drugs also drive, and the number of drugs screened for detecting impaired driving will have to be increased. Approximately 50 drivers who were detained because of erratic driving in Orange County, California had levels of PCP in their blood ranging from 10 to 180 ng/ml, with a mean of 73 ng/ml. Such levels would generally indicate severe intoxication compatible with impairment of driving (15). Those plasma concentrations are somewhat lower

than those found in other nonfatal intoxications. Levels ranging from 6 to 240 ng/ml were found in 26 patients; the lower limit of sensitivity of the gas chromatography-mass spectrometry method was 10 ng/ml (35). Plasma of 22 patients with PCP intoxications showed concentrations ranging from less than 10 to 812 ng/ml as determined by gas chromatography with a nitrogen detector. Only the systolic blood pressure showed a significant correlation with plasma concentrations (6).

Even children are not immune from poisoning by PCP. Six cases were observed at the UCLA Medical Center, all 5 years old or younger. Presumably, most were poisoned by accidental ingestion of the drug, which was available in the house; one child, only 11 days old, was presumably poisoned by passive inhalation of the smoke produced by the adults around him. The most common clinical manifestations in these youngsters was bizarre behavior, lethargy, ataxia, and nystagmus (48).

Overdoses

Deaths from overdoses of other types of hallucinogens are rare, but not with PCP. Poisoning with this drug is a major medical emergency and requires great skill in management. Fortunately, the means are available for successful treatment.

The level of severity of intoxication determines the extent of the therapeutic endeavors. If the patient is conscious, a stage I intoxication may be inferred; if he is not conscious but responds to deep pain, stage II is present; if he is unconscious and unresponsive, the intoxication is stage III. A stage I intoxication probably results from a small dose (2.5 mg) and will show blood levels of 25 to 90 ng/ml. Reduction of external stimuli, reassurance, diazepam (10–30 mg), ascorbic acid (0.5 to 1.5 g) to acidify the urine, and propranolol (40–80 mg orally) will probably suffice. A stage II intoxication is produced by doses of 5 to 25 mg and is associated with blood levels of 90 to 300 mg/ml. Such patients are vulnerable to hyperthermia and need larger doses of all the above-mentioned drugs, as well as a dose of furosemide (40 mg i.v.). Stage III intoxications are caused by doses of more than 25 mg and are associated with blood levels of more than 300 ng/ml. Active cooling procedures, intravenous fluids, repeated diuretics, and ascorbic acid are required. Orotracheal intubation and a large-bore nasogastric tube should be placed, the latter for continual gastric suction. Propranolol should be used aggressively with diazoxide available for a 300 mg i.v. push if needed for acute hypertension. Anticonvulsants may be required if seizures supervene (37).

The two best means of ridding the body of PCP are by increasing urinary excretion and by interfering with gastroenteric cycling. Acidification of urine to pH 5.5, using either ammonium chloride or ascorbic acid, keeps the drug in the ionized form and hastens its excretion (19). Potent diuretics also are helpful. Gastric lavage is useful only when the drug has been taken orally and soon after intake. Continual gastric suction, however, may reduce the gastrointestinal recycling of the drug and should be done routinely (5).

An analysis of 19 deaths from PCP overdose that occurred in two California counties from 1970 to 1976 showed that 12 were accidental, five suicidal, and two homicidal. Eight of the 12 accidental deaths were from drowning. Blood concentrations ranged from 1,250 to 2,300 ng/ml. Virtually all patients with levels of 1,000 ng/ml or more had coma, with the possible evolution of death due to medical complications, seizures, or respiratory depression. Levels greater than 2,000 ng/ml were almost always fatal (12).

Treatment of PCP Dependence

As PCP use is most often in the context of multiple drug use, no specific treatment program for this particular drug dependence has been developed. The most important aspects for treating dependence on hallucinogens is the desire and motivation of the patient to stop drug use and the feasibility of removing him from the drug culture.

Desipramine has been used to facilitate withdrawal from chronic PCP use. The rationale is that PCP depletes norepinephrine concentrations in brain, and that this tricyclic antidepressant is the most selective blocker of norepinephrine uptake. Consequently, some of the deficiency of the neurotransmitter could be remedied. A dose of 25 to 50 mg was said to reduce craving for several hours. Six of eight patients treated with this drug were successfully withdrawn, while none of the eight offered other types of programs were successful (45).

OTHER HALLUCINOGENS

Anticholinergics are rarely used. One wonders why they are used at all, for in most cases, the experience is unpleasant or frightening. Still, stories are told of people who separate scopolamine and other anticholinergics from cold remedies, or people who use jimson weed, and of those who abuse prescription anticholinergics, such as amitryptyline, trihexyphenidyl, or benztropine mesylate. One can only assume that for some people, any alteration of consciousness, even though it may not be pleasant, is desirable.

Cannabis in large amounts has some hallucinogen-like activity. Nevertheless, the other features of this intoxication are sufficiently different to merit a separate classification for this drug.

For practical purposes, therefore, the present problem with hallucinogens is largely due to the newcomer PCP and the prototype of the modern era LSD.

CONCLUSIONS

Hallucinogenic drugs will continue to be used socially in the future as they have been used throughout man's history. Changing fashions may make one or another drug the current object of choice. Many of the popular drugs are creations of the laboratory, unknown 30 years ago. It remains to be seen whether still different types of hallucinogens will be created in the laboratory, or, more

importantly, become recognized and available to those who would use them socially.

The original hope that these drugs would lead us to a better understanding of naturally occurring mental disorders has not been realized; neither have they proved to be effective therapeutic agents for any mental disorders. Still, the fact that relatively small quantities of these chemicals can so markedly affect mental functions commands our attention. If, by learning how they act, we remain ignorant of the cause of schizophrenia, we may still learn a lot more about how the brain regulates behavior.

The greatest current challenge is to make experimentation with these drugs more attractive to scientists and less attractive to social users.

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Effects of Hallucinogens on Unconditioned Behaviors in Animals

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RECEPTOR SYSTEMS THAT MIGHT MEDIATE EFFECTS OF HALLUCINOGENS

The present chapter discusses the effects of hallucinogens on unconditioned behaviors. Studies in which hallucinogens modulate ongoing behaviors or elicit new behavior are reviewed. Ongoing behaviors modulated by hallucinogens include behaviors with a clearly defined (external) eliciting stimulus, such as spinal reflexes and acoustic or tactile startle reflexes, as well as those with less clearly defined eliciting stimuli, such as locomotor and exploratory behaviors. Behaviors elicited by hallucinogens (emergent behaviors) are characterized by their extremely low frequency of occurrence in the absence of drug administration.

Electrophysiologic and receptor binding studies have indicated that hallucinogens interact with central serotonin (5-HT) systems. Hence many behavioral studies have sought to determine if the effects of hallucinogens are mediated by activation of 5-HT receptors. Electrophysiologic studies have provided evidence for the presence of anatomically distinct inhibitory and excitatory 5-HT receptors (4,130). Two models based on these receptor types have provided a framework for investigations into the mechanism(s) of hallucinogen action.

Model I: Inhibitory 5-HT Receptors

Early electrophysiologic studies suggested that inhibitory 5-HT receptors were located at both presynaptic (autoreceptors on 5-HT cell bodies) and postsynaptic (forebrain target areas) sites (83). Three important findings from this work have major implications for the interpretation of the behavioral effects of hallucinogens: (a) The inhibitory effects of 5-HT at either receptor are not blocked by the classic antagonists, which were effective at peripheral 5-HT synapses (84). Thus behavioral effects of hallucinogens mediated through inhibitory receptors would

not be expected to be blocked by 5-HT antagonists. (b) Indoleamine hallucinogens [e.g., lysergic acid diethylamide (LSD) and N,N-dimethyltryptamine (DMT)] are more potent at stimulating presynaptic than postsynaptic receptors (3,83), thus suggesting the possibility that hallucinogens might have dose-related biphasic effects on behavior. (c) The postsynaptic inhibitory receptors are located in limbic or sensory regions of the brain. Hence, low doses of hallucinogens might increase emotional or sensory function by an autoreceptor-mediated disinhibition of these postsynaptic areas. Conversely, high doses of hallucinogens might depress these functions by directly inhibiting the 5-HT postsynaptic areas involved in sensation and affect.

Model II: Excitatory 5-HT Receptors

In addition to stimulating inhibitory 5-HT receptors, more recent evidence indicates that 5-HT can activate receptors that facilitate the excitatory effects of afferent input to postsynaptic neurons. These excitatory 5-HT receptors have been found on motoneurons in the facial motor nucleus (130) and the ventral horn of the spinal cord (193). In contrast to 5-HT-mediated inhibition, the facilitatory effects of 5-HT on motoneurons are blocked by 5-HT antagonists. Thus behavioral effects of hallucinogens that are blocked by 5-HT antagonists could be attributed to stimulation of these excitatory postsynaptic receptors. Furthermore, it is interesting to note that the inhibitory receptors described in the first model are found primarily in sensory/limbic areas, whereas the excitatory receptors are localized primarily (although not exclusively) on motoneurons. This anatomic dichotomy suggests a possible although speculative functional dichotomy: Hallucinogen effects on postsynaptic inhibitory 5-HT receptors might depress behavior by inhibiting the transmission of sensory information important for the elaboration of that behavior, whereas hallucinogen effects on postsynaptic excitatory 5-HT receptors might enhance behavior by facilitating the motor performance.

With respect to the models provided above, the following questions are addressed: (a) What are the effects of hallucinogens on unconditioned behaviors? (b) Do excitatory (i.e., reversed by 5-HT antagonists) or inhibitory (not reversed by 5-HT antagonists) 5-HT receptors mediate these behavior effects? It should be acknowledged that in many cases, little evidence is available to answer these questions with specific reference to the effects of hallucinogens. It is hoped that the above framework will be of heuristic value in guiding future investigations into the behavioral effects of hallucinogens.

MODULATION OF ONGOING BEHAVIORS BY HALLUCINOGENS

Spinal Reflexes

A comprehensive review and discussion of studies investigating serotonergic modulation of spinal reflexes has been presented previously (10). This section

focuses on studies that have investigated the effects of hallucinogens on spinal reflexes and the interactions of these drugs with descending 5-HT systems. These studies have utilized primarily two techniques for measuring spinal reflex activity: (a) force transducer measurement of contractions of hindlimbs or individual hindlimb muscles, and (b) electrophysiologic recording of intact or dissected spinal roots or single unit recording of neurons within the dorsal and ventral horns of the spinal cord. Electrophysiologic studies are important in distinguishing drug effects on polysynaptic (long-latency) reflexes (PSRs) from those on monosynaptic (short-latency) reflexes (MSRs). Furthermore, many of these studies have analyzed functionally different muscles or muscle groups (i.e., extensors versus flexors).

An important methodologic point about the majority of these studies is that they use a "reduced" preparation, in which the spinal cord is neurally isolated from the brain by a complete transection (129). The rationale for using this simplified preparation is that spinal reflex activity can be analyzed in the absence of supraspinal influences. However, transection may introduce other variables (i.e., ischemia, disruption of the blood-brain barrier, loss of tonic neural activity from supraspinal systems), which may result in drug effects on spinal reflexes that are quantitatively or even qualitatively different than those seen in the intact animal. Thus the following review of hallucinogen effects on spinal reflexes is organized into two main categories: (a) studies in transected animals, and (b) those in decerebrate or intact preparations.

Spinally Transected Preparations

Most studies on spinal reflexes have utilized spinally transected animals. This preparation allows for the evaluation of drug actions on spinal postsynaptic 5-HT receptors without the potential confounding influences of tonic descending 5-HT activity or the influence of supraspinal 5-HT neuronal or receptor activity.

A large number of functional and electrophysiologic studies in transected animals support the conclusion that hallucinogens facilitate spinal MSRs and PSRs in both flexor and extensor muscles. Furthermore, these studies show that 5-HT antagonists effectively block the observed excitatory behavioral effects, suggesting mediation by spinal excitatory 5-HT receptors.

Studies in spinal cats showed that administration of the indole hallucinogens DMT, psilocybin, and psilocin facilitated the knee jerk reflex, whereas administration of bufotenine (which does not readily cross the blood-brain barrier) did not (31). Although hallucinogens per se have not been tested, evoked potential studies have found that a variety of other agents that enhance serotonergic transmission enhance the amplitude of the MSR. Thus tryptamine facilitated the MSR in spinal cats; this effect was blocked by pretreatment with the 5-HT antagonist cyproheptadine but not by phenoxybenzamine (183). Similarly, 5-HTP produced a facilitation of the MSR in acute spinal cats that was blocked by the 5-HT antagonists cinanserin, cyproheptadine, and methysergide (13,168). Curiously, LSD blocked the excitatory effect of 5-hydroxytryptophan (5-HTP)

(consistent with its peripheral action as a 5-HT antagonist). This blockade, however, may have been obscured by depressant effects of LSD on the MSR attributable to its action as a 5-HT agonist. Finally, monoamine oxidase inhibitors (MAOI) also have been shown to facilitate the MSR (9).

A number of functional studies have provided evidence that hallucinogens facilitate polysynaptic extensor and flexor reflexes by stimulating spinal excitatory 5-HT receptors. The early work of Andén and his colleagues (6,7) suggested that hallucinogen-induced increases in spinal 5-HT transmission enhanced the hindlimb extensor reflex elicited by pinching the base of the tail of an acutely spinalized rat. Thus the indole hallucinogens LSD (1.0–5.0 mg/kg), DMT (10–50 mg/kg), psilocybin (1–50 mg/kg) (6,7), and 5-methoxy-DMT (5-MeODMT) (1.0–5.0 mg/kg) (64) produced increases in the extensor reflex. Although antagonism studies were not reported, it was also found that administration of the 5-HT precursor 5-HTP or tryptophan (either alone or in combination with the MAOI nialamide) facilitated the hindlimb extension reflex (6,7,138). The 5-HTP effect was specific in that it was blocked by pretreatment with a central decarboxylase inhibitor (which prevented the conversion of 5-HTP to 5-HT) but not by pretreatment with the adrenergic antagonist phenyoxybenzamine or the dopaminergic antagonist haloperidol (6,7). Furthermore, intravenous infusion of 5-HT did not produce facilitation, suggesting that peripheral contributions to the observed effects were negligible.

Further evidence for serotonergic mediation of the effects of hallucinogens was provided by a report on the development of functional supersensitivity in the rat with a chronic denervation of spinal 5-HT neurons. Nygren et al. (138) reported that rats pretreated with intracisternally administered 5,6-dihydroxytryptamine (5,6-DHT), a 5-HT neurotoxin, subsequently showed greater hindlimb extensor facilitations to 5-MeODMT or L-tryptophan + nialamide at 1 week versus 1 day following pretreatment.

Using a standardized method for eliciting flexion (electrical stimulation of the base of the hindpaw) and a quantifiable method of contraction measurement (force transducer attached to the hindpaw), Nozaki et al. (136,137) found that LSD (10 μg/kg) and tryptamine both increased the flexor reflex in acutely spinalized rats. Both these effects were blocked by pretreatment with the 5-HT antagonist cyproheptadine. A similar LSD effect was reported in spinal cats (118).

Studies measuring the contraction [force transducer or electromyogram (EMG) activation] of single flexor muscles (tibialis anterior, semitendinosus, psoas) following stimulation of the footpad have reported effects of hallucinogens on flexor reflexes that are consistent with those reported for whole limb flexion. Thus administration of the indole hallucinogens LSD (2–10 μg/kg) (121,124), DMT (2.0 mg/kg) (123), or 5-MeODMT (12) all produced increases in the single muscle flexor reflex. Similarly, administration of the phenethylamine hallucinogen mescaline increased the amplitude of tibialis anterior flexion (122). In addition, other treatments that have been suggested to facilitate 5-HT transmission, such as quipazine (140), tryptamine (128), 5-HTP or L-tryptophan (121), and the 5-HT releasing agents parachloroamphetamine (PCA) and fenfluramine (121,123), facilitated the flexion reflex. Finally, in all the above cases, pretreatment with the 5-HT antagonist cyproheptadine blocked the reported excitatory effects, whereas no consistent pattern of antagonism was found with catecholamine antagonists.

As with the extension reflex, functional supersensitivity was observed with the flexion reflex, as indicated by increased responsiveness to LSD, 5-HTP, and tryptamine in chronically (2 months) versus acutely (1 day or less) transected rats (136).

Evoked potential studies showed that LSD facilitated a PSR; this effect was blocked by cyproheptadine (18). The 5-HT agonist quipazine augmented a PSR; this effect was blocked by cinanserin but (curiously) not by metergoline (80). Finally, tryptamine (183) and L-tryptophan (19) have been reported to increase PSRs in a cyproheptadine-reversible manner.

Most of the data reported thus far indicate that hallucinogens can have facilitatory effects on MSRs and PSRs in spinalized animals, and that these effects occur in both flexors and extensors. Furthermore, since these effects are reversed by antagonists, they may be attributed to stimulation of excitatory postsynaptic 5-HT receptors that have been shown to facilitate motoneuron activation in the ventral horn of the spinal cord (134).

Nevertheless, there are some indications that 5-HT stimulation may produce depressant behavioral effects. Although these studies have not included hallucinogens, they are of theoretical importance in relation to the effects of hallucinogens on sensory transmission in other behavioral tests. Evoked potential studies have reported that 5-HTP administration depressed polysynaptic and dorsal root reflexes. This effect was not blocked by 5-HT antagonists (e.g., methysergide, cyproheptadine, cinanserin). This pattern, in direct contrast to the effects reported on a MSR, suggests that 5-HTP depressed the PSRs by increasing 5-HT transmission at inhibitory 5-HT receptors in the dorsal horn. Bell and Matsumiya (20), acknowledging contradictory reports in the literature, found that local infusion of 5-HT into the dorsal horn depressed a long-latency polysynaptic C-fiber reflex and, to a lesser degree, a short-latency PSR, whereas infusion into the ventral horn produced facilitatory effects. Thus these data supported the idea that stimulation of 5-HT receptors in the dorsal and ventral horns could exert opposite effects on spinal reflexes, and that these effects could be differentially mediated through inhibitory and excitatory postsynaptic 5-HT receptors. Clearly, more studies utilizing hallucinogens must be conducted.

Decerebrate or Intact Preparations

The spinal-transected preparation allows evaluation of the role of postsynaptic spinal 5-HT receptors in mediating the effects of hallucinogens on reflex behavior. Indeed, the data cited above indicate that the potentiating effects of hallucinogens on spinal reflexes are attributable to an activation of postsynaptic excitatory 5-

HT receptors located in close proximity to the motoneurons in the ventral horn. These receptors probably are innervated by descending 5-HT neurons originating in several of the caudally situated raphe nuclei (e.g., obscurus and pallidus) (23). The presence of an anatomically distinct 5-HT innervation of the dorsal horn from the raphe magnus suggests that activation of dorsal horn 5-HT receptors could mediate the depressant effects on reflexes described above.

The use of the spinal-transected preparation may be of limited value in understanding how 5-HT systems (and perhaps, therefore, hallucinogens) modulate spinal reflexes in the normal animal. Aside from possible nonspecific consequences (e.g., ischemia and electrolyte imbalances), transection eliminates the influence of tonic activity in descending neurons on postsynaptic receptors. It is well documented that 5-HT neurons in the raphe nuclei are tonically active (4), and that many hallucinogens depress this spontaneous activity by acting on autoreceptors. Hence it is reasonable to expect that descending 5-HT neurons could exert tonic effects on spinal reflexes, and that these effects could be altered by hallucinogens. In the intact animal, hallucinogens might produce complex effects on spinal reflexes by reducing tonic facilitation or inhibition, in addition to directly acting on postsynaptic receptors. This framework will help in the interpretation of complex effects of hallucinogens reported in studies that have utilized preparations in which the spinal cord is still connected to part (i.e., the decerebrate) or all of the brain.

In man, the indole hallucinogens LSD, psilocybin, and DMT have been reported to facilitate the monosynaptic knee jerk reflex (96,146). Unfortunately, there is a paucity of reports on hallucinogen effects on MSRs in intact animals. Reports utilizing nonhallucinogenic drugs that act on 5-HT systems nonetheless illustrate some important points. Transection may disrupt a tonic facilitatory influence on the extensor (soleus) MSR reflex that can be restored by 5-HTP administration (5) (this point is discussed below). Although data gathered using transected animals suggest that hallucinogens may enhance spinal reflexes by acting at the level of the motoneuron, studies by Sastry and Sinclair (147–149) have indicated that descending 5-HT neurons may interact with spinal MSR mechanisms in subtle and perhaps multiple ways. Thus enhancement of 5-HT transmission (e.g., with 5-HT reuptake blockers) was found to reduce recurrent inhibition of motoneurons (147), reduce presynaptic inhibition of extensors from antagonist flexors (149), and block pre- and postsynaptic inhibition of the MSR produced by bulbospinal stimulation (148). Furthermore, these studies indicated that tonic serotonergic influences on these spinal mechanisms were present.

Recent data utilizing a polysynaptic withdrawal reflex suggest that, in intact rats, a disinhibition hypothesis may be necessary to explain some of the facilitatory effects of hallucinogens. Low to moderate doses of the hallucinogen 5-MeODMT administered into the lateral ventricle facilitated (i.e., decreased the latency of) the tail flick response to radiant stimulation of the tail (22). Furthermore, either spinal transection alone or systemic administration of 5-HT antagonists in intact

(but not transected) rats mimicked the facilitatory effect of 5-MeODMT (21). It was suggested that 5-MeODMT facilitated the reflex in intact rats by an autoreceptor-mediated inhibition of tonically inhibitory descending serotonergic neurons. The most direct way to evaluate the involvement of descending 5-HT neurons would be to specifically lesion the spinal 5-HT terminals by intrathecal administration of the 5-HT neurotoxin 5,7-DHT (91) and subsequently determine if (a) the loss of 5-HT terminals produced a transection-like or antagonist-like facilitation of the tail flick reflex, and (b) if the excitatory effects of low doses of 5-MeODMT were abolished.

In addition to the excitatory effects described above, there is some evidence that administration of hallucinogens can depress MSRs and PSRs in intact animals. These depressant effects, however, do not appear to be simply mediated by stimulation of inhibitory postsynaptic 5-HT receptors in the spinal cord, since they are blocked by 5-HT antagonists.

Barasi and Roberts (14) reported that LSD (15 μg/kg) reduced the amplitude of the MSR in either intact (anesthetized) or decerebrate (unanesthetized) rats. Since there is no evidence in transected animals that hallucinogens depress MSRs, it is reasonable to suggest that the depressant effect of LSD was due to an autoreceptor-mediated reduction in activity of descending 5-HT neurons that tonically facilitate motoneurons. In fact, several lines of evidence support the idea of a tonically active, facilitatory descending 5-HT system. (a) The 5-HT antagonists cinanserin (15) and methysergide (32) both reduced the amplitude of the MSR in intact cats. This depression could be attributed to a blockade of postsynaptic excitatory 5-HT receptors in the ventral horn. (b) An earlier study found that the spinal transection-induced loss of the tonic stretch reflex in an extensor (soleus) muscle was restored by 5-HTP administration, probably through increased activation of alpha- and gamma-motoneurons (5). Interestingly, 5-HTP administration has been reported to depress the tonic stretch reflex in the decerebrate rat (36). One could speculate that, in the presence of maximal tonic postsynaptic 5-HT activation, 5-HTP depressed the reflex by stimulating presynaptic inhibitory receptors, thereby reducing tonic activity. If this were the case, then specific lesions of the spinal 5-HT terminals with 5,6-DHT should depress MSR amplitude and block the depressant effect of LSD.

These studies illustrate the point that the analysis of hallucinogen effects on spinal reflexes in intact animals may provide important information regarding the role of tonically active functionally depressant descending systems that would otherwise be lacking in the spinally transected preparation.

Electrical stimulation in the vicinity of the raphe nuclei has been reported to produce depressant effects on MSRs (32,142). These depressant effects could be attributed to activation of postsynaptic inhibitory receptors analogous to those characterized in the forebrain, except for the fact that the depression was blocked by 5-HT antagonists. The effectiveness of the antagonists suggests that the receptor is more akin to the excitatory 5-HT receptor characterized on motoneurons (134,184). The depressant behavioral effects could result from

activation of an inhibitory interneuron that depresses transmission at the level of the primary afferent fiber. Indeed, Carstens et al. (30) have reported that 5-HT applied iontophoretically in the dorsal horn produced consistent increases in the threshold of excitability of type A and C primary afferent fibers.

Intraventricular administration of low doses of 5-MeODMT was reported to produce a facilitation of the polysynaptic tail flick reflex (see above). In fact, 5-MeODMT had a biphasic dose effect on this reflex, in that intermediate doses (50–200 μg) exerted mixed excitatory/depressant effects, and high doses (400 μg) produced frank inhibition (22). The authors suggested that the data were consistent with a disinhibition model, whereby high doses stimulated inhibitory postsynaptic receptors in the spinal cord that overcame the low dose autoreceptor-mediated inhibition of tonic 5-HT activity. Again, however, 5-HT antagonists attenuated the effects of 5-MeODMT, suggesting the involvement of an excitatory postsynaptic 5-HT receptor. In fact, a number of other studies measuring the effects of treatments that enhance 5-HT transmission in the spinal cord on PSRs indicate that functionally depressant effects are mediated by excitatory 5-HT receptors. Thus intrathecally administered 5-HT or 5-HTP depresses the tail flick reflex; these effects are reversed by methysergide (194,195), which can produce hyperalgesia by itself when given intrathecally (144). Consistent with this behaviorally defined depression of PSRs, electrical stimulation of the raphe magnus has been found to reduce the excitability of dorsal horn interneurons (16,57,59,143); this depressant effect was blocked by 5-HT antagonists. Furthermore, iontophoretically applied 5-HT depressed the firing of nociceptive neurons in the substantia gelatinosa of the dorsal horn. In some cases, this effect was blocked by methysergide (17,81,86,109,145).

Summary

The data discussed in this section suggest that hallucinogens act in a complex manner to affect spinal reflexes. In general, the following conclusions may be justified:

1. The most convincing data indicate that hallucinogens augment spinal reflexes by stimulating spinal, excitatory (postsynaptic antagonist-reversible) 5-HT receptors, which probably exist on or in close proximity to alpha-motoneurons.
2. Data gathered using a few hallucinogens indicate that these agents may depress spinal reflexes by interacting with antagonist-reversible receptors that are located in the dorsal horn of the spinal cord.
3. Hallucinogens may interact with tonically active descending 5-HT systems to facilitate reflexes by disinhibition or depress reflexes by reducing tonic facilitation; both these influences may be mediated through antagonist-reversible postsynaptic receptors.
4. The net effect of hallucinogens on spinal reflex behaviors will depend on a complex balance between the behaviorally excitatory ventral horn 5-HT receptors and the behaviorally depressant dorsal horn 5-HT receptors, as well as on effects on tonic activity in descending 5-HT systems.

Acoustic and Tactile Startle Reflexes

Several lines of evidence suggested that acoustic and tactile startle reflexes might be affected by hallucinogens. Startle reflexes elicited by auditory or tactile (e.g., air-puffs) stimuli have provided a sensitive stimulus-response system to analyze the effects of many drugs on behavior (42). Moreover, it seemed likely that hallucinogens would alter startle, given their profound effects on sensory perceptions in humans. In addition, the seminal work of Key and Bradley (113) suggested that psychotomimetics might exert their effects by altering the rate of behavioral habituation. Since startle had been widely used to study habituation, this suggestion provided another reason to analyze the effects of hallucinogens on startle.

Indole Hallucinogens

Early work on the effects of hallucinogens on startle centered around the disinhibition hypothesis; that is, activation of autoreceptors in the raphe nuclei results in decreased transmission in (inhibitory) postsynaptic areas. The impetus for this notion came from the fact that depletions of 5-HT produced by PCPA (37), raphe lesions (48,74), 5,7-DHT (72), or L-tryptophan-free diets (186) enhanced acoustic or tactile startle reflexes. Conversely, infusion of 5-HT intraventricularly (43,76) or directly into the hippocampus (68) depressed startle. If low doses of hallucinogens preferentially depress raphe cell firing, then low doses should increase startle; if higher doses also inhibit areas postsynaptic to the raphe, then they should depress startle. Thus hallucinogenic compounds should have biphasic dose-response effects; low doses should increase startle, whereas high doses should depress startle. This is indeed what we found for acoustic startle. Low doses of DMT (0.5–2.0 mg/kg) produce a small increase in startle, whereas higher doses (>2 mg/kg) depress acoustic startle (45,50). Similarly, low doses of psilocybin or psilocin (0.5–1 mg/kg) increase startle, whereas higher doses (>3–4 mg/kg) depress startle (52).

The pattern of results is only slightly different for LSD. Low doses of LSD (20–80 μg/kg) increase startle (46,47,49,51,132). In fact, LSD is more efficacious in increasing acoustic startle than either DMT or psilocybin, perhaps because it has a greater difference in potency between its pre- and postsynaptic ED_{50} doses than DMT or psilocin (3). High doses of LSD (greater than 300 μg/kg) depress startle. The depressant effect is somewhat delayed, however, and follows an initial excitatory effect (M. Davis, *unpublished data*). Moreover, the non-hallucinogenic bromo-LSD, which is relatively ineffective in depressing raphe cell firing rates, does not alter startle (49).

Using tactile startle, bufotenin, a hallucinogen that does not cross the blood-brain barrier readily, also produced biphasic dose-response effects when given intraventricularly (76). After systemic administration, however, low doses of indole hallucinogens have not been reported to increase tactile startle (73). Thus LSD (20–80 μg/kg), DMT (0.25–1.0 mg/kg), and psilocin (2.5–5.0 mg/kg) did not increase tactile startle. A slightly higher dose of LSD (100 μg/kg) did increase startle toward the end of the test session, perhaps because of blocking habituation (see below).

These data suggest that acoustic and air-puff startle differ slightly in how they are affected by indole hallucinogens, since air-puff startle is not increased by these compounds. However, LSD will increase air-puff startle to the first stimulus when a more intense air-puff is used to elicit the response (73). Thus the effects of the hallucinogens seem to be critically dependent on the characteristics of the stimuli used to elicit startle. In fact, with acoustic startle, the normal excitatory effect of LSD can be eliminated by testing at low levels of background noise (49) or by presenting tones at a rapid rate (51). These findings suggest that the hallucinogens alter startle by affecting the sensory rather than the motor side of the reflex arc. This conclusion is consistent with the profound effects of these compounds on perception in humans.

In contrast to the rather weak effects produced by these indole hallucinogens, another indole hallucinogen, 5-MeODMT, produces a marked increase in acoustic startle (44). In this case, the excitatory effect is monotonically related to the dose over a range from 0.03 to 8 mg/kg. In fact, 5-MeODMT is one of the most efficacious drugs we have found in increasing acoustic startle. Thus far, the effects of 5-MeODMT on tactile startle have not been tested.

Phenylethylamine Hallucinogens

Phenylethylamine derivatives, which have hallucinogenic properties in humans, increase air-puff-elicited startle (73). The order of potency in increasing startle in the rat correlates positively with the order of potency in producing hallucinations in humans, 2,5-dimethoxy-4-methylamphetamine (DOM) being the most potent. Although the effects of these compounds on acoustic startle have not been extensively studied, it has been reported that neither mescaline (25 mg/kg) nor 3,4-dimethyoxyphenylethylamine (50 mg/kg) altered acoustic startle (26). In contrast, mescaline does have excitatory effects on air-puff-elicited startle (73,75). However, because different test conditions were employed across these studies, they are difficult to compare. Recently, we have found that mescaline (2.5–20 mg/kg) increases acoustic startle using test procedures similar to those of Geyer et al. (75) (M. Davis, *unpublished data*). In contrast to the indole hallucinogens, mescaline has a simple excitatory effect that is monotonically dose related up to the highest dose tested (20 mg/kg).

Effects of Hallucinogens on Habituation and Sensitization of Startle

As mentioned above, earlier studies suggested that hallucinogens might alter the process of behavioral habituation that typically occurs when the same stimulus is presented repetitively. For example, injection of LSD had been shown to reinstate a formerly habituated arousal response (113) and to increase the number of trials necessary to reach a criterion of arousal habituation (111). Depending on the dose and the intensity of the eliciting stimulus, cats injected with LSD may show no decrement of behavioral or electroencephalographic arousal responses to repetitive stimulation, as long as the drug is acting (113). In related studies, it was suggested that LSD may potentiate the distracting influence of irrelevant stimuli. Key (112) found that the increase in shuttle time to a light conditioned stimulus (CS) when novel tones were presented was potentiated when cats were injected with LSD. Similarly, Uyeno (182) reported that LSD increased the running time of rats in a maze only if a novel barrier were introduced.

To test for a possible effect of hallucinogens on habituation to acoustic startle stimuli, the effects of DMT on within- and between-session habituation were evaluated (45). DMT (1–16 mg/kg) depressed startle likelihood and impaired 24-hr retention of startle habituation. It did not impair retention of startle habituation if a long (i.e., 30-sec) rather than a short (8-sec) interstimulus interval was used during training and testing, indicating that the exact stimulus conditions used have important influences on the effects of the drug on habituation. Moreover, DMT did not seem to impair within-session habituation of acoustic startle, although this was difficult to determine given its generally depressant effects on initial startle amplitude.

Miliaressis and St. Laurent (132) concluded that LSD impaired habituation of acoustic startle at doses ranging from 60 to 240 μg/kg given 30 to 40 min earlier. However, their data show that the absolute rate of response decrement was actually greater in the LSD-treated rats, and that differences in habituation only occurred when percentage data were analyzed—a questionable procedure when initial startle levels vary markedly.

Davis and Sheard (49) found that LSD (40 μg/kg) did not alter the rate of within-session startle habituation when injected 15 min before a 15-min test session. Instead, LSD seemed to potentiate the normal facilitatory effect of background white noise on startle, since its effect on initial startle amplitude could be prevented by testing in a quiet chamber. Interestingly, however, LSD did seem to retard startle response decrement at the end of the test session, when quiet test conditions prevailed. Perhaps similarly, LSD also retarded response decrement of tactile startle toward the end of a 60-min test session (24), an effect which is not reproduced by the nonhallucinogenic congener of LSD, lisuride, at doses from 15 to 60 μg/kg (M. A. Geyer, *unpublished data*). Most interestingly, however, is the finding that repeated injections of LSD (100 μg/

kg/day) for 8 days enhanced its initial excitatory effect on startle (24). Thus rather than drug tolerance, drug sensitization seemed to occur. Finally, mescaline does not appear to alter habituation of either tactile (73) or acoustic (M. Davis, *unpublished data*) startle.

Receptor Systems that Might Mediate the Effects of Hallucinogens on Startle

Model I: inhibitory 5-HT receptors

The idea that indole hallucinogens might increase startle by interacting with presynaptic autoreceptors has received some experimental support. Davis and Sheard (49) found that lesions of the dorsal and median raphe nuclei blocked the usual excitatory effect of a low dose (40 μg/kg) of LSD on acoustic startle. Moreover, other treatments that decreased raphe cell firing rates also blocked the excitatory effects of LSD on startle. For example, pretreatment with chlorimipramine (CIMI), which decreases raphe cell firing indirectly by blocking 5-HT reuptake (153), blocked the usual excitatory effect of LSD on startle without preventing the entry of LSD into the brain (47). These data were consistent with the disinhibition hypothesis.

In that same study (47), however, other tricyclic compounds, such as desipramine or chlordesipramine, also blocked the excitatory effects of LSD on startle at doses that do not depress raphe cell firing but instead depress firing rates of norepinephrine-containing neurons in the locus ceruleus. Moreover, the fact that mescaline can increase both acoustic and air-puff-elicited startle without consistently inhibiting cells in the raphe nucleus (82) argues against a presynaptic action for mescaline. In fact, Geyer et al. (75) found that lesions of the median raphe nucleus did not prevent the usual excitatory effects of mescaline on tactile startle.

The ability of high doses of hallucinogens to depress startle may involve activation of postsynaptic inhibitory 5-HT receptors, although no direct evidence is available. Direct infusion of 5-HT, DMT, or 5-MeODMT intraventricularly depresses startle (35,43,76). The 5-HT antagonists cyproheptadine or cinanserin do not block the depressant effects of intraventricular 5-HT (43) or high doses of systemically administered DMT (M. Davis, *unpublished data*). What is needed, however, is some positive evidence to implicate 5-HT receptors in these effects. For example, one would expect that the depressant effects of hallucinogens (e.g., DMT) would be enhanced by prior depletion of 5-HT via 5,7-DHT due to the development of supersensitivity, although this prediction awaits testing.

Model II: excitatory 5-HT receptors

The fact that 5-HT and hallucinogens can facilitate motor transmission in the spinal cord (see above) suggested that these compounds might increase startle by actions on spinal excitatory 5-HT receptors. Consistent with this expectation, we have found that direct infusion of 5-HT or 5-MeODMT into the subarachnoid space of the lumbar spinal cord markedly increases the amplitude of acoustic startle (11,35,43,44). The excitatory effects of intrathecal 5-HT or 5-MeODMT are blocked by systemic administration of the 5-HT antagonists cyproheptadine or cinanserin, as are the excitatory effects of systemically administered 5-MeODMT (11,43,44). On the other hand, DMT does not increase startle when given intrathecally (35), which may explain why it has only inhibitory effects on startle at high doses. Thus far, the effects of other hallucinogens have not been tested on startle after intrathecal administration.

Summary

Low doses of indole hallucinogens tend to enhance acoustic startle but have little effect on tactile startle. Phenylethylamine hallucinogens increase both acoustic and tactile startle. Disinhibitory effects via 5-HT autoreceptors are not sufficient to account for these effects. Possible interactions between 5-HT and norepinephrine systems may be involved. High doses of many indole hallucinogens depress acoustic startle, perhaps by acting on postsynaptic 5-HT receptors. This hypothesis must be tested. High doses of selected hallucinogens (5-MeODMT) markedly increase acoustic startle, probably by acting as 5-HT agonists on motoneurons in the brainstem and spinal cord. These effects are blocked by 5-HT antagonists.

Locomotor and Exploratory Behavior

The effects of hallucinogens and serotonergic manipulations on the spontaneous behavior of animals, particularly rats, have been investigated in a variety of contexts. Locomotor activity is generally considered to be fundamentally a motor response, and the monitoring of animal behavior is largely limited to the detection of motor output. Nevertheless, the study of serotonergic influences and effects of hallucinogens on measures of locomotion has provided instructive examples of the profound importance of sensory responsivity in the modulation and expression of locomotor activity. The interpretation of observed changes in locomotion following the administration of hallucinogens or manipulations of central serotonergic systems is critically dependent on the precise nature of the environmental context in which the animals are tested. Such interpretations are facilitated by the concurrent assessment of explicit measures of the animals' tendency to investigate environmental stimuli and/or by systematic comparisons of the effects of the manipulations in different sensory contexts.

5-HT and Activity

With respect to central serotonergic pathways, considerable evidence converging from a variety of experimental approaches has suggested a general inverse

relationship between the functional activity of brain 5-HT and the level of behavioral activity. For example, locomotor activity is typically reduced by increasing brain levels of 5-HT by systemic treatments with tryptophan (28,169) or by intraventricular administration of 5-HT (79,187). Conversely, hyperactivity is frequently although not invariably produced by treatments that deplete brain 5-HT, such as parachlorphenylalanine (PCPA) (27,58,141), PCA (63,117,119,120,167), fenfluramine (170), midbrain raphe lesions (114,115,120,160,197), or the serotonergic neurotoxins 5,6- and 5,7-DHT (25,54,55,163). Although much of this evidence derives from global changes in 5-HT produced by systemic manipulations, more anatomically specific investigations indicate that this relationship is primarily dependent on the status of the mesolimbic serotonergic pathway, which originates in the median raphe and projects to sensory and limbic structures in the forebrain (54,74,107,160).

There appear to be important exceptions to the rule that a decrease in the availability of 5-HT in the mesolimbic pathway leads to increases in locomotor and investigatory activity. In contrast to the dramatic and pervasive hyperactivity produced by electrolytic lesions of the median raphe, similar depletions of 5-HT following the neurotoxic dihydroxytryptamines produce relatively subtle effects that appear to be related to the environmental context in which the behavior is monitored. For instance, microinjections of 5,7-DHT into the median raphe had no effect on the level of activity in a novel environment, whereas the same animals were hyperactive in a familiar environment (54).

Similarly, Hole et al. (88,89) found no significant change in the activity of 5,7-DHT-lesioned rats tested in their home cages and a reduced activity in treated rats tested in a novel open field. Since the lesioned animals were demonstrably hyperreactive to environmental stimuli, and the open field was brightly illuminated, the authors interpreted the reduced activity as reflective of an increase in reactivity or emotionality.

Another instructive example of the relevance of ambient stimuli to the nature of the effect of serotonergic manipulations on locomotor activity is provided by Brody's (27) study of PCPA. He monitored the locomotion of vehicle- and PCPA-treated rats in an open field to which the animals had been previously familiarized. Animals were tested either with or without additional stimulation in the form of flashing lights and 90 dB(A) noise bursts. Without stimulation, PCPA-treated rats were less active than controls; with stimulation, PCPA-treated rats were more active. The results of these and other such studies indicate that the central serotonergic systems may not directly modulate the level of locomotor activity per se, but they may profoundly influence locomotor activity by virtue of their effects on the sensory responsivity of the animal to a wide variety of environmental stimuli.

In keeping with the apparent importance of the environmental context in the interpretation of changes in locomotor activity associated with manipulations

of brain 5-HT, disparate and seemingly contradictory results have been found with respect to the effects of hallucinogens on locomotion, depending on the dosage parameters and the particular environmental circumstances in which the animals were studied. Most of these studies have focused on doses that are high relative to those effective in humans and have restricted their observations to measures of ambulation and rearing over rather brief (3-min) test periods. Such short tests maximize the influence of handling stress on the measured behavior. While a reduction in rearing behavior is produced most consistently by LSD and other hallucinogens, the influence of these drugs on horizontal locomotion is variable. It is most likely that the abnormal postures and apparent ataxia of the hindlimbs characteristic of the effects of most hallucinogens in rats may contribute to the reduction in rearing. In contrast to the relative independence of this rearing effect from the specifics of the testing environment, the effects of hallucinogens on ambulation are demonstrably dependent on the time since administration of the drug (110,196), size of the experimental chamber (93), manner in which the animals are handled (70), nature and degree of stimulation from the test environment (40), and degree of familiarity of the animal with the test environment (1,171). It should be noted that these latter three factors also have considerable impact on the qualitative features of the psychologic responses of humans to hallucinogens, as reflected in the oft-cited importance of "set and setting" in the human literature.

Effects of Hallucinogens of Locomotor Activity

Kabes et al. (110) examined the effects of LSD (80–500 μg/kg) on ambulation and rearing activity in a rectangular box with which the rats were thoroughly familiar. Preinjection intervals ranged from 5 to 270 min before 10-min tests. Ambulation was not significantly affected at any dose or preinjection time. Rearing was increased in the 5-minute group but was markedly decreased with longer preinjection intervals. Since the former effect was significant only in the first half of the session, it may have been related to an interaction of the drug with the handling occurring just prior to test start. In contrast, the reduction of rearing of LSD was unrelated to the amount of time spent in the chamber and was evident for at least 4 hr. The authors noted that the rats were observed "crawling around on the floor," although the duration and dose dependency of this effect was not noted. Similarly, Cohen and Wakeley (34) reported that doses of 30 to 3,200 μg/kg LSD had no effect on the activity of rats during hour-long sessions in circular open fields. When tested in a more complex maze with a 15-min preinjection interval and 15-min test period, however, LSD produced a dose-dependent reduction in intraalley movements from 30 to 1,000 μg/kg. In contrast, interalley movements were reduced only at the highest doses (320 and 1,000 μ/kg).

Dandiya et al. (41) observed rats for just 2 min beginning 15 min after injection of doses of LSD ranging from 2 to 500 μg/kg. They reported a dose-dependent increase in ambulation beginning at a dose of 136 μg/kg. Rearing and grooming exhibited inverted U dose-response curves, with the inversion occurring at doses higher than 8 μg/kg. The authors further reported that the increase in ambulation consisted of stereotyped circling of the open field and contrasted this effect with amphetamine-treated animals who explored the entire open field and reared as well. No mention was made of the dose dependency of these pattern effects, however, despite the wide range of doses used. While the investigators concluded that LSD increases stereotyped behavior, this circling during 2-min tests could have been due to enhanced neophobia with avoidance of the more exposed center of the field or even attempts to escape.

Silva and Calil (154) also observed rats in an open field and found that 100 μg/kg LSD had no effect on locomotion but depressed rearing when administered either 2 or especially 10 min before a 3-min test. They also studied a variety of other hallucinogens and nonhallucinogenic drugs to assess the usefulness of the open field as a behavioral screening test for hallucinogens. None of the measures, including defecation counts, were both consistently affected by hallucinogens and not similarly affected by nonhallucinogens.

In an attempt to better characterize the effects of hallucinogens on behavior and to improve the sensitivity of the traditional open field test to psychoactive drugs in general, Cunha and Masur (40) modified the test by adding external stimuli. For the first 5 min, observations were made in the "dark" (red lights only); for the next 5 min, an odor perfused the chamber (vanillin); from 10 to 15 min, a 78-dB noise came on; and from 15 to 20 min, bright lights illuminated the field. Both LSD (100 and 200 μg/kg) and psilocybin (0.5 and 1.0 mg/kg) produced dose-dependent reductions in rearing that were partially ameliorated when the lights were presented. While the higher dose of psilocybin suppressed ambulation throughout the session, neither dose of LSD affected ambulation during the first 15 min of the test. When the lights were turned on, however, both doses of LSD significantly increased locomotion. This peculiar sensitivity to light was not seen with any other drug tested, including psilocybin, tetrahydrocannabinol, caffeine, and amphetamine. Both doses of LSD also increased the time spent immobile during all conditions, except for the light-on condition. Since LSD did not correspondingly reduce measures of ambulation, the authors inferred that LSD-treated animals must exhibit bursts of locomotion followed by long pauses. This characteristic was also shared by diazepam and pentobarbital. Thus only sensitivity to light was unique to LSD.

Another example of the importance of the nature of the stimuli in the environment with respect to the effects of LSD on measures of locomotion is provided by the work of Hughes (93). He placed rats in compartmentalized square boxes for 60 min with a partition separating the "novel" from the "familiar" half. The rats were removed for 30 min and immediately injected, or

injected after 20 min, and 10 min later returned to the familiar half of the chamber with the partition removed. Visual observations were made for 10 minutes. There was no significant effect of LSD on novelty preference. Doses of 100 and 200 but not 10 μg/kg reduced rearing and ambulation and increased the amount of time spent sitting motionless. Both effects were more dramatic in the 10- as opposed to the 30-min preinjection group. Hughes (93) attributed the reduced level of activity to "heightened emotionality" rather than ataxia or reduced exploratory drive, because he noted that several of the high dose animals would "slowly back into a corner of the apparatus and then freeze for long periods of time while appearing to fixate some unseen object. This was often followed by a burst of locomotion then a repeat of the sequence in some other part of the chamber." In an explicit attempt to reconcile these results with the opposite effects reported by Dandiya et al. (41), additional rats were tested in a larger open field. In this more open setting, both 50 and 100 μg/kg LSD increased rather than decreased ambulation.

While the majority of studies have focused on LSD, some evidence suggests that hallucinogens derived from the phenylethylamine nucleus affect locomotion in a manner that is interpretable only by considering the environmental context. For example, the substituted amphetamine DOM produces a dose-dependent (0.5–10 mg/kg) reduction in locomotor activity when rats are tested in a novel open field, while a slight but significant increase in activity is observed in a familiar environment (171). This report corroborates the separate findings of DOM-induced hyperactivity in rats or mice in a familiar chamber (29,196) and hypoactivity in mice in an unfamiliar setting (92). Mescaline (10 mg/kg) has also been reported to increase locomotion in rats in a familiar environment (196).

In summary, as in studies of serotonergic manipulations, conventional open field measures based on brief tests have not proven useful in distinguishing the behavioral effects of hallucinogenic from nonhallucinogenic drugs. When such studies have included measures of stimulus responsivity and/or longer test sessions (40,71,171), however, better discriminations have been achieved. The variability of the effects of hallucinogens on measures of locomotion suggests that locomotion per se is not directly affected by these drugs, as it appears to be with traditional stimulants or depressants. In contrast to behaviors controlled by reinforcement contingencies or eliciting stimuli, the spontaneous locomotion of an animal is strongly influenced by a variety of factors. Hallucinogens may affect locomotion indirectly by virtue of their pervasive influences on the sensitivity of the animals to environmental stimuli.

Effects of Hallucinogens on Investigatory Behavior

One component of behavior that is thought to contribute to the spontaneous locomotion of an animal in an open field situation involves the propensity of

animals to investigate environmental stimuli, that is, exploratory behavior. Among the most widely used measures of exploration is an open field arena with holes placed in the floor and/or walls. These holes serve as specific stimuli which burrowing animals, such as rats, readily investigate, typically with their snouts. Thus measures of the frequency and/or duration of "holepokes" are viewed as reflective of the animal's investigatory tendencies (61).

In a series of studies, Geyer and Light (70) utilized an open field with three floor holes to characterize the effects of LSD on investigatory responding. Doses of 40 to 160 μg/kg LSD produced a dose-dependent alteration in the temporal distribution of holepokes consisting of an initial reduction and subsequent increase during a 24-min test. This peculiar temporal distribution of responding was found to be unaltered by variations in preinjection time, suggesting that it was related to drug-induced alterations in responsiveness to the environment rather than time course of drug action. File (60) also reported that 2 mg/kg DMT produced a reduction in investigatory holepoking that was limited to the initial period of time in a novel chamber. Subsequent studies showed that the initial decrease in exploration was attributable to an interaction between the drug effect and the stimuli associated with handling and introduction of the rat to the novel chamber and may have reflected a potentiation of neophobia by LSD (70).

Qualitatively similar effects were produced by DMT, psilocin, mescaline, and DOM but not by nonhallucinogenic drugs, such as amphetamine, CIMI, scopolamine, PCPA, clonidine, or methysergide (71). The effect was shown to be characteristic of both phenylethylamine and indoleamine hallucinogens. In addition, when a homologous series of congeners of DOM (differing only in the length of the alkyl chain at the 4-position of the phenyl ring) was tested, all three of the congeners active in humans, but not the two inactive in humans, produced the characteristic alteration of holepoke distribution. The nonhallucinogenic congener of LSD, 2-bromo-LSD, was also inactive in the test. Of the nonhallucinogenic drugs tested, only apomorphine produced an effect similar to LSD. The neurochemical substrates of this characteristic effect of hallucinogens on exploratory behavior have yet to be determined, although it is known that LSD is effective in animals with either electrolytic or neurotoxic lesions of forebrain serotonergic pathways (72).

More recent studies on the effects of hallucinogens on locomotor and investigatory behaviors have utilized a multivariate behavioral pattern monitor (2,69) to more thoroughly characterize the qualitative aspects of the effects of these drugs. This system combines standard measures of response frequency and duration for locomotion, rearing, and holepoking with more qualitative measures of the spatial and temporal patterns of locomotor and exploratory activity. In addition, the optional use of a home cage connected to the open field arena (free exploration) provides more explicit tests of the influences of environmental factors on the drug-induced changes in behavior.

When rats were tested by placing them directly into a novel chamber (forced exploration), the most significant and reliable effect of LSD (10–160 μg/kg) was a dose-dependent reduction of exploratory activity (activity and holepokes) in the first half of an hour-long session (1). This initial suppressant effect was absent when animals were tested in a familiar environment, suggesting that LSD induced this effect by potentiating the normal neophobia exhibited by rats confronted with a novel environment. When rats were tested in a free exploration test, which allowed them to enter and leave the novel chamber at will, LSD produced a dose-dependent reduction of time spent in the chamber without an alteration in the overall rate of locomotor or investigatory responses while in the chamber (2). In both circumstances, the suppression by LSD of initial activity was independent of preinjection intervals, confirming that it reflected potentiated neophobia, since the temporal characteristics of the effect were related to duration of exposure to the novel chamber rather than to temporal alterations in brain levels of drug. It is of interest to note that the most dramatic effects of 5,7-DHT-induced depletions of forebrain serotonin in this free exploration paradigm are a marked increase in the time spent in the novel chamber and a disproportionate increase in entries into the central part of the chamber (116), effects opposite to those of LSD.

In both free and forced exploration tests, spatial analyses of locomotor patterns revealed that the initial suppressant effects of LSD were best correlated with a reduction in entries into and time spent in the central region of the chamber (1). LSD still produced an initial reduction and subsequent increase in entries into and time spent in the center of the chamber when rats were tested in a familiar environment, despite the absence of any overall reduction in activity. Thus LSD may also potentiate agoraphobia (fear of open spaces), which is believed to be a major factor underlying the normal thigmotaxis exhibited by rats in large, open spaces. The fact that neophobia and agoraphobia were distinguishable, yet affected by LSD in the same direction, suggests that LSD produced an intensification of all types of "fear." Similar conclusions were reached by Tonge and Leonard (172) on the basis of their observations of animals treated with 100 μg/kg LSD or 5 mg/kg mescaline. Qualitatively similar reductions in initial activity and avoidance of the central region of a novel chamber have subsequently been found with both the indoleamine DMT (0.5–2 mg/kg) and the phenylethylamine DOM (0.1–1 mg/kg) (L. M. Adams, *unpublished data*).

Graphic reconstructions of the spatial patterns of locomotion exhibited by control and LSD-treated rats in the situation in which a home cage was attached to a novel chamber also showed that the drug disrupted the normal patterns of exploration (2). Controls explored the novel chamber by making a series of excursions or round trips from the home cage to various regions of the chamber and back. During 1-hr sessions, control excursions evolved from partial excursions along the walls to full excursions down the center, culminating in a few preferred

and simple routes. In contrast, rats treated with 20 to 30 μg/kg LSD made more round-about excursions, which were seldom retraced. Particularly late in the session, LSD-treated animals made a series of meandering excursions punctuated not by returns to the home cage but by pauses at seemingly random spots en route. Statistical comparisons of activity patterns seen in the first and last halves of the session revealed that the routes most preferred by controls in the first half reliably predicted the routes favored in the last half. In contrast, no correlation was seen in the spatial patterns of LSD-treated animals between the first and last halves of the session (2). Higher doses of LSD resulted in such prolonged avoidance of the novel chamber that no conclusions could be drawn concerning their effects on locomotor patterns.

As with most hallucinogens, LSD produced a dramatic dose-dependent reduction of rearing, which, in contrast to its other effects, was associated with an actual reduction of response rate in the free exploration test (2). Furthermore, rats treated with 30 μg/kg LSD still exhibited a reduction of rearing when tested in a familiar environment. These results indicate that, unlike its effects on crossovers and holepoking, the effect of LSD on rearing is independent of its effect on neophobia. Visual observations indicated that the reduction of rearing was related to the abnormal posture adopted by rats treated with doses of 30 μg/kg LSD or greater. The LSD-treated rats would alternate between lying or crawling (using forelimbs only) on their abdomens, spending more time prone with increasing dose.

Several factors indicate that the potentiation of neophobia and agoraphobia by hallucinogens in rats might be analogous to the increased lability and intensity of affective responses produced by hallucinogens in humans (1). Innumerable reports of variations in the affective response to hallucinogens appear to be primarily due to variations in the environmental setting (33,131). In novel and/or threatening situations, the primary affectual response induced by hallucinogens consists of anxiety, paranoia, or even terror; in benign situations, anxiety is minimal and euphoria predominates (131). In rats, the potentiation of neophobia and agoraphobia was dose-dependent in doses ranging from 30 to 160 μg/kg. In humans, the anxiogenic effects of LSD emerge at moderate doses (1–2 μg/kg), where only minor perceptual distortions and "elementary hallucinations" (with eyes closed) are seen (96–98). At higher doses (3 μg/kg or greater), paranoia, true hallucinations, and loss of insight occur. Thus the potentiation of neophobia by LSD in rats roughly corresponds to its anxiogenic potency in humans if species differences in metabolic rate are considered (62). The potentiation of neophobia in rats showed partial tolerance 24 hr after a single injection of 30 μg/kg, and complete tolerance following five daily injections (1). These results parallel the conditions for tolerance to its psychologic effects in man (97).

Another criterion for determining the relevance of behavioral effects in animals to mental effects seen in humans is that both show the same pharmacologic specificity. Lisuride, a derivative of isolysergic acid, does not produce the perceptual distortions or intensification of affect in man seen with LSD (87). In rats, low doses of lisuride produced sedation, with an apparent absence of neophobia (1). With increasing dose, the sedative effects of lisuride were replaced by hyperactivity; at no dose did lisuride produce the disrupted spatial patterns of locomotion so characteristic of low dose LSD. A further distinction between the behavioral effects of lisuride and LSD was revealed by their interactions with the dopamine antagonist haloperidol (1); 15 μg/kg haloperidol blocked the hyperactivity produced by 60 μg/kg lisuride in a manner consistent with competitive antagonism at dopamine receptors. This result is consistent with other reports demonstrating behavioral effects of lisuride that appear to be caused by a dopamine agonistic action in both animals (65,90) and man (99). In contrast, haloperidol failed to alter the potentiation by LSD of neophobia or agoraphobia. Similarly, haloperidol (0.25–5 mg/kg) is reportedly ineffective in blocking the fear-related effects of LSD and mescaline in rats (172).

Receptor Systems Related to Effects of Hallucinogens on Activity

Unfortunately, the relevance of central serotonergic systems to the effects of hallucinogens on locomotor and exploratory behaviors has not been adequately evaluated. The effects of both hallucinogens and serotonergic manipulations on ongoing behavior depend on the precise nature of the ambient stimuli, the manner in which the animals are handled, and the familiarity of the animals with the test environment. Too few studies have directly compared the effects of hallucinogens and serotonergic manipulations in identical paradigms to enable a more precise specification of this suggested similarity.

Model I: inhibitory 5-HT receptors

In general, the available evidence does not support the possibility that the effects of hallucinogens on locomotor and investigatory behaviors are mediated by inhibitory autoreceptors in the raphe nuclei. First, qualitatively similar behavioral effects are seen with both indole and phenylethylamine hallucinogens, despite the inconsistent effects of the latter on raphe unit firing. Second, tolerance develops rapidly to these effects of hallucinogens but not to the suppression of raphe firing. Third, neither electrolytic nor neurotoxic lesions of the midbrain raphe nuclei preclude these effects of LSD. Fourth, the opposite effects noted with 5,7-DHT and LSD in the free exploration paradigm are inconsistent with the idea that the effects of LSD result from a decrease in 5-HT transmission. Last, lisuride does not produce similar behavioral effects but does reduce raphe firing rates.

As with the other categories of behavior reviewed in this chapter, there is a paucity of evidence relevant to the logical possibility that inhibitory 5-HT re-

ceptors on target neurons in sensory and limbic structures mediate the effects of hallucinogens on locomotion and exploration. The similar reductions in locomotor activity produced by hallucinogens or intraventricular infusions of 5-HT might support such a model. This support would be greatly strengthened if the hypoactivity during 5-HT infusions were demonstrated to reflect heightened neophobias rather than a more direct sedative effect. It is clear that more work is needed to assess this possibility.

Model II: excitatory 5-HT receptors

In contrast to the other behaviors reviewed here, there is remarkably little evidence regarding the possible importance of the excitatory postsynaptic 5-HT receptors in the mediation of the effects of hallucinogens on behavioral activity. In fact, the only report we have found in which a classic 5-HT antagonist was used to address this question is that of Tonge and Leonard (172), who reported that methysergide (0.5 to 10 mg/kg) markedly potentiated the fear-related effects of both LSD and mescaline. This result contrasts with the more commonly observed blockade of the effects of hallucinogens on other behaviors following 5-HT antagonists, such as methysergide. Clearly, more studies are warranted to confirm and extend this potentially important finding.

Summary

Low doses of both indole and phenylethylamine hallucinogens potentiate the normal neophobia exhibited by rats placed into a novel environment, which typically results in an initial suppression of locomotion and investigation. These effects are extremely susceptible to the influences of ambient stimulation and handling. The action of hallucinogens on inhibitory 5-HT autoreceptors does not appear to be responsible for these effects. The relevance of either inhibitory or excitatory 5-HT receptors on target neurons to these effects of hallucinogens should be more thoroughly examined.

HALLUCINOGEN-ELICITED BEHAVIORS

Administration of hallucinogenic agents produces a number of distinct and apparently spontaneous motor responses in a variety of laboratory animals. These behaviors include the 5-HT syndrome in rats and mice, limb flicks in cats, and limb jerks in primates. These behaviors have in common (a) the apparently spontaneous (involuntary) nature of the response, and (b) the fairly well-established role of excitatory postsynaptic 5-HT receptor activation in the mediation of the effects.

The 5-HT Syndrome in Rats and Mice

Production by Hallucinogens and Other Treatments

Administration of agents that presumably increase serotonergic transmission in the central nervous system (CNS) produces a number of characteristic stereotyped behavioral effects in rodents. These effects include resting tremor, rigidity and hypertonus, reciprocal forepaw treading, hindlimb abduction, Straub tail, lateral head weaving, head and body shakes, salivation, hyperactivity, and hyperreactivity. The various components of this syndrome, studied separately in early investigations by Corne et al. [head twitches (38)], Gessner [tremor (67)], and Grahame-Smith [hyperactivity (77)], have recently been grouped together under the name "5-HT syndrome" (for reviews, see refs. 66 and 101).

The effects of hallucinogens on the 5-HT syndrome have been extensively studied; to date, every hallucinogen examined has been reported to produce the syndrome. This list includes LSD and related indolealkylamine [DMT, 5-MeODMT, diethyltryptamine (DET)] hallucinogens (39,53,56,67,108,152,155, 159,162,166,176,180,185,198), as well as phenethylamine (DOM, mescaline) hallucinogens (135,159,198).

Although there are subtle differences in the occurrence of various components of the syndrome (56,108), this chapter reviews these behaviors collectively, since (a) in the majority of cases, the various components of the syndrome occur together, and (b) the neuropharmacologic mechanism for the production of these components (as described below) appears to be the same, i.e., the activation of postsynaptic excitatory 5-HT receptors. Therefore, the term 5-HT syndrome is used to described the presence of any or all of these various components.

Evidence for the role of 5-HT receptor activation in the production of the syndrome comes from a number of laboratories employing a number of neuropharmacologic agents, including 5-HT-releasing compounds, 5-HT precursors, 5-HT uptake blockers, and agents that stimulate 5-HT receptors. Enhancing the release of synaptic 5-HT produces the syndrome in rats and mice. For example, the 5-HT-releasing agents PCA and fenfluramine and high (15–80 mg/kg) but not low doses of *d*-amphetamine have been reported to produce the syndrome. These effects can be antagonized by pretreatment with the 5-HT synthesis inhibitor PCPA, while the catecholamine synthesis inhibitor alpha-methylparatyrosine (AMPT) was without effect (155–159,176). In addition, a number of phenethylamine derivatives appear to produce the syndrome by releasing 5-HT, since (a) these effects are prevented by PCPA (152), and (b) these agents enhance the release of ^{3}H-5-HT from brain synaptosomes (95).

Increasing the concentration of 5-HT by substrate loading has also been reported to produce the 5-HT syndrome. Administration of tryptophan, the substrate amino acid for 5-HT synthesis, in conjunction with a MAOI produces the syndrome (38,53,66,77,94,95,101,108). This effect is potentiated by pre-

treatment with the 5-HT uptake blockers fluoxetine, paroxitine, and zimelidine (94). Trazadone and amitryptyline, agents that are much weaker 5-HT uptake blockers, did not potentiate the effects of tryptophan and MAOI (94). A number of reports suggest that treatment with the 5-HT precursor 5-HTP alone also produces the syndrome in mice and rats (133,135,157,174); however, the efficacy of 5-HTP administration alone in producing the syndrome has been reported to be quite weak (164,165). There is clear agreement that the syndrome-inducing effects of 5-HTP are markedly potentiated by pretreatment with MAOI (101,133,139,163) or the 5-HT neurotoxin 5,7-DHT (101,161,162,164,165,174). Furthermore, the effects of 5-HTP are antagonized by pretreatment with the centrally acting decarboxylase inhibitors (157,158,163–165), suggesting that decarboxylation of 5-HTP to 5-HT is necessary for the production of the syndrome.

Finally, treatments that directly stimulate 5-HT receptors also produce the 5-HT syndrome. First, intraventricular administration of 5-HT, although ineffective in control rats, produces a pronounced syndrome in 5,7-DHT-pretreated subjects (157,188). Systemic administration of 5-HT was ineffective (163), indicating that this effect was centrally mediated. Second, with the exception of one report in mice (94), the direct-acting 5-HT agonist quipazine has been reported to produce the syndrome also (39,108,161,185).

The 5-HT syndrome can also be produced by a number of treatments whose primary actions are not expressed at serotonergic receptors. For example, in MAOI-pretreated rats, the intraventricular administration of dopamine or systemic treatment with the dopamine precursor *l*-dihydroxyphenylalanine (*l*-DOPA) in combination with an MAOI results in the 5-HT syndrome (53,100,158). The neuropharmacologic mechanism for the syndrome-inducing effect of dopamine and of *l*-DOPA appears to involve serotonergic and not catecholaminergic systems. This conclusion derives from studies in which depletion of 5-HT by treatment with PCPA or 5,7-DHT blocks the syndrome-producing effects of dopamine and *l*-DOPA, while depletion of catecholamines with AMPT did not (100,158). Furthermore, the syndrome-inducing effects of MAOI plus *l*-DOPA are attenuated by 5-HT but not by dopamine antagonists (100,158). These data suggest that *l*-DOPA produces the 5-HT syndrome via release of 5-HT from 5-HT terminals.

The catecholamine-releasing agent beta-phenylethylamine (PEA) also produces the 5-HT syndrome (156) by direct activation of 5-HT receptors. The 5-HT antagonists methysergide and mianserin blocked the syndrome-producing effects of PEA, while depletion of 5-HT by PCPA or 5,7-DHT treatments was not effective. A possible role of catecholamines in the syndrome-producing effects of PEA cannot presently be discounted.

A puzzling finding regarding the 5-HT syndrome is the report that the deaminated indoles 5-hydroxyindoleacetic acid (5-HIAA; the primary metabolite of 5-HT) and indoleacetic acid (IAA) are effective in producing the syndrome when administered intraventricularly to 5,7-DHT-treated rats (188). Although the neuropharmacologic mechanism for the syndrome-inducing effects of these deaminated indoles has not been exhaustively investigated, the 5-HT antagonists cyproheptadine and methiothepin are at least partially effective in antagonizing these effects, suggesting a role of excitatory 5-HT receptors in this effect. Clearly, the syndrome-inducing effects of these agents, which previously were assumed to be simply inactive metabolites of 5-HT, represent an interesting finding that deserves more attention.

Thus there is considerable evidence to suggest that the 5-HT syndrome results from the activation of 5-HT receptors in the CNS. Results from many lines of investigation suggest that although inhibitory 5-HT receptors may be involved in the modulation of the 5-HT syndrome produced by hallucinogens and other agents, it is the activation of excitatory postsynaptic 5-HT receptors that is necessary for the production of the syndrome.

Receptor Systems that Mediate the 5-HT Syndrome

Model I: inhibitory 5-HT receptors

Considerable evidence opposes the activation of inhibitory 5-HT autoreceptors in the raphe nuclei as being sufficient for the production of the syndrome in rats. First, for many agents, the doses required for the depression of raphe firing are considerably less than those required for the production of the 5-HT syndrome often differing by as much as a factor of 100. Moreover, there is little correlation between the potency of these agents to depress raphe activity and their potency in producing the syndrome. Second, although mescaline effectively produces the syndrome, it does not consistently depress raphe firing (82). Third, certain aspects of the syndrome (e.g., Straub tail, tremor) can be elicited in spinal-transected animals following treatment with 5-MeODMT (J. H. Kehne, R. L. Commissaris, and M. Davis, *unpublished data*) or a combination of pargyline and L-tryptophan (103). Thus it is unlikely that the activation of inhibitory 5-HT receptors on raphe neurons can cause the 5-HT syndrome. However, these inhibitory 5-HT receptors, along with the inhibitory postsynaptic 5-HT receptors, might be involved in the modulation of the syndrome-producing effects of various agents.

Perhaps the best illustration of this possible modulatory influence of inhibitory 5-HT receptors on the syndrome comes from studies employing various doses of LSD. This agent appears to affect the syndrome in a triphasic manner, which is dependent on the dose employed. A low dose (10 μg/kg i.p.) potentiates the syndrome-producing effects of 5-MeODMT (159). Somewhat higher doses (200 μg/kg) attenuate the effects of 5-HTP in 5,7-DHT-treated rats (164). Finally, in general, high doses of LSD (1–5 mg/kg) are required to elicit the syndrome when administered alone (67,159). These data are in agreement with the hy-

pothesis that selective activation of the autoreceptor by low doses of LSD would "disinhibit" neuronal systems modulated by inhibitory postsynaptic sites to potentiate the syndrome, while somewhat higher doses of LSD would overcome this autoreceptor effect and result in activation of these inhibitory postsynaptic sites to inhibit the syndrome. Finally, high doses of LSD would produce the syndrome by interacting directly with an excitatory 5-HT receptor. Although this model is clearly speculative, it does provide a means by which these variable effects of LSD on the 5-HT syndrome can be explained.

Model II: excitatory 5-HT receptors

Studies employing the 5-HT antagonists have indicated that the syndrome produced by hallucinogens and other treatments that increase synaptic 5-HT is the result of the activation of excitatory postsynaptic 5-HT receptors. For example, the syndrome-producing effects of 5-HTP and tryptophan treatments are blocked by pretreatment with 5-HT antagonists (53,66,100,101,135,161–165). The syndrome-producing effects of quipazine also are blocked by cyproheptadine (185). Although contrary findings have been reported (108,152), the syndrome-inducing effects of these hallucinogens, in general, are effectively antagonized by the 5-HT antagonists (135,157,159,166,185,198). Although the syndrome-producing effects of treatments are not generally blocked by the alpha-antagonist phentolamine, the dopamine antagonist pimozide, haloperidol, or the cholinergic antagonist atropine (157,161), the 5-HT syndrome is antagonized by other agents (e.g., propranolol, morphine, amitryptyline, chlorpromazine, clonidine) not recognized as 5-HT antagonists. Of these agents, propranolol and related beta-adrenergic agents have received the greatest attention (39,53,78,108,135,139,152,166,190). The results of the studies with these beta-adrenergic agents have been interpreted by these authors as evidence for either (a) the facilitatory effect of beta-adrenergic systems on 5-HT transmission (139), or (b) a direct interaction of propranolol and related compounds with 5-HT receptors (53,152,189,190). Moreover, the results of a recent study by Niemegeers et al. (135) suggest that the apparently anomalous antagonism of the syndrome by many other agents thought not to be 5-HT antagonists might actually be due to direct or indirect interactions of these drugs with 5-HT neurons and/or receptors and not to the nonspecific nature of the syndrome itself.

In an exhaustive series of experiments, Niemegeers et al. (135) examined numerous compounds for their potential antagonism of a number of behaviors, including the 5-HT syndrome (measured as mescaline- or 5-HTP-induced head twitches and tryptamine-induced tremor and seizures), apomorphine-induced stereotypy, intravenous norepinephrine-induced lethality, compound 48/80-induced lethal shock [histamine (H1) agonist effect], and physostygmine-induced mydriasis and lethality. The ED_{50} values were calculated for each antagonist in each behavioral test. Correlation (pA2) analyses were conducted comparing the potency of these antagonists against mescaline-induced head twitches to the potency of these agents in antagonizing each of the other behaviors.

The investigators found high ($r = 0.90$) correlations when ED_{50} values for antagonizing the 5-HTP-induced head twitches or tryptamine-induced tremor and seizures were compared to ED_{50} values for antagonizing mescaline-induced head twitches. This finding is consistent with the hypothesis that mescaline, 5-HTP, and tryptamine work through a common mechanism to produce their effects.

The correlations between the ED_{50} values for the antagonism of mescaline-induced head twitches and the antagonism of the other behaviors examined were considerably less impressive ($r = 0.35$), indicating dissimilar receptor mechanisms. The authors (135) concluded that mescaline- and 5-HTP-induced head twitches and tryptamine-induced tremor and seizures result from the activation of a common receptor or set of receptors which were distinct from those receptors (dopaminergic, adrenergic, histaminergic, and cholinergic) mediating the other behaviors examined. They also found a significant ($r = 0.83$) correlation between the ED_{50} values of these antagonists against mescaline-induced head twitches and IC_{50} values of these agents in displacing ^{3}H-spiperone binding to 5-HT receptor sites. Thus it is likely that the 5-HT syndrome produced by hallucinogens results from agonist actions of these agents at 5-HT receptors. Since, as mentioned above, the syndrome-inducing effects of hallucinogens can be antagonized by a number of 5-HT antagonists, these 5-HT receptors probably are of the excitatory postsynaptic variety.

A number of studies support the hypothesis that at least some of the excitatory 5-HT receptors involved in the generation of the 5-HT syndrome are located in the brainstem and/or spinal cord. First, the syndrome can be produced by the administration of *l*-tryptophan to pargyline-pretreated rats decerebrate at the midcollicular level (103), indicating that ascending 5-HT systems are not involved in the production of the syndrome. Second, as discussed above, the hindlimb tremor and Straub tail still can be observed in spinal-transected rats following *l*-tryptophan and pargyline (103) or 5-MeODMT (J. H. Kehne, R. L. Commissaris, and M. Davis, *unpublished data*) administration. Third, selective destruction of 5-HT terminals in the spinal cord (but not brain) by the intraspinal injection of 5,7-DHT potentiates the 5-HT syndrome-producing effects of 5-MeODMT (53).

In summary, hallucinogenic agents produce the 5-HT syndrome in rats and mice by activating postsynaptic excitatory 5-HT receptors, many of which appear to be located in the brainstem and/or spinal cord. In addition, action of these agents at inhibitory 5-HT receptors may modulate the syndrome-producing effects of hallucinogens.

Limb Flicks in Cats

Production by Hallucinogens

Jacobs and co-workers (105,106,177) reported that the administration of LSD and related hallucinogens produced a number of unusual behavioral effects in

cats, most notably limb flicking, abortive grooming, and investigatory play behavior. Limb flicking was described as a behavior seen in normal cats in response to placing a foreign substance, such as water, on the paw. The paw is then lifted and rapidly flicked outward in an attempt to dislodge the substance. Abortive grooming was scored by these investigators when the cat oriented itself to groom but did not emit the normal consummatory response (biting, licking, or scratching). Investigatory play behavior was scored when the cat was observed to be pawing or sniffing at objects or was biting/batting at pieces of food or feces. These behaviors were not observed in control cats but were reliably produced in cats following the administration of a number of hallucinogenic compounds (LSD, psilocybin, psilocin, DOM, DMT, 5-MeODMT, mescaline), while many nonhallucinogenic agents (bromo-LSD, *d*-amphetamine, tryptamine, atropine, caffeine, chlorpheniramine) were found to be ineffective in producing these behaviors. Subsequent investigations, however, did find that limb flicking could be elicited by nonhallucinogenic agents, such as methysergide (126), lisuride (125), pilocarpine (127), apomorphine (191), or quipazine (173,191).

Receptor Systems that Mediate Production of Limb Flicks

Model I: inhibitory 5-HT receptors

Initial studies on the neuropharmacologic basis for the production of limb flicks focused on the autoreceptor model (102) and were correlative in nature, comparing the activity of single cells in the midbrain raphe nuclei (serotonergic neurons) in awake cats with the occurrence of limb flicks. These studies supported the hypothesis that decreases in serotonergic transmission (via activation of these autoreceptors) were necessary for the production of limb flicks. For example, studies with the hallucinogen 5-MeODMT indicated a strong correlation among the onset, offset, and peak for the occurrence of limb flicks and the onset, offset, and peak for the depression of raphe neuron firing (179).

Subsequent studies with LSD provided slightly different results, however. Although LSD administration produced both limb flicks and a depression of raphe firing in the same cats, the temporal characteristics of these two measures varied considerably. Specifically, a high dose (50 μg/kg) of LSD produced a significant increase in limb flicks for 6 to 8 hr, while raphe firing was depressed approximately only 4 hr. Also, although tolerance developed to the limb flick-producing effects of LSD over 2 days of consecutive testing, no tolerance to the effects of LSD on raphe activity was observed over this same period (175,178).

These disparate findings regarding tolerance to limb flick-producing effects and the lack of tolerance to raphe-depressing effects of hallucinogens suggested that the inhibition of raphe neurons per se is not a sufficient condition for the production of limb flicks. Moreover, recent reports have indicated that limb flicks may be produced by administration of apomorphine (191) and pilocarpine (127), agents that have no effect on the activity of serotonergic neurons in the raphe. Thus it appears that raphe inhibition per se is a condition that is neither sufficient nor necessary for the production of limb flicks in cats. It is possible, however, that the actions of hallucinogens at inhibitory 5-HT receptors may serve to modulate limb flick behavior in the cat.

Model II: excitatory 5-HT receptors

Recently, evidence has been presented suggesting that limb flicks may result from agonist actions of hallucinogens and other agents at facilitatory 5-HT receptors. For example, the 5-HT agonist quipazine produces limb flicks. This effect is antagonized by the classic 5-HT antagonists cinanserin, methysergide, and cyproheptadine (173,191). In addition, Marini and Sheard (126) and Jacobs et al. (104) found that the limb flicks produced by LSD and DOM were effectively antagonized by the 5-HT antagonists methysergide, mianserin, and cyproheptadine. Finally, White et al. (192) have reported that the limb flicks produced by LSD and lisuride can be blocked by pretreatment with another 5-HT antagonist, BC-105 (pizotifen). Although there are reports that the limb flick response can be attenuated by pretreatment with agents that are not 5-HT antagonists (85,192), it has been demonstrated that in some cases, this antagonism is attributable to general behavior depression in cats (192).

In summary, the data suggest that limb flicks produced by hallucinogen administration to cats result from the activation of excitatory postsynaptic 5-HT receptors in the CNS. In addition, the effects of these agents on autoreceptors in the raphe nuclei could modulate the limb flick response; to date, however, no data address this possibility.

Limb Jerks in Primates

Production by Hallucinogens

Over the past few years, the effects of hallucinogens on the behavior of the Stumptail macaque have been investigated by Schlemmer and his colleagues (150,181). Behaviors observed after the administration of hallucinogenic agents include ptosis, hypo- and hyperactivity, increased vigilance ("checking"), and various forms of social withdrawal. Most interesting, however, is the appearance of two emergent behaviors, namely, limb jerks (spasms of an extremity) and body shakes (like a dog emerging from water). Limb jerks have been observed in the macaque following the administration of every hallucinogen tested to date. Moreover, the doses required for the production of limb jerks correlate well with human hallucinogenic doses. Body shakes have been reported following the administration of all but three hallucinogenic agents (DET, psilocin, psilocybin). In addition, bromo-LSD and lisuride, two nonhallucinogenic LSD analogs, have been tested in the macaque and do not produce limb jerks. Thus limb jerks appear to be a sensitive and reliable assay for studying the effects of hallucinogenic agents in nonhuman primates.

Receptor Systems that Mediate the Production of Limb Jerks

Studies on the neuropharmacology of limb jerks in the macaque have indicated that these agents are acting, not surprisingly, as agonists at excitatory 5-HT receptors. First, the 5-HT agonist quipazine has been reported to produce limb jerks in the macaque (R. F. Schlemmer, *personal communication*). Second, a number of classic 5-HT antagonists (methiothepin, cinanserin, methysergide, cyproheptadine, metergoline) have been shown to antagonize the limb jerk-inducing effects of the hallucinogen 5-MeODMT (150,151). Other hallucinogen-5-HT antagonist test combinations examined (LSD-cinanserin, LSD-methiothepin, DMT-cyproheptadine) have provided similar results (150), suggesting that limb jerks are the result of excitatory postsynaptic 5-HT receptor activation.

Summary: Hallucinogen-Elicited Emergent Behaviors

Together, studies on the neuropharmacologic basis for the production by hallucinogens of the 5-HT syndrome in rats and mice, limb flicks in cats, and limb jerks in primates point to a common mechanism, i.e., the activation of postsynaptic 5-HT receptors. The classic 5-HT antagonists are effective in antagonizing these various hallucinogen-induced emergent behaviors, suggesting that these behaviors result from the activation of excitatory 5-HT receptors. Furthermore, although the localization of the excitatory 5-HT receptors mediating the limb flick and limb jerk behaviors has not been investigated, studies on the 5-HT syndrome in rats have indicated that at least some components of this behavior can still be elicited in spinal-transected animals, suggesting that these excitatory 5-HT receptors are located in the brainstem and/or spinal cord. Since the excitatory 5-HT receptors in the spinal cord are found on motoneurons in the ventral horn, it is likely that at least certain components of the 5-HT syndrome produced by hallucinogens result from the activation of excitatory 5-HT receptors on motoneurons in the spinal cord. Although similar analyses into the localization of the excitatory 5-HT receptors involved in the limb flick and limb jerk behaviors have not been conducted, it is not unlikely that these effects could be the result of activation by hallucinogens of excitatory 5-HT receptors on motoneurons.

SUMMARY: THE ROLE OF INHIBITORY AND EXCITATORY 5-HT RECEPTORS IN MEDIATING THE EFFECTS OF HALLUCINOGENS ON UNCONDITIONED BEHAVIORS

In this chapter, we have attempted to answer two questions. First, what are the effects of hallucinogens on unconditioned behaviors? As might be expected, they are complex and varied. Hallucinogens have generally excitatory effects on startle reflexes, spinal reflexes, and locomotor activity. They also produce or elicit unique behavioral syndromes in rats, cats, and monkeys that rarely occur in the nondrugged state. However, hallucinogens can also depress spinal

reflexes, acoustic startle, and locomotor activity. These depressant effects generally occur at high doses and depend on the exact compound being tested (e.g., DMT versus 5-MeODMT).

Second, do excitatory or inhibitory 5-HT receptors mediate these behavioral effects? The presynaptic inhibitory 5-HT receptor has been implicated in some of the weak excitatory effects of indolealkylamine hallucinogens on the acoustic startle response. Interactions with these receptors may also explain some of the paradoxic effects of hallucinogens on spinal reflexes when they are measured in intact (i.e., nonspinalized) animals. The role of these receptors in locomotor activity and emergent behavior produced by hallucinogens is not clear. However, the absence of specific antagonists for this receptor prevents any definitive conclusions regarding the role of this receptor in any of the behavioral effects observed.

Some of the depressant behavioral effects of hallucinogens may involve inhibitory postsynaptic 5-HT receptors. For example, depressant effects of hallucinogens on startle and locomotor activity may result from activation of these receptors, since 5-HT itself has similar effects. Studies on supersensitivity are lacking, however, and, again, the absence of selective antagonists prevents definitive conclusions.

Since most of the effects of hallucinogens on unconditioned behavior are blocked by 5-HT antagonists, their effects can be attributed to actions at these excitatory postsynaptic receptors. These behaviors include most of the actions of hallucinogens on spinal reflexes, the excitatory effects of at least one hallucinogen (5-MeODMT) on acoustic startle, and the production of the 5-HT syndrome, limb flicks, and limb jerks.

IMPLICATIONS FOR THE USE OF THESE BEHAVIORS AS "ANIMAL MODELS" OF HALLUCINOGENIC AGENTS

As indicated above, the majority of the behavioral effects of hallucinogenic agents on unconditioned behaviors can be blocked by 5-HT antagonists. Moreover, many of the effects ascribed to actions on other 5-HT receptors have not been examined for their potential antagonism by the 5-HT antagonists and could, possibly, be blocked by these agents. In addition to these unconditioned behaviors, the effects of hallucinogens on the drug discrimination paradigm and in the disruption of operant responding are blocked by the 5-HT antagonists (Appel and Rosecrans, *this volume*). Thus the 5-HT antagonists are extremely effective in attenuating nearly all hallucinogen-induced behavioral changes in animals.

A critical question to ask at this juncture is whether any of these behavioral changes in animals is relevant to the hallucinogenic effects of this class of drugs in humans. In other words, which if any of these animal behaviors might closely model human hallucinations? To answer this question, one must examine the

clinical data regarding the efficacy of drugs, such as 5-HT antagonists, in reversing the effects of hallucinogens in humans.

In fact, there is now evidence that 5-HT antagonists may not be effective in blocking the psychotomimetic effects of hallucinogens in man. In perhaps the only study of its kind, investigators at the University of Chicago have examined the effects of the 5-HT antagonist cyproheptadine on two measures of the effects of DMT in humans: (a) the spinally mediated H-reflex, and (b) psychotomimetic effects, as measured by several rating scales. DMT treatment enhanced the H-reflex, and this effect was blocked by cyproheptadine in all five subjects examined (J. Metz, P. Tueting, N. Boutros, B. K. Rhoades, and H. Y. Meltzer, *personal communication*). DMT also produced hallucinations, but these effects were not antagonized by cyproheptadine pretreatment (Boutros, Tueting, Rhoades, Metz, and Meltzer, *personal communication*). In fact, cyproheptadine actually enhanced the hallucinogenic effects of DMT in four of the five subjects. Whether these findings will generalize to other hallucinogens and to other 5-HT antagonists remains to be determined.

The findings suggest a clear distinction between the nonhallucinogenic effects of DMT versus its hallucinogenic effects based on the ability (or inability) of cyproheptadine to antagonize these separate actions. The implication of these findings to the evaluation of the various animal models is enormous. In particular, these findings suggest that the effects of hallucinogens on animal models in which the classic 5-HT antagonists are effective may relate to the motor-facilitating effects of hallucinogens (e.g., as measured with the H-reflex) but not to their psychotomimetic effects. On the other hand, effects that are uniquely produced by hallucinogens that cannot be blocked by 5-HT antagonists may relate to psychotomimetic effects. Since effects of hallucinogens in essentially all animal models currently used to analyze these drugs are reversed by the 5-HT antagonists, none of these models may be relevant to the psychotomimetic effects of hallucinogens in humans. This implies that activation of excitatory 5-HT receptors may not be sufficient to account for psychotomimetic effects of hallucinogens in humans. Moreover, as discussed elsewhere in this volume, activation of either pre- or postsynaptic inhibitory 5-HT receptors does not seem sufficient to account for these effects in humans. Therefore, interactions with 5-HT receptors alone may not account for the psychotomimetic actions of hallucinogens in humans. Future research on hallucinogens that focuses on possible effects of these drugs on other transmitter systems, perhaps in terms of how they might interact with the 5-HT effects, should be especially profitable.

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Behavioral Pharmacology of Hallucinogens in Animals: Conditioning Studies

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This chapter considers the effects of indolealkylamine (LSD-like) and phenylalkylamine (mescaline-like) hallucinogens on learned behavior. We concentrate on those approaches that have shed the most light on underlying neuronal mechanisms or that show promise of becoming useful (*in vivo*) animal models of hallucinogenic drug action. Thus we are selective rather than exhaustive, a luxury made possible in part because several more empirically oriented reviews have been published recently (14,16,34,35).

RESPONDENT (PAVLOVIAN) BEHAVIOR

Historically, respondent (pavlovian) conditioning, which involves the contiguous association (pairing) of conditional or conditioned (CS) and unconditional or unconditioned (US) stimuli, has been considered to be the most simple or, at least, the most mechanical (reflexive or involuntary) kind of learning. Unfortunately, the effects of hallucinogens on this procedure have not been studied extensively, at least by western European and American psychopharmacologists, and are poorly understood. For example, relatively high doses of lysergic acid diethylamide (LSD) (0.05–0.45 mg/kg) appear to decrease the key pecking behavior of pigeons maintained under an appetitive conditioning (automaintenance) procedure, in which the brief illumination of a response key, CS, is paired with food delivery, US. This effect is not specific to LSD (or to hallucinogens), however, since it also occurs following other psychoactive but nonhallucinogenic agents, such as quipazine, pentobarbital, and *d*-amphetamine (14,56). Under defense conditioning procedures (in which a CS, such as a tone, is paired with a noxious or aversive US, such as electric shock), results have not been consistent. Some investigators find that LSD enhances responding in an Estes-Skinner (31) conditioned fear paradigm (42), but others report few reliable effects (14).

We mention these studies primarily as a cautionary preface to suggesting that one preparation, the classically conditioned nictitating membrane response (NMR) of the rabbit, might prove to be useful in analyzing the behavioral pharmacology of hallucinogens because of its relative simplicity and, more important, apparent sensitivity. That is, LSD and related compounds enhance acquisition of the NMR at doses comparable to those that produce hallucinations reliably in humans (1,63). For example, in a defense conditioning experiment involving a compound CS (light plus tone) presented 800 msec before a 100-msec electric shock US (delivered to the skin over the paraorbital region of the head), LSD (0.3–30 μg/kg i.v. 30 min before conditioning sessions) caused a dose-related increase of the NMR in the period prior to shock onset (ED_{50} = 3.3 nmoles/kg or 1.1 μg/kg), an effect that could not be attributed to sensitization, pseudoconditioning, or drug-induced changes in baseline levels of responding (33). Subsequent investigation showed that: (a) enhanced acquisition also occurred in an appetitive conditioning situation, in which the conditioned response (CR) was jaw movement and the US was water (38); (b) the effects of LSD on acquisition (of both CRs) is attributable, at least in part, to "the drug's enhancement of the sensory processing of the CS" (37,38); and (c) the effect has some pharmacologic generality as well as specificity in that it occurs, to a lesser extent, following other, less potent hallucinogens, such as 2,5-dimethoxy-4-methylamphetamine (DOM) but not nonhallucinogenic congeners of LSD, such as *d*-2-bromo-LSD (BOL) (41).

Because of the low doses involved, these data are intriguing. However, classical conditioning procedures are, at present, of limited pharmacologic value; to our knowledge, they have not yet been used to analyze underlying (neuronal) mechanisms.

OPERANT (INSTRUMENTAL) BEHAVIOR

In many respects, the effects of hallucinogens on behavior maintained by its consequences (i.e., operant or instrumental behavior) do not differ from those of other psychoactive compounds and, therefore, need not be described in detail. In general, LSD and functionally related compounds, such as psilocybin and mescaline, alter ongoing operant responses in ways that critically depend on pharmacologic parameters, such as dose and time after administration (6,14), as well as on behavioral parameters, such as response rate and schedule of reinforcement (6,30,65). For example, sufficiently high doses of LSD (>0.04 mg/kg i.p. in the rat) completely disrupt bar pressing maintained at high rates under various fixed ratio (FR 5–FR 40) schedules of milk or water reinforcement by inducing periods of nonresponding (32). These dose-dependent periods begin 4 to 8 min after intraperitoneal injection and are followed by behavioral recovery. Moreover, when 130 μg/kg is administered daily, complete (behavioral) tolerance occurs in 7 to 10 days; acute (pharmacologic) tolerance also occurs when 130 μg/kg LSD is given at 3 hourly intervals with the animals being tested only after the last injection (32). Cross tolerance has been observed to other indole and phenylalkylamine hallucinogens (11). Similar effects were also reported for other hallucinogens (10) with an order of potency that paralleled that seen in humans (2); that is, the (hallucinogenic) *d*-isomer of LSD was about 10 times as potent as psilocybin and 100 times as potent as mescaline (10).

Recently, the parameters of FR disruption have been quantified, and the phenomenon has been renamed hallucinogen-induced pausing (24–28). Indeed, disruption of FR has been found to be a sensitive test or behavioral assay in that it can detect the effects of relatively low doses, at least of LSD (20–40 μg/kg). It also appears to be reasonably robust and reliable but not particularly specific; that is, many psychoactive compounds interfere with bar pressing, although they do so in a manner that is said to differ (quantitatively) from hallucinogen-induced pausing (26). More important, disruption has been sensitive to manipulations that alter the functioning of 5-hydroxytryptamine (5-HT) neurons in various ways and thus extends *in vitro* observations to at least one *in vivo* (behavioral) situation involving intact organisms (see later).

At doses comparable to those that disrupt responding on FR schedules, LSD also causes less drastic suppression of the somewhat lower but nonetheless relatively high rates of responding maintained under certain fixed interval (FI) or variable interval (VI) schedules and generally increases behaviors that normally occur at low rates (5,7,44,48).

Responding under the control of negative reinforcers (escape and avoidance conditioning) does not appear to be affected uniquely by indolealkylamine and phenylalkylamine hallucinogens. Generally, escape behavior is altered only by large (behaviorally toxic) doses of LSD (>0.5 mg/kg). The direction of such alterations (facilitation or suppression) depends on the specific apparatus and procedure used for analysis (14). At one time, it was argued that a certain (Bovet-Gatti) schedule of shock avoidance (behavior maintained by postponement of an aversive stimulus) might be a useful model of hallucinogenic drug actions, because this schedule was affected in a unique, biphasic way by mescaline and some of its congeners (69–71). These data have not been confirmed by all investigators (21), however, and the results have not been reliable at behaviorally relevant dosages (14).

Because of their sensitivity, the best aversive conditioning procedures for studying hallucinogens are those that involve conflict, i.e., situations in which behavior is simultaneously reinforced and punished. For example, a dose as low as 1 μg/mg LSD appears to decrease significantly the suppressive effect of electric shock on the licking behavior of rats trained to drink from a tube to obtain water (66). Similar, although less potent, attenuation is also obtained with mescaline (10–30 mg/kg) and with the tryptophan hydroxylase inhibitor α-propyldopacetamide and the 5-HT receptor antagonist cyproheptadine but not with N,N-dimethyltryptamine (DMT) nor with Δ^9-tetrahydrocannabinol (THC) (66).

While these results, which were attributed to drug-induced decreases in activation of serotonergic neurons, are interesting, they are limited by their lack of specificity. The disinhibition or release of suppressed responding is a characteristic so common to other, nonhallucinogenic agents, such as chlordiazepoxide and phenobarbital, that conflict situations are commonly used to screen anxiolytics (43). Moreover, more recent data suggest that the antisuppressive effect of hallucinogens is neither robust nor reliable (14). Interestingly, if such an effect does occur, it may be one of the few induced by low doses of these drugs that does not involve 5-HT mechanisms (24,46).

A final operant paradigm in which hallucinogens have been shown to have highly specific effects is drug discrimination (DD). In this situation, the behavior of an experimental subject comes under the stimulus control of a given drug because reinforcement is contingent upon responding appropriately under a drug "state" or stimulus (DS) at a given time. Procedurally, a subject is trained to emit one response, usually for food or water reinforcement (e.g., press the left lever in a two-lever operant chamber) when under the effects of a drug such as LSD; the same subject must make another response (press the right lever) to obtain reinforcement following the administration of a drug vehicle such as saline (Fig. 1). Control of behavior will occur following several training sessions with both LSD (80 μg/kg) and saline. During test sessions (no reinforcement following either response), animals will make 90 to 100% of their responses on the LSD-appropriate lever (0–10% of responses on the saline-appropriate lever) when administered LSD, while they will emit 90 to 100% of their responses on the saline-appropriate lever (0–10% on the LSD-appropriate lever) following saline. In a sense, the DS model does not evaluate the behavioral effects of hallucinogenic (or other) agents as do other operant procedures (58); rather, it tests the ability of an animal to detect a specific drug effect or to differentiate an effect from the nondrug condition. Thus response choice provides a means of quantifying the level at which a drug, such as LSD, exerts discriminative stimulus control (i.e., the intensity of the drug cue).

The ability of an animal to utilize a psychoactive agent as a DS appears to be contingent upon an interaction of the drug with some centrally located neural substrate, which is highly specific within a given pharmacologic class. For example, LSD appears to exert its DS effects through an agonistic action at some 5-HT receptor. This can be demonstrated in a variety of ways, not the least of which is the ability of purported 5-HT antagonists to attenuate the LSD cue (Table 1). The specificity of this antagonism is evidenced further by the fact that the DS effects of LSD have yet to be antagonized by any class of receptor antagonist other than 5-HT antagonists (50). In addition, drugs, such as mescaline, 5-methoxy-N,N-dimethyltryptamine (5-OMeDMT), and DOM, that produce subjective effects in humans similar to those of LSD, have LSD-like DS effects in rats that can also be blocked by suspected 5-HT antagonists (Table 1). The specificity of this relationship is documented further by the fact that rats trained to discriminate LSD from saline do not generalize to other psychotomimetic

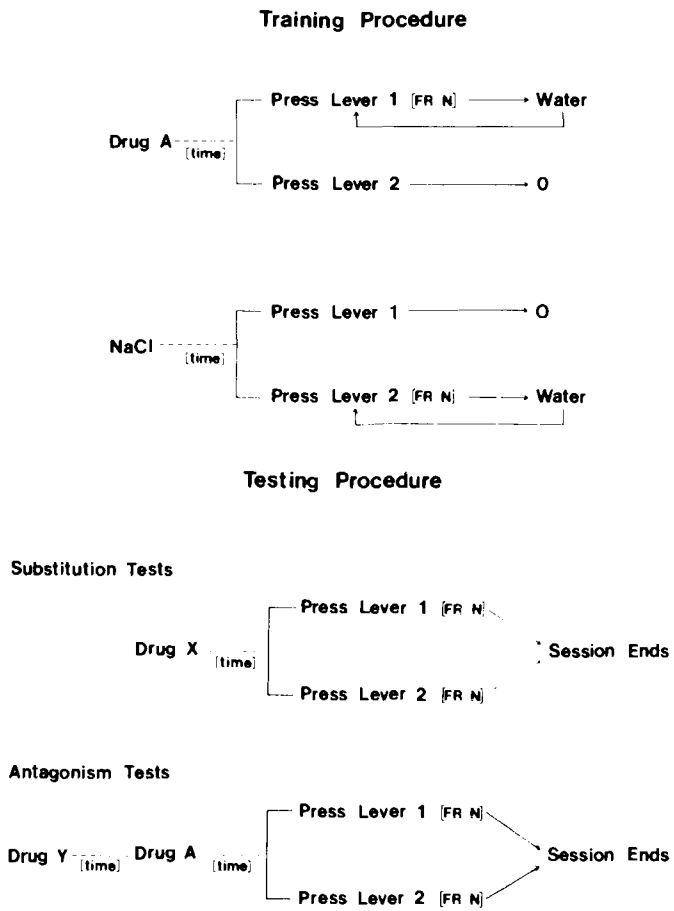

FIG. 1. Training substitution and antagonism test procedures. During training, animals are reinforced with water for pressing lever 1, *N* times (e.g., 32) 15 min after intraperitoneal injection of drug A (LSD) or for pressing lever 2 following saline (NaCl). This continues for 20 to 30 min. During substitution tests, a lower dose of the training drug or "novel" drug (drug X) is given (instead of drug A), and the session ends without reinforcement after *N* responses occur on one or the other of the two levers. During antagonism test, specific neurotransmitter antagonists (drug Y) are given in conjunction with drug A, and the session ends without reinforcement after *N* responses occur on one or the other lever. (From ref. 16, with the permission of ANKO International Inc. for *Neuroscience and Biobehavioral Reviews*.)

or dysphorigenic agents, such as phencyclidine, ditran, and cyclazocine (49). In fact, LSD-like hallucinogens do not share stimulus properties with any drugs (stimulants, sedatives, opiates) other than those that act through similar neuronal mechanisms, e.g., 5-HT agonists (16,35). It should be added that this degree of pharmacologic specificity occurs with all drugs that have DS properties. The sensitivity and specificity (16) of the hallucinogen DS, as well as the fact that there is a high correlation ($r = 0.97$) between hallucinogenic potency in humans

TABLE 1. *Putative 5-HT antagonists reported to attenuate a variety of hallucinogen-induced drug stimuli*[a,b,c]

Antagonist dose (mg/kg)	LSD (0.05–0.130 μg/kg) (%)	Mescaline (5–15 mg/kg) (%)	5-OMeDMT (1.5 mg/kg) (%)	DOM (0.3–1.0 mg/kg) (%)	DOET (0.3 mg/kg) (%)	Psilocybin (1.0 mg/kg) (%)
Pirenpirone	>98	>98	>98	>98		
0.16	(8,22,35)	(35)	(35)	(35)		
Ketanserin	>98	>98	>98	>98		
0.48	(8,35)	(35)	(35)	(35)		
BC-105	70–90	95–98	84	99	81	
0.63–3.0	(22,59,78,81)	(53,78)	(80)	(79,81)	(78)	
Cyproheptadine	40–82	55–86	84			
2.0–2.5	(22,50,54)	(20,53)	(60)			
Cinanserin	32–86	66–95	39	78–95	95	97
2.5–10	(22,67)	(20,78)	(62)	(67,78)	(67)	(67)
Methylsergide	20–70	42	15	90		
2.5–10	(22,50,54)	(53)	(62)	(67)		
Methiothepin	7–70	66	16–32			
1.0	(50,54,60)	(53)	(60,62)			
Metergoline	40		32			
0.16–0.63	(22)		(62)			
BOL	30–40					
0.25–10	(22,50)					

[a] Data are presented as percent inhibition of drug-appropriate responding by a specific antagonist and were calculated from numerical data or approximated from figures provided in the references presented (in parenthesis). Antagonists are presented in order of efficiency and relative potency in attenuating each agonist; doses represent the highest dose producing the greatest level of attenuation. Antagonists were usually administered from 30 to 45 min prior to testing (see Fig. 1).

[b] The range of doses of agonists used as DS are provided below each hallucinogen.

[c] Two other antagonists, minanserin (0.63–2.5 mg/kg) and metitepine (0.04–0.16 mg/kg) have been studied by Colpaert et al. (22) and produced an LSD antagonism of ~50 or ~30%, respectively.

and DS potency in rats (35), have made this assay popular in behavioral neuropharmacology (23).

NEURONAL SUBSTRATES OF HALLUCINOGENIC DRUG EFFECTS ON BEHAVIOR

We suggest that two operant procedures or animal models have been particularly useful in analyzing hallucinogenic drug action(s) *in vivo*. Both (a) drug-induced disruption of bar pressing maintained under FR schedules of food or water reinforcement (hallucinogen-induced disruption or pausing), and (b) discriminative DS properties indicate that the effects of indolealkylamine and phenylalkylamine hallucinogens are mediated by serotonergic neuronal systems, although many questions concerning the specific nature and site(s) of such mediation remain unanswered. To explore these questions further, we summarize (a) experiments using both models to evaluate the role of serotonergic systems in general and of the dorsal raphe nucleus (DRN) specifically in the effects of hallucinogens, and (b) efforts to correlate behavioral and receptor binding events.

Effects of Altering 5-HT on the Behavioral Effects of Hallucinogens

One approach used to determine the significance of central serotonergic systems in FR and DS involves pretreatment with agents that are known to alter the functional activity of serotonergic neurons. Thus in the first of a series of FR disruption experiments, reserpine (total dosage, 1.4 mg/kg given over 5 days), a neuroleptic and hypotensive agent that depletes indoleamines and catecholamines nonspecifically by destroying vesicular binding sites, increased sensitivity to otherwise nondisruptive (subthreshold) doses of LSD (9). This is interesting because pretreatment with the same compound also enhanced LSD-induced changes in 5-HT metabolism (61).

A second, more extensive experiment involved oral administration of three daily doses (100 mg/kg) of parachlorophenylalanine (PCPA). This tryptophan hydroxylase inhibitor (47), like reserpine, enhanced the behavioral effects of LSD (13); moreover, hypersensitivity occurred when 5-HT, but not other monoamine, concentrations were below normal in both forebrain and hindbrain (13). That is, effects were observed at 5 and 12 days (when 5-HT was depleted to 10–20% and 60–70% of normal) but not at 21 days (when 5-HT had returned to normal). Control experiments (13) indicated that: (a) the interaction of PCPA, 5-HT, and LSD was probably not caused by generalized hyperactivity or hyperirritability sometimes seen after PCPA (73); (b) PCPA does not affect threshold doses of other psychoactive but nonserotonergic compounds, such as *d*-amphetamine (0.3 mg/kg); and (c) pretreatment with α-methylparatyrosine, a tyrosine hydroxylase inhibitor which depletes catecholamines rather than indoleamines, does not alter sensitivity to LSD.

These results have been confirmed and extended. We have observed, for

example, that PCPA enhances the disruptive effects of the 5-HT precursor 5-hydroxytryptophan (18). In addition, electrolytic lesions of the DRN, the principal site of cell bodies of 5-HT neurons, have been shown to deplete whole brain serotonin (by about 40%) and facilitate the behaviorally disruptive effects of 40 μg/kg LSD (15). More recent studies have involved chemical (functional) lesions with compounds that act selectively on specific, chemically defined neuronal systems. Thus 200 μl of the serotonergic neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) (17), given intracerebroventricularly, like PCPA, enhances the behaviorally disruptive (45) and discriminable (77) effects of LSD as well as the disruptive effects of several related compounds, including psilocybin, mescaline, and quipazine (12).

The effects of hallucinogens on appetitively reinforced bar pressing behavior maintained under FR schedules and their probable mediation by serotonergic neuronal mechanisms have been analyzed further in at least three additional laboratories. Sparber and Tilson (72,74,75), like Appel and Freedman (10), used duration of behavioral disruption to estimate relative potencies, and a group in Houston (19,20) reported that 5-HT systems may play an important role in controlling the behaviorally disruptive effects of mescaline and other phenylalkylamines, a result that has been extended to DOM, DMT, and other compounds by Commissaris, Rech, and their colleagues at Michigan State University (24–28). The Michigan State group also reported that (a) depletion of brain catecholamines by pretreatment with intraventricular 6-hydroxydopamine (6-OHDA) reduced baseline FR 40 rates and attenuated the disruptive effects of *d*-amphetamine but failed to modify the dose-response patterns of indoleamine and phenethylamine hallucinogens; and (b) injection of 5,7-DHT into the medial forebrain bundle at the hypothalamic level slightly potentiated LSD, attenuated DOM, and did not affect the pausing produced by mescaline (58).

A different strategy was used by Minnema and Rosecrans (55), who studied the ability of 70- to 80-day-old rats, which had been treated neonatally (57) with either 5,7-DHT or 6-OHDA [plus desmethylimipramine (DMI)], to discriminate either LSD or *d*-amphetamine from saline. Even though concentrations of 5-HT were reduced by 51 to 95% of control values in different brain areas, and dopamine concentrations were less than 50% of controls (norepinephrine levels were unaffected by both treatments), animals learned to discriminate both drugs as well as rats given either drug vehicles or neurotoxins alone. In addition, neither LSD nor *d*-amphetamine dose-response curves (generalization gradients) were altered by 5-HT depletion. In adult animals, however, the administration of either PCPA or 5,7-DHT (intracerebroventricularly) shifts LSD generalization gradients to the left (77).

In another series of experiments, rats trained to discriminate LSD (96 μg/kg i.p.) from saline were implanted stereotactically with cannulae aimed at the DRN (59). The ability of the peripherally elicited LSD cue to generalize to LSD injected directly into the DRN was then evaluated over a wide range of doses (2–60 μg/kg). The results are shown in Fig. 2. Interestingly, the dose of LSD injected via the cannulae required to produce DS control was extremely high,

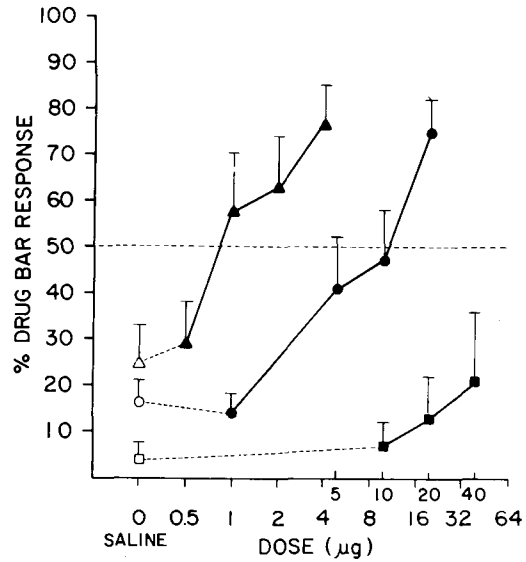

FIG. 2. Comparison of the discriminative stimulus properties of LSD, morphine, and methadone when injected into the DRN of the rat. Rats were trained to discriminate LSD (120 μg/kg s.c.), cannulae implanted, and generalization from peripheral to central administration determined over a variety of doses of each drug. (Redrawn from the research of Rosecrans and Glennon, ref. 59.) △, I.C. saline, ▲, I.C. morphine in morphine trained rats, ○, I.C. saline, ●, I.C. LSD in LSD trained rats, □, I.C. saline, ■, I.C. methadone in methadone trained rats.

i.e., 63% of the (peripheral) training dose (60 μg/kg). By contrast, rats trained to discriminate 3.0 mg/kg morphine (administered subcutaneously) generalized to only 0.009 mg/kg morphine injected directly into the raphe (0.3% of the peripherally administered dose). These data suggest that the DRN is insensitive to LSD (at least in the DD paradigm), a surprising finding when one considers the electrophysiologic work of Haigler and Aghajanian (39,40), but not surprising when one considers other behavioral data (15,30).

In an attempt to reconcile these results, an additional investigation was carried out. This study utilized a behavioral disruption procedure, in which various doses of LSD were injected into the DRN while rats were bar pressing under a FR 10 schedule of food reinforcement (Fig. 3). As in the DS study, the DRN appeared relatively insensitive to LSD; the dose required to disrupt behavior via the DRN route was 20 μg/kg, whereas the systemic dose was 60 μg/kg. An analysis of brain distribution data (61) would predict that LSD should have been active at a dose range of about 100 to 200 ng/kg when applied directly into the DRN; neither study approached this range.

Behavior-5-HT Binding Correlations

All the data suggest that neither the DRN nor the presence of 5-HT presynaptically is essential for LSD to disrupt behavior or to serve as a discriminative

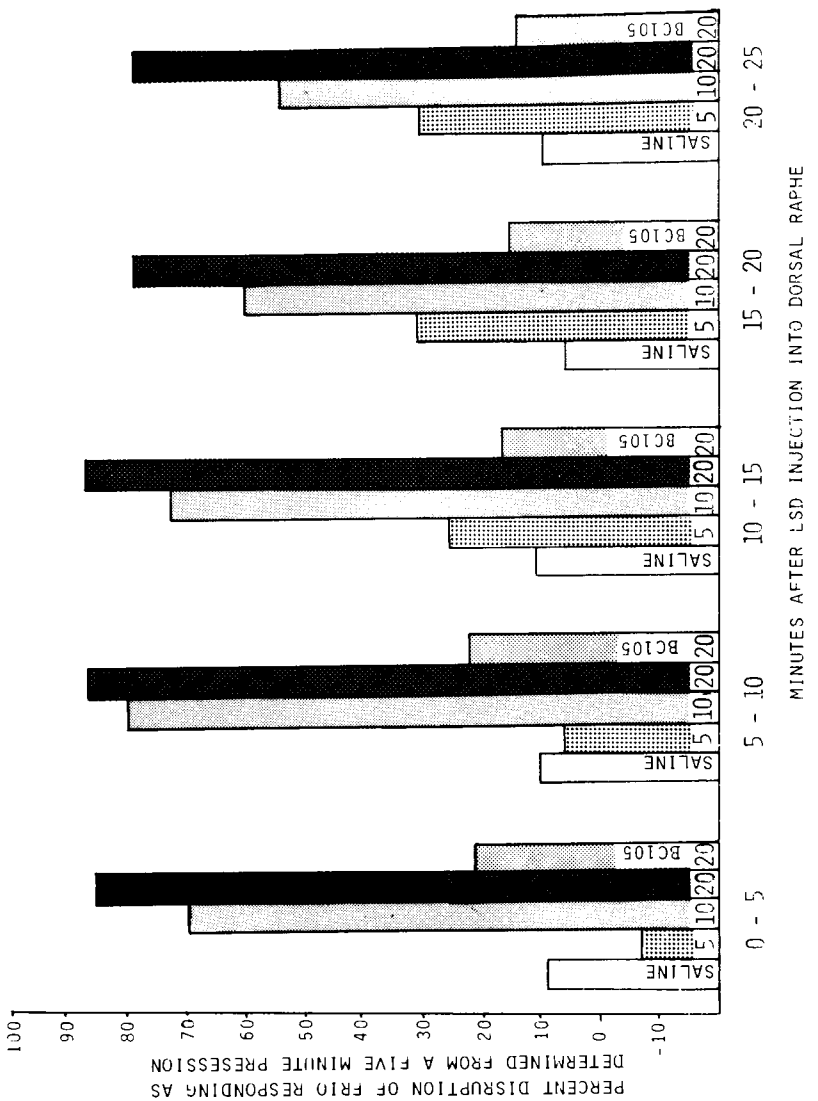

FIG. 3. Disruption of operant behavior (FR 10) by the application of various doses of LSD to the DRN of rats. These data provide a time course of the disruptive effects of LSD over a dosage range of 5, 10, and 20 μg/kg. BC-105 was injected to a 20 μg/kg dose of LSD. (Taken from ref. 53.)

stimulus. There does seem to be a consensus that the behavioral effects of both phenylalkylamine and indolealkylamine hallucinogens are mediated by a common, postsynaptic 5-HT receptor or group of receptors. This hypothesis has evolved from several *in vivo* models of hallucinogenic activity (16,27,34,68). In addition to these behavioral results, 5,7-DHT and PCPA appear to increase the ability of ^{3}H-LSD to bind to rat cortex (16), thus providing evidence that there is a positive correlation between the effects of LSD on behavior and actions at postsynaptic 5-HT receptors (Fig. 4). Interestingly, parachloroamphetamine (PCA), a 5-HT-releasing drug and putative neurotoxin at B-9 cells (64), has little effect on either the LSD DS or on ^{3}H-LSD binding. Moreover, there seems to be a close association between drugs that cause hallucinations in humans and ability to act at 5-HT receptors in various animal tissues, including brain (76) and rat fundus (36). In fundus, for example (36), hallucinogenic potency, among a variety of different compounds from different chemical classes, correlates highly with 5-HT binding (pA_2) (34,35). Finally, the 5-HT antagonist cyproheptadine has been reported to attenuate the psychotomimetic effects of DMT in humans (52).

While many data demonstrate the ability of various 5-HT antagonists to attenuate the DS properties of hallucinogens (Table 1), some points should be

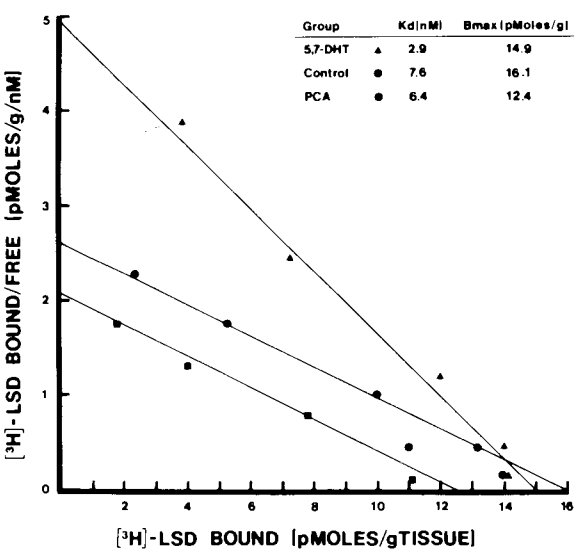

FIG. 4. Scatchard analysis of specific ^{3}H-LSD binding to crude homogenates of cortex from rats treated with either 200 μg intraventricular 5,7-DHT, 20 mg/kg i.p. PCA, or saline 45 days prior to assay. Specific binding of ^{3}H-LSD (final concentrations from 1–100 nm) was defined as the difference between ^{3}H-LSD binding in the absence and presence of 10 μM 5-HT. Each point represents the mean of three rats. The dissociation constants (K_D) of 5,7-DHT- and saline-treated rats were significantly different ($p < 0.05$; *t*-test). (From ref. 16, with the permission of ANKO International Inc. for *Neuroscience and Biobehavioral Reviews*.)

made with respect to better understanding potential drug-receptor interactions. The first, which has been underscored by Colpaert et al. (22), is that several of the purported 5-HT antagonists may (also) be partial 5-HT receptor agonists. Thus rats trained to discriminate LSD from saline sometimes make LSD-appropriate responses when given only antagonists, such as mianserin, metergoline, methysergide, and cyproheptadine (22). In many cases, these compounds also have neurophysiologic effects that are similar to those of LSD; for example, methysergide, LSD and cinanserin antagonize neurons excited by 5-HT in the cerebral cortex and reticular formation but do not affect cells inhibited by the iontophoretic application of 5-HT in the ventral lateral geniculate or amygdala (3,4). Some similarity between the behavioral effects of LSD and those of 5-HT antagonists might be predicted; what also becomes obvious is that LSD appears to have antagonist effects at central 5-HT receptors.

A second point concerns the differential antagonism of several hallucinogens. For example, mescaline and DOM are antagonized readily (20,67), whereas LSD and 5-OMeDMT are antagonized only with difficulty by cinanserin (50,62), except when tests are conducted in rats already trained to discriminate mescaline (78). Similar data are presented in Table 2, which also shows that pizotifen (BC-105) antagonizes the three hallucinogen cues equally well. Comparable results were obtained when metergoline was studied as an antagonist of drug-induced disruption of operant behavior (29,58); that is, pretreatment with this agent shifts the LSD and DMT dose-response curves for pausing to the right (by a factor of 2–3) but shifts the DOM and mescaline dose-response curves to a much greater extent. Thus even though both phenylalkylamine and indolealkylamine hallucinogens appear to be acting at a common postsynaptic 5-HT receptor, the neuronal path leading to this receptor might be affected differentially by different hallucinogens. This hypothesis might also be helpful in understanding why mescaline, which produces a similar spectrum of behavioral

TABLE 2. *Comparison of the antagonism of various hallucinogenic-induced discriminative stimuli by two 5-HT antagonists*

Agonist	Percent drug-correct responding ± SEM		
	Saline (1 mg/kg)	Pizotifen (1 mg/kg)	Cinanserin (5.0 mg/kg)
LSD[a] 80 μg/kg	94 ± 6	17 ± 4	65 ± 14
Mescaline[a] 10 mg/kg	88 ± 7	1.5 ± 1	13 ± 4
5-OMeDMT[b] 1.5 mg/kg	93 ± 4	13 ± 4	55 ± 10

[a] Rats were trained to discriminate LSD (N = 12) from saline using a FR 10 schedule of reinforcement. Antagonists were administered 45 min prior to agonist testing. The generalization of LSD to mescaline and their antagonism were studied in the same 12 rats. (Reproduced from ref. 53.)

[b] Rats were trained to discriminate 5-OMeDMT from saline using a VI 15 sec schedule of reinforcement. Antagonists given as above. (Data reproduced from ref. 80.)

effects in both humans and animals, is unable to inhibit the rate of firing of 5-HT-containing neurons in the DRN as does LSD (39).

A word of caution is in order concerning the relative binding affinities of agonists and antagonists for the (common) 5-HT receptor. For example, because of its low binding affinity, cinanserin might be less able to compete with LSD than with mescaline for the 5-HT receptor (Table 2). Because of its much higher affinity, BC-105 might be better able to compete with LSD and thus antagonize both LSD and mescaline equally well. Evidence of these differential binding relationships, especially at the S_2 site, is presented in Table 3. This table also shows that LSD has a much greater affinity for the S_2 site than mescaline, a fact that might also explain why cinanserin so easily antagonizes the DS properties of mescaline.

It should be realized that we are making comparisons between *in vivo* and *in vitro* data, which can be misleading. It is important to consider the physicochemical properties of receptor-substrate complexes before drawing conclusions from neurophysiologic or behavioral experiments. Notwithstanding these comments, it does appear that various hallucinogens act at a common 5-HT site; the extent to which neuronal pathways, receptor kinetics, or other factors, such as the pharmacokinetics of individual agonists or antagonists, determine differences in observed effects has not yet been established.

The question as to where the common 5-HT and/or hallucinogen receptor is located is an intriguing one that cannot be answered convincingly at present. An important lead to its eventual characterization comes from the work of Leysen and Tollenaere (51) and Colpaert et al. (22), who describe two selective 5-HT/LSD antagonists, pirenperone and ketanserin. Investigators in our laboratories have confirmed the specificity of these compounds and observed an

TABLE 3. *Comparison of the affinities of various compounds at 5-HT S_1 and S_2 binding sites*[a]

Compounds	S_1 binding hippocampus (^{3}H-5-HT) (K_i = nM)	S_2 binding frontal cortex (^{3}H-ketanserin) (K_i = nM)
Pirenperone	⩾1.000	0.28
Ketanserin	⩾1.000	0.39
Pizotifen	1,500	0.28
Cyproheptadine	700	0.44
Cinanserin	3,500	2.00
Metergoline	20	0.28
Methylsergine	99	0.94
LSD	20	2.50
5-HT	7.8	296
Mescaline	70,000	5,900

[a] The ligand hippocampal binding was ^{3}H-5-HT and in the frontal cortex was ^{3}H-ketanserin. Competitors were studied in the presence of each radioactive ligand and individual K_i values determined. (Data reproduced from ref. 51.)

antagonism of both LSD and DOM that is several times more potent than that of BC-105 (Table 1).

An examination of their binding characteristics indicates that these antagonists bind to sites at which 5-HT has relatively low affinity (Table 3). Using ^{3}H-ketanserin, it was found that this ligand has a high affinity for binding sites in the rat frontal cortex (S_2 sites), while ^{3}H-5-HT has a greater affinity for S_1 sites in the hippocampus (51). ^{3}H-Ketanserin did not bind to hippocampus, while ^{3}H-5-HT binding at this site was 39 times greater than that observed in the frontal cortex. Interestingly, LSD and mescaline also have a greater affinity for S_2 sites, while most of the 5-HT antagonists studied, in contrast to pirenperone and ketanserin, bind to S_1 as well as S_2 sites but generally have a greater affinity for the latter (51). As we have suggested previously, it is often difficult to specify the functional role of *in vitro* data and their relationship to the hallucinogen DS (or to other behavioral effects), but they do suggest a beginning. Clearly, delineating the characteristics of the S_2 site is essential to understanding the mechanism of action of hallucinogens *in vivo* as well as *in vitro*.

SUMMARY AND CONCLUSIONS

In this chapter, we have reviewed the effects of indolealkylamine and phenylalkylamine hallucinogens on respondent (classical or Pavlovian) and operant (instrumental) behavior. Both the classically conditioned NMR and bar pressing or licking that is simultaneously reinforced with food or water and suppressed by punishment appear to be particularly sensitive to low doses of LSD- or mescaline-like agents. To date, however, neither of these behaviors has provided substantial amounts of information regarding specific, underlying neuronal mechanisms.

The abilities of hallucinogens to disrupt bar pressing maintained under FR schedules of reinforcement (hallucinogen-induced pausing) and to function as discriminative stimuli in DD situations have proven to be two of the most valuable *in vivo* assays of hallucinogenic drug actions. Data from many laboratories in which one or the other of these animal models has been used are in agreement with ever-increasing amounts of biochemical (receptor binding), electrophysiologic (lesion, single-unit recording), and pharmacologic (pretreatment and antagonism) data, which indicate that the behavioral effects of indolealkylamines and phenylalkylamines are mediated primarily if not exclusively by serotonergic systems in general and by those containing S_2 receptors in particular. Some of the more interesting questions yet to be answered by these experiments include: (a) the extent to which a common receptor and neuronal pathway is involved in the actions of different classes of hallucinogenic drugs (e.g., LSD- and mescaline-like agents), (b) the locus and nature of this receptor or receptor complex, and (c) the extent to which 5-HT-mediated actions can be modified by other neuronal systems.

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Medicinal Chemistry and Structure-Activity Relationships of Hallucinogens

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Elucidation of the mechanism of action for virtually all biologically active substances has been a collaborative effort between scientists in a variety of disciplines. In the area of drug research, medicinal chemists have played important roles by providing series of homologs and congeners of prototype compounds. The development of potency series, where the *in vivo* action can be correlated with *in vitro* or biochemical effects, has often played a pivotal role in formulating hypotheses about mechanism of drug action at the molecular level.

Hallucinogens present a unique challenge to medicinal chemists who attempt the development of useful potency series, primarily because of limitations on the ability to gather clinical or meaningful *in vivo* data. Second, even when clinical results are available, problems are presented because the mental state produced by hallucinogens is extremely difficult to quantitate. Nevertheless, for several years, we have been involved in attempts to elucidate structure-activity relationships and mechanism of action for hallucinogens. These efforts have been directed toward the synthesis and evaluation of structural congeners and novel analogs of known hallucinogenic drugs. The development of correlations between *in vitro* and *in vivo* data, based on such series, can play an important role in identifying neuronal and receptor systems involved in the process of hallucinogenesis.

Compounds in these series may also prove to be useful pharmacologic tools in the study of normal sensory processing. For example, there are a number of phenethylamine and tryptamine derivatives that have been categorized as hallucinogens but which do not produce severe sensory disruption and intoxication at moderate doses; rather, they alter consciousness in subtle ways. Some of these compounds have been described as amplifying empathy, facilitating intellectual function and the flow of ideas, and promoting access to subconscious material and long-term memory. Indeed, one compound has even been reported which

seems to selectively lower the perceived pitch of musical tones (202)! Considering the broad range of pharmacologic effects that the hallucinogens are capable of producing, it is possible that careful and systematic structural modification will lead to compounds that have a specific or selective effect only on one sensory modality. In such cases, following a complete characterization of the human psychopharmacology, studies of the pharmacology in animals and *in vitro,* as well as examination of regional brain distribution and receptor binding characteristics, should lead to a greater understanding of the role of the various neural substrates in the processing of those particular sensory data.

At the outset, the reader should be cautioned regarding the nature of the biologic data used in this chapter. It will be apparent after reading other chapters in this book, that hallucinogenic drugs represent a unique pharmacologic classification. If one wishes to develop useful therapeutic agents, models are generally available that have easily measured quantitative endpoints. This is true for virtually all drug classes. Hallucinogens, however, produce a unique state of human consciousness that cannot be adequately modeled in nonhuman species. Ethical considerations and legal proscription have largely prevented the assay of hallucinogenic drugs in man. Furthermore, complete dose-response studies have not always been conducted when human subjects have been employed. With the exception of the extensive work reported by Dr. A. T. Shulgin and his co-workers, much of which is cited in this chapter, few recent clinical data are available for hallucinogens. This is unfortunate, since all models thus far developed depend for validation on the degree to which activity in the model can be correlated with human potency.

The paucity of clinical data reflects the expense and difficulty of obtaining permission to carry out clinical studies with a class of drugs that presents little or no recognized therapeutic value. Hence the apparent benefit-to-risk ratio is infinitesimally small. It is, perhaps, unfortunate that therapeutic reality must ignore some of the most basic processes that occur in the human brain. For these reasons, a number of animal models have been used, not through choice but by necessity. Our reliance on animal and *in vitro* models has been essential to the development of structure-activity relationships for hallucinogens. In general, conclusions from animal models are accepted as valid. We have attempted to place these approaches in perspective, however, by referring to the particular animal model that was used. When a particular compound has been tested in man, it is stated. If one assumes that the models employed are appropriate and can be expected to reflect human potency, the knowledge of structure-activity relationships can be viewed as considerably expanded in recent years. Nevertheless, unless a particular compound has been tested in humans, one cannot be certain that all the structure-activity relationships described in this chapter will apply in the clinical situation. Based on our collective experience, it is likely that the most common error found in animal models is the identification of "false positives." That is, the models may indicate a compound to be active, whereas actual testing in humans reveals inactivity. It is clear that no present

animal models correlate with the qualitative differences between hallucinogens observed in humans.

Examples of common animal models that have been used over the last decade include the following: (a) disruption of the conditioned avoidance response in rats (27), (b) mouse head twitch (43), (c) rabbit hyperthermia (1), (d) cat rage response (244) and cat limb flick (121), (e) mouse ear scratch (135,251), (f) flexor and stepping reflex in chronic spinal dog (140,143), (g) serotonin syndrome in rats (118), (h) tactile startle response in rats (68), and (i) two-lever drug discrimination in rats (84).

The variety in the above examples is illustrative of the long and frustrating search for valid animal models to correlate with clinical findings. While none of the listed models is ideal, perhaps the last, two-lever drug discrimination, is the best. The drug discrimination procedure, in fact, is a drug "detection" method that employs a subtle behavioral paradigm, as one intuitively feels that such an assay should be, and is, exquisitely sensitive (38). Furthermore, within limits, by choice of appropriate training drug, one can obtain certain qualitative and quantitative data (82). The rapid and increasing acceptance of this model for the study of a variety of behaviorally active drug classes attests to its usefulness and power (39). The reader is referred to the chapter in this book by Appel and Rosecrans for further information regarding this method.

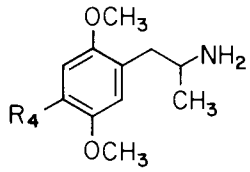
The application of the drug discrimination method to the study of hallucinogenic agents has been recently reviewed (84). Using this paradigm with DOM (see Table 1) as the training drug, Glennon and co-workers (84,88,91) have demonstrated that certain members of each of the classes of agents discussed herein, the phenylalkylamines, N,N-dialkyltryptamines, alpha-methyltryptamines, beta-carbolines, and lysergic acid diethylamide (LSD), are capable of producing similar stimulus properties in rats. Animals apparently recognize these agents at a particular dose as producing a common interoceptive cue. Although the nature of this cue is unknown, there is an excellent correlation between the ED_{50} values of a group of 33 such agents in the drug discrimination study and their overall human hallucinogenic potencies (84). Thus the use of the drug discrimination paradigm should prove to be a useful tool for studying the structure-activity relationships and mechanism of action of hallucinogenic agents. Specific and more detailed comments on some of the above assays can be found in chapters on conditioned and unconditioned behavior elsewhere in this volume.

For the purposes of this chapter, hallucinogens are divided into two separate categories. The first section covers the substituted phenylalkylamines, with the prototype for these structures being mescaline. The second category includes indole-based compounds, including various substituted tryptamines, beta-carbolines, and LSD.

Most of the structure-activity work that has been done lends itself to such a division. Within each category, one can make meaningful comparisons. At present, the possible functional and pharmacologic relationship between these

TABLE 1. *Human hallucinogenic potencies of 2,5-dimethoxy-4-substituted phenylisopropylamines*[a]

4-Substituent	Trivial designation	Potency (MU)[b]
H	2,5-DMA	8
OCH_3	TMA-2	20
OCH_2CH_3	MEM	20
SCH_3	paraDOT (aleph-1)	40
$SCH(CH_3)_2$	Aleph-4	40
F	DOF	—[c]
Cl	DOC	—[c]
Br	DOB	400
I	DOI	400
CH_3	DOM (STP)	80
C_2H_5	DOET	100
C_3H_7	DOPR	80
$isoC_3H_7$	DOIPR	—[d]
C_4H_9	DOBU	40
$sec\text{-}C_4H_9$	DOSB	—[d]
$iso\text{-}C_4H_9$	DOIB	20
$tert\text{-}C_4H_9$	DOTB	—[d]
$n\text{-}C_5H_{11}$	DOAM	10



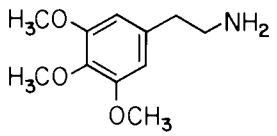
[a] See refs. 194, 196, and 197 for extensive listings.
[b] Human activity expressed in mescaline units (MUs) (205). An approximate effective oral dose in milligrams can be obtained by dividing 400 mg by the MU value.
[c] Not tested in humans.
[d] Not active at acute oral dosages of the hydrochloride salt up to 10 mg.

two general categories remains speculative. However, some general comments are presented, which concern the potential structural and/or functional similarities between the phenethylamines and the tryptamines.

Our goal in this discussion is to present the types of structural variations that have been studied in the various classes of hallucinogens and to explain how these changes affect biologic activity. Where possible, reasonable explanations for these differences are offered. Since we are just beginning to scratch the surface in our search for useful structure-activity relationships, the reader will soon note that most of the correlations are empirical, with no readily apparent biochemical or pharmacologic rationale.

PHENYLALKYLAMINES

The natural prototype for the phenylalkylamines is mescaline (Structure **1**), isolated from the peyote cactus (*Lophophora williamsii*) by Heffter in 1896 (100) and subsequently obtained synthetically by Spath in 1919 (218). Used for many centuries in the form of peyote by Indians in Mexico and the American Southwest (3), it is often referred to as one of the classic hallucinogens, along with psilocybin, psilocin, and LSD. Little structure-activity work was directed toward mescaline or its congeners until 1955, when Peretz et al. (174) reported that α-methyl mescaline (TMA) (8), which represented a "hybrid" of the structure



Structure 1. Mescaline.

of mescaline and amphetamine, possessed approximately twice the potency of mescaline in humans.

A great deal of structural modification work has ensued in the subsequent years. At present, however, the level of effort and number of laboratories involved in this area are small compared to that during the 1960s and 1970s, when hallucinogens were a popular topic in the lay media. It will be easiest to describe this work by focusing on specific types of molecular modifications and how they affect activity.

Orientation of Aromatic Substituents

The most potent compounds thus far studied invariably possess a 2,4,5-trisubstitution pattern. The second most common orientation is 3,4,5-trisubstitution, as seen in mescaline. Selected compounds with other substituent orientations (e.g., 2,4,6-) are active; but the 2,4,5- and 3,4,5-trisubstituted analogs are the most numerous and comprise the bulk of active compounds reported to date. Numerous reviews are available covering work through about 1980 (1,24,172,193,194,196,197,205).

It has been suggested that compounds with 2,5-dimethoxy substituents may be O-demethylated to generate reactive quinone species, and that this may play a role in their high activity (193,197,205). However, this substitution also leads to high-energy molecular orbitals. Furthermore, transposing the 4-methyl of 2,5-dimethoxy-4-methylamphetamine (DOM) (see Table 1) or the 4-bromine of 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane (DOB) to the 3-position results in a 100-fold decrease in receptor affinity, as well as a loss of behavioral activity in animals (78,82). This structural modification would lead to a twisting out of plane for the 2-methoxy and a consequent loss of the resonance overlap between the pi system and the *n* electrons of the oxygen. The result of this would be a decrease in the energy of the molecular orbitals, one possible explanation for the observed loss of biologic activity. Domelsmith et al. (52–54) have demonstrated correlations between human potency and the ionization potentials of substituted phenethylamines. These findings are in agreement with many suggestions that hallucinogens may form a charge-transfer complex with an electron acceptor at the receptor (125,212,220). Furthermore, *in vivo* activity generally parallels *in vitro* assays, where metabolism is not a factor. Thus the 2,5-dioxygenation pattern serves in an electronic capacity to confer optimal molecular orbital properties to the molecule (53). This appears to be the best explanation, based on the available data.

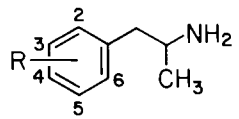
Substituent orientation is largely responsible for determining the relative importance of various possible qualitative components of action. For example, the effects of 3,4,5- or 2,4,5-substituted compounds typify what is more commonly thought of as "hallucinogenic action." On the other hand, those that are 4-monosubstituted, or others with certain disubstitution patterns, may possess striking qualitative differences in man. Often, these have a powerful amphetamine-like stimulant effect. Several workers have commented on the fact that "hallucinogens" actually fall into a broad pharmacologic spectrum, ranging in action from amphetamine-like to LSD-like (1,88,143,155). A recent study by Glennon et al. (82) suggests that it may be possible to study certain of these qualitative differences using the two-lever drug discrimination assay in rats, based on the stimulus generalization that occurs to the training drug selected. It is unlikely, however, that any nonhuman model will be developed which can reliably predict these properties in advance. This is simply due to the large number of possible component processes involved, including not only direct receptor effects but also the release of various endogenous neurotransmitters (31,32,160,233,234) and blockade of their reuptake (139). Each of these component processes will have its own structure-activity relationships. The net result of the administration of a given drug will depend on the degree to which its particular substitution pattern allows it to interact with each possible component in the biologic system.

The agents of major interest that have been evaluated in man are listed in Tables 1 and 2. Although the potencies of these are given relative to mescaline, the foregoing discussion should make it clear that the intoxication at the effective dose for each of these may vary widely in its qualitative aspects.

Nature of Substituents

It has become clear that there are severe limitations on the type of substituents that may be present at the 2- and 5-, or 3- and 5-positions of the phenethylamines. For 2,4,5-substituted compounds, no substituent at the 2-position, other than methoxy, has demonstrated significant clinical activity. The replacement of the 2-methoxy with a methyl (5), methylthio (115), ethoxy (191), or bromine (11,188) destroys or dramatically attenuates activity. Replacement of the 2-methoxy by hydrogen in 2,4,5-trimethoxyphenylisopropylamine gives 3,4-dimethoxyphenylisopropylamine (3,4-DMA) (Table 2), which is inactive. Replacement of the 2-methoxy of DOM (see Table 1) with a hydrogen gives a compound that retains activity in mice (104), but which has lost its activity in other animal models (1) and which is clinically inactive at doses up to 25 mg, acutely (199). It appears that a methoxy precisely fulfills critical steric and electronic requirements. A recent study using the discriminative stimulus paradigm has further emphasized the importance of the 2-methoxy (87). *In vitro* and animal behavioral data suggest that a 2-hydroxy may also lead to active compounds (79), but no clinical trials confirm this. Only one important exception exists: 3,4-methylenedioxyamphetamine (MDA; Structure **3a**). This compound has approximately twice the potency of mescaline in humans (205). The subjective effects produced by MDA and other methylenedioxy-substituted compounds are considerably different than those with 2,5-dimethoxy substituents (190,207). This illustrates the problem of clinical potency assessment; on a weight basis, MDA is more potent than mescaline, but at effective dosages, it produces a qualitatively different intoxication state.

TABLE 2. *Hallucinogenic potencies in humans for selected alkoxy-substituted phenylisopropylamines*[a]



Trivial designation	Substituent at position 2	3	4	5	6	Potency (MU)[b]
PMA	H	H	OCH_3	H	H	6
3,4-DMA	H	OCH_3	OCH_3	H	H	1
2,4-DMA	OCH_3	H	OCH_3	H	H	6
TMA-3	OCH_3	OCH_3	OCH_3	H	H	2
TMA-4	OCH_3	OCH_3	H	OCH_3	H	4
TMA-5	OCH_3	OCH_3	H	H	OCH_3	10
TMA-6	OCH_3	H	OCH_3	H	OCH_3	10
MMDA	H	OCH_3	$O\text{-}CH_2\text{-}O$		H	3
MMDA-2	OCH_3	H	$O\text{-}CH_2\text{-}O$		H	10
MMDA-3a	OCH_3	$O\text{-}CH_2\text{-}O$		H	OCH_3	10
MMDA-3b	$O\text{-}CH_2\text{-}O$		OCH_3	H	H	3
MMDA-5	$O\text{-}CH_2\text{-}O$		H	H	OCH_3	10
DMMDA	OCH_3	$O\text{-}CH_2\text{-}O$		OCH_3	H	12
DMMDA-2	OCH_3	OCH_3	$O\text{-}CH_2\text{-}O$		H	5

[a] Taken from ref. 197.
[b] Human activity expressed in mescaline units (MUs) (205). An approximate effective oral dosage in milligrams can be obtain by dividing 400 mg by the MU value.

The 5-methoxy seems less critical; its replacement by methylthio or ethylthio groups, especially in 3,4,5-substituted compounds, has recently been explored by Jacob and Shulgin (116). Activity in this series is not reduced. Recently, the authors (117) prepared the 2- and 5-thio isosteres of DOM and DOET. With a 2-thiomethyl, activity was retained but was attenuated to about 1/20 to 1/25 of the oxygen isosteres. The 5-thiomethyl isomers possessed two to four times the activity of the thiomethyls at the 2-position. When both the 2- and 5-methoxys were replaced by thiomethyl groups, activity was essentially abolished.

The most interesting and fruitful area of structural modification is at the 4-position, i.e., para to the side chain. Virtually every type of substituent tried has yielded active compounds in one series or another. Some of the more important compounds are listed in Table 1.

Specific data are discussed later; but the 4-substituent has potential importance in one or more of the following ways: (a) to increase general lipophilicity, facilitating passive diffusion into the CNS (13); (b) to confer metabolic stability on the molecule by simultaneously blocking aromatic hydroxylation at this site and by providing a group that is relatively resistant to oxidative metabolism (194); and (c) by possibly providing a group to interact with a hydrophobic region which is proposed to be located at a complementary site on the serotonin receptor (54,80,131,158,164). Much of the recent structure-activity work on phenethylamine hallucinogens has focused on manipulation of the para substituent.

The types of para substituents that have been examined include halogen, alkyl, and alkoxy or alkylthio. The halogens Br and I have both yielded highly active compounds in human trials. The 4-bromo homolog of DOM, DOB, is the most potent hallucinogenic amphetamine yet prepared. It has an oral threshold dose of about 0.2 mg and is approximately 400 times more potent than mescaline (206). Its ease of synthesis and high potency have led to illicit manufacture and abuse (48,198). Unfortunately, cases have been reported where chronic high dosages of DOB have led to gangrene due to peripheral vasoconstriction, and at least one death has been attributed to DOB abuse (198). It has been previously shown that DOB is a potent peripheral vasoconstrictor (32,56). This vasoconstriction is probably mediated by the serotonin-like agonist action of DOB, which has been demonstrated in vascular smooth muscle from dog and sheep and in the rat stomach fundus (32,56,72). Although at high doses DOB apparently has an LSD-like quality, the initial clinical report, at relatively low dosages, described central nervous system (CNS) effects that were relatively mild and involved primarily changes in mood and affect similar to those elicited by MDA. The iodine homolog DOI is quite potent and apparently presents a clinical picture similar to that of DOB (see Table 1) (197). The chlorine homolog DOC is about equipotent to DOB in rabbit and cat models (1) but has not been tested in man. The fluorine homolog DOF has been evaluated in rats in a two-lever drug discrimination assay (88). It has relatively high potency in this model and might be expected to be clinically active, but no human studies have been reported. In this study by Glennon et al. (88), the (−) isomers of DOB, DOI, and the nitro homolog DON all proved to be more potent than their racemates in stimulus generalization tests in rats trained to discriminate DOM from saline. Previously, the racemates of DON and DOC had been tested in a general rat behavioral screen and had been found to be equipotent to DOM (44).

In the 2,5-dimethoxy substituted series, when the 4-substituent is alkoxy, a methoxy group gives optimum activity. (Compare, for example, TMA-2 and MEM in Table 1.) The 4-ethoxy group does not lead to an increase in activity, despite increased lipophilicity. This is in sharp contrast to 3,4,5-substituted compounds (discussed below), where an analogous transformation leads to an activity increase of nearly an order of magnitude.

An alkylthio substituent at the 4-position increases activity and also brings

about a qualitative change in the intoxication. The first member of the series "para-DOT" was synthesized in 1976 (163) using the rationale that the sulfur atom might prove labile to oxidative metabolism. This was contrasted with the metabolic stability of a group such as bromine. Shulgin and his co-workers (116,197,204) have characterized the clinical effects of para-DOT as well as several other 4-alkylthio substituted compounds. At low dosages, these compounds are described as having the ability to enhance intellectual function and promote the flow of ideas without otherwise impairing sobriety. These workers have termed this the "aleph" effect.

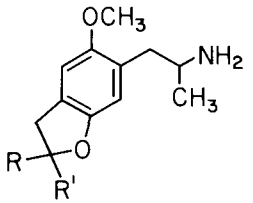
Once again, clinical studies reveal a divergence between potency and qualitative effect. No *in vitro* or animal model studies have yet indicated any major difference between oxygen at the 4-position and its sulfur isostere, although there are changes in their experimentally measured ionization potentials (54).

Compounds with a 4-alkyl seem to produce the most severe sensory disruption. The prototype of these is DOM (Table 1), which received notoriety following its introduction into the illicit market in 1967. Extension of the alkyl to ethyl (DOET) and *n*-propyl (DOPR) gives further potency increases (203). In early reports, the low dosage effect of DOET was characterized as nonhallucinogenic (211,215); it is clear, however, that this is dose dependent.

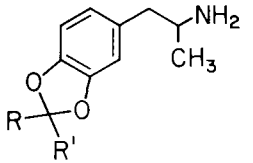
The variation of human or whole animal potency as the para-alkyl is modified may be due in part to metabolic or pharmacokinetic factors. Simply substituting a para-alkyl enhances affinity for serotonin receptors in the rat fundus preparation (78). Extension of a methyl to ethyl or higher homologs, however, or branching of the alkyl apparently has little further effect on affinity (77). For the series of 2,5-dimethoxy-4-alkyl substituted phenylisopropylamine derivatives, human activity does not seem to parallel *in vitro* assays (77), and whole animal models provide better correlations (88,149). In the two-lever drug discrimination paradigm, with rats trained to discriminate 5-methoxy-N,N-dimethyltryptamine from saline, the training stimulus only generalizes completely to the 4-methyl compound (DOM). The other 4-alkyl homologs do not completely generalize, suggesting that a complete exploration of the human psychopharmacology of the active members of this series might reveal qualitative differences. On the other hand, if DOM is used as the training drug, stimulus generalization occurs with DOET and DOPR but not with DOTB or DOAM.

Branching in the 4-alkyl group is deleterious, at least if the branch is adjacent to the aromatic ring, as in such compounds as DOIPR, DOTB, and DOSB. Branching in the alkyl, if it is more distal from the ring, may lead to compounds that retain high activity (e.g., DOIB). These observations may be related to a possible requirement for the aromatic ring of the phenethylamines to closely approach the receptor surface, presumably to form a charge-transfer complex, as noted earlier. Bulky, branched alkyls attached to the ring would hinder this interaction (165). By contrast, branching further removed from the ring would not be expected to have as severe an effect.

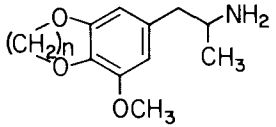
It has been suggested that the receptor that interacts with hallucinogenic



Structure 2. a: R=R′=H, **b:** R=H, R′=CH_3, **c:** R=R′=CH_3.



Structure 3. a: R=R′=H, **b:** R=H, R′=CH_3, **c:** R=R′=CH_3.

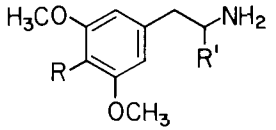


Structure 4. a: n = 2, **b:** n = 3.

phenethylamines can be modeled as a planar surface (162,166). This would be consistent with the above arguments. There are additional data to support this idea. For example, in the homologous series **2a,b,c** and **3a,b,c** the latter compound in each (Structures **2c** and **3c**) is inactive.

In the case of **2c,** no activity was apparent in human experiments (24), while **3c** was inactive in mice (159). Both **3a** (MDA) and **3b** possess human activity, although **3b** is apparently much reduced in potency (199). Clinical activity for compounds **2a** and **2b** has not been confirmed, although it was communicated several years ago that both were quite potent in man (231). The lack of activity for **4a** and **4b** (190) may also be explained by considering the steric effects introduced by puckering in the heterocyclic ring.

These results suggest that one face of the aromatic ring must be relatively free of steric bulk. This would be consistent with a requirement for close approach of the ring face to an electron acceptor moiety at the receptor, assuming that charge-transfer complex formation is an important receptor event. Similar reasoning has been advanced recently by Knittel and Makriyannis (133) to explain the lack of activity for TMA-3 (Table 2), where the methoxy groups are perpendicular to the ring plane but staggered 180° apart. The resulting projection of methoxy groups toward each face of the molecule would thus hinder access to the receptor surface. However, other arguments may be equally valid. For example, if the receptor geometry can be represented as a groove or slot in the membrane, one edge of this groove may simply be able to accommodate protruding steric bulk more easily than the other. In any case, it is likely that the receptor does discriminate between the two faces of the aromatic ring.



Structure 5. a: R=H, R′=CH_3, **b:** R=OCH_2CH_3, R′=H, **c:** R=OC_3H_7 R′=H, **d:** O-i-C_3H_7 R′=H.

One of the interesting features in 3,4,5-substituted series is the dramatic enhancement of activity that occurs on modification of the 4-substituent (21). The absence of a 4-substituent (3,5-DMA; Structure **5a**) leads to little change in receptor affinity from that of 3,4,5-TMA (8), as measured in the rat fundus preparation (78). However, DOM-stimulus generalization to 3,5-DMA does not occur in rats (87). No human data have been reported for 3,5-DMA.

Homologation of mescaline to the 4-ethoxy (escaline; **5b**) increases potency about sixfold (21). The 4-propoxy (proscaline; **5c**) is nearly as active, as is the isopropoxy, **5d.** A 4-butoxy at this position, while less active than ethoxy or propoxy, is still more potent than mescaline, although the qualitative aspect of the intoxication has not yet been fully characterized. In these series, it is clear that the 4-substituent must be twisted to a conformation where the alkyl-oxygen bond is nearly perpendicular to the aromatic ring (58). Certainly large alkoxy groups, such as isopropoxy, will be even more severely constrained. This would seem to negate the possibility of significant resonance overlap between the pi system and the unshared electrons of the 4-oxygen atom. Thus, while a methoxy may be optimal or even a requirement in the 2-, 3-, or 5-position of some series, there is no such requirement at the 4-position. Indeed, in 3,4,5-substituted compounds, hydrophobic groups, such as alkyl, alkylthio, or halogen, greatly increase potency (21).

It is interesting that alkoxy groups larger than methoxy at the 4-position in 2,4,5-substituted compounds do not increase potency in the way they do in the 3,4,5 series. Based on the out-of-plane conformation of the 4-substituent in 3,4,5-substituted series, it is tempting to speculate that any hydrophobic site or accommodating region on the receptor at this position does not lie in the plane of the aromatic ring, but rather might be visualized as a surface that is more nearly perpendicular to the aromatic ring plane. This could be visualized schematically in Fig. 1. By contrast, a 4-alkoxy in the 2,4,5-substitution series will prefer to lie coplanar with the aromatic ring in order to maximize overlap of the *n* electrons with the pi system (6). The alkyl of the alkoxy, therefore, would not be favorably oriented to interact with a region of the receptor having such geometry. Furthermore, the bulk of the larger alkyl, now attempting to reside in the plane of the ring, may direct unfavorable steric interactions toward other portions of the receptor.

The preferred conformations of methoxy groups attached to aromatic rings in the phenethylamines have recently been investigated using theoretical approaches, gas phase experimental methods, and nuclear magnetic resonance (NMR) techniques for the molecules in aqueous solution. *Ab initio* theoretical calculations and experimental gas phase results have indicated that when two

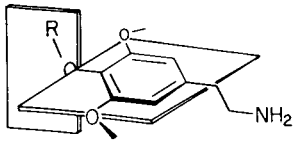
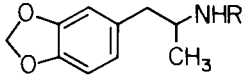


FIG. 1. Illustration of a proposed hydrophobic surface, normal to the plane of the aromatic ring, which can accommodate lipophilic 4-substitutents in 3,4,5-trisubstituted phenethylamine derivatives.

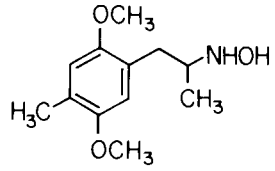
methoxy groups are adjacent to each other, one prefers to twist out of plane (5,6). However, solution NMR measurements have indicated that both methoxy groups prefer to remain coplanar with the aromatic ring (133,145).

N-Substituents

In contrast to the *in vivo* action of the tryptamines, N-alkylation of the phenethylamines abolishes or greatly attenuates biologic activity (105,197). Two noteworthy exceptions are the 3,4-methylenedioxy-substituted compounds Structures **6a** (204) and **6b** (22). These retain potency nearly comparable to the parent **3a** (MDA) but present a different qualitative picture. Their duration of action is reduced to about $1\frac{1}{2}$ to 2 hours, and they produce only minor disruption of normal sensory processing. They apparently amplify empathy and would seem to be ideal candidates as adjuncts to psychotherapy (psycholytic therapy) (197). The mechanism of action for **6a** also seems to be different than that of the nonmethylated parent **3a.** The evidence for this comes primarily from studies of the *R* and *S* enantiomers of **6a** and **3a** (4). In the nonmethylated parent **3a,** it is the *R* enantiomer that shows highest biologic activity. In contrast, it is the *S* enantiomer of **6a** that is most active. Furthermore, there is no cross tolerance between **6a** and **3a.** This is also a good case to use to illustrate the utility of the drug discrimination assay. Recently, using rats trained to discriminate DOM from saline, it was found that the DOM stimulus generalized to racemic **3a** or its clinically active *R*-(−) enantiomer (92). However, DOM stimulus generalization was not observed to the *S* enantiomer of **6a.** Thus the results of this animal model also are in agreement with the clinical findings. The fact that the *S* enantiomer of **6a** has the same absolute configuration as (+)-amphetamine has led to speculation that **6a** may owe its activity to the ability to induce release of endogenous transmitter (4). It has been shown that the *S* enantiomer of **6a** is in fact more potent in inducing release of ^{3}H-serotonin from prelabeled rat whole brain synaptosomes (160). It seems likely that other monoamines may also be involved, since Marquardt et al. (139) have shown that the *S* enantiomer of **3a** is more potent in inhibiting the uptake of norepinephrine into rat brain synaptosomes. The possibility of multiple components of action for hallucinogenic phenethylamine derivatives must be kept in mind.



Structure 6. a: R=CH_3, **b:** R=CH_2CH_3, **c:** R=OH.



Structure 7.

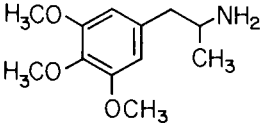
Homologation of the N-substituent beyond ethyl generally abolishes activity (22). N,N-dialkylation does not lead to active compounds, even with 3,4-methylenedioxy substitution (197). It should be noted, however, that only a few N,N-dialkyl compounds have been clinically evaluated. N-alkylation also decreases *in vitro* serotonin receptor affinity (80). Certain N-propyl, N-cyclopropylmethyl, and N-allyl derivatives show weak antagonism against mescaline-induced disruption of swimming behavior in mice (50).

Two reports have appeared for compounds with an N-hydroxy. Compound **6c** retains clinical activity nearly comparable to that of **6a** (22), while Structure **7** shows weak activity in rats (44).

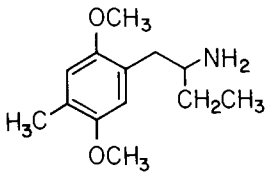
Side Chain Modifications

While mescaline is a simple 2-phenethylamine derivative, the addition of an alpha-methyl group to the side chain yields Structure **8** (TMA). This simple hybrid of the structures of mescaline and amphetamine retains the hallucinogenic effects of mescaline but possesses about twice the potency of the latter (174,200). Addition of the alpha-methyl to other 3,4,5-substituted compounds generally brings about an approximately twofold increase in potency. The addition of an alpha-methyl to 2,4,5-substituted compounds, however, may dramatically increase activity. For example, 2-(2,4,5-trimethoxyphenyl) ethylamine apparently is clinically inactive (195). Addition of an alpha-methyl gives TMA-2 (Table 1), with 20 times the potency of mescaline. However, the addition of an alpha-methyl does not significantly increase *in vitro* receptor affinity in either 3,4,5- or 2,4,5-series (72,78). Thus it is probable that the alpha-methyl may confer metabolic stability *in vivo.* It could also be speculated that this protection is more important in the 2,4,5-substituted series than in 3,4,5-substituted compounds.

Little work has been done in this area. Clark et al. (36), however, reported that mescaline is more extensively deaminated by a soluble rabbit liver amine oxidase preparation than is 2,4,5-trimethoxyphenethylamine. One should also note that the addition of the alpha-methyl will increase the octanol-water partition



Structure 8.



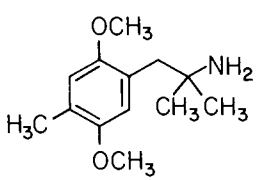
Structure 9.

coefficient by a factor of about 3. In most cases, this increase in lipid solubility will lead to higher drug concentrations in the CNS. This is especially true of mescaline, which has poor lipid solubility. The small increase in *in vivo* activity for alpha-methylated 3,4,5-substituted compounds may be due largely to increased lipid solubility. On the other hand, Cooper (40) has suggested that the potentiating effect of the alpha-methyl on potency may be due to the preferential stabilization of one of the two possible staggered conformations of the side chain. Nevertheless, several compounds that possess substantial activity do not have the alpha-methyl group. Most noteworthy are the nonalpha-methylated homologs of DOM and DOB. Although neither is as potent as the alpha-methyl congener, both possess relatively high activity (201).

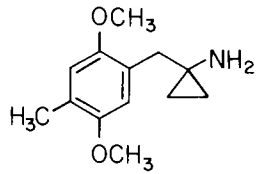
The introduction of a methyl, or other alkyl, into the side chain also introduces asymmetry into the molecule. Numerous studies of the resulting (+) and (−) enantiomers have now been reported. These will be discussed in detail later.

Extension of the alpha-methyl to an ethyl or longer alkyl homolog completely abolishes activity in both 3,4,5- and 2,4,5-substituted compounds (189,219). The most thoroughly studied example is the alpha-ethyl homolog of DOM, Structure **9** (BL-3912A). This compound was evaluated for potential mood elevating properties (219) and facilitation of learning (42,230). In sheep umbilical artery smooth muscle, it showed mixed serotonin agonist/antagonist activity, whereas DOM was a pure agonist (55). The dynamic behavior of DOM and its alpha-ethyl homolog **9** do not appear to differ, either as studied in solution using NMR techniques (47,144) or as calculated using empirical potential functions (246). The lack of activity for **9** almost certainly must be due to a steric effect, presumably an interaction between the alpha-ethyl group and some feature of the receptor.

Dialkyl substitution on the alpha-carbon also abolishes activity. the α,α-dimethyl analog of DOM, Structure **10,** is inactive in a variety of assays (10). Linking the two alpha-methyls to give the cyclopropyl analog Structure **11** restores activity in a cat behavioral model (10). The difference in activity between **10** and **11** has been ascribed to the inability of **10** to adopt an antiperiplanar



Structure 10.



Structure 11.

conformation, which is presumably a requirement for receptor binding (247). Bond angle distortion in the cyclopropane ring reduces this problem in **11** and restores conformational mobility.

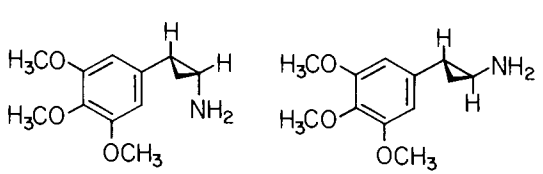
Adding the second alpha-methyl to MDA gives a compound that apparently is only weakly active in man (199). Again, the 3,4-methylenedioxy substitution seems anomalous. This may also be due to an indirect effect, such as release of endogenous neurotransmitter from nerve terminals. However, neither this α,α-dimethylated MDA analog nor α,α-dimethyl-4-methoxy-β-phenethylamine had any ability to induce the release of ^{3}H-serotonin from rat whole brain synaptosomes (160).

The addition of a beta-methyl to the side chain dramatically attenuates activity in animal models (1,155). An α,β- or β,β-dimethyl substitution also abolished hallucinogen-like activity in animal models (1).

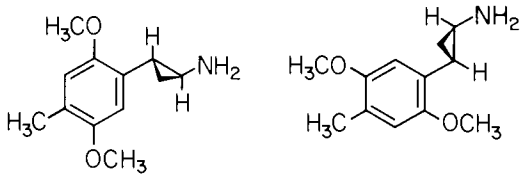
Phenylalanine derivatives, substituted either with 3,4,5-trimethoxy or 2,5-dimethoxy-4-methyl substituents did not show activity (46). Although these would yield potentially active phenethylamines if decarboxylated *in vivo,* neither is likely to be a substrate for decarboxylases in the CNS (62). Several additional side chain alkylated compounds are discussed in the next section as rigid analogs.

Rigid Analogs

Since the phenethylamines are flexible molecules, it has been natural to speculate on the conformation that they adopt at the receptor. Such studies have been based on crystallographic observations (35) or calculated preferred conformations (128). There is now general recognition that the active conformation need not be of lowest energy, nor need it be that observed in the solid state. Since no methodology presently exists to study the active binding conformation of the phenethylamines at receptor sites, a number of workers have designed rigid analogs in order to fix the side chain into a particular conformation (166). Activity for several of these has led to inferences about the binding conformation of the nonrigid prototypes. Perhaps the simplest rigid analogs are the 2-phen-



Structure 12. Cis, **left;** trans, **right.**



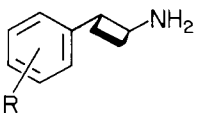
Structures 13 (left) and 13R (right).

ylcyclopropylamines. The first of these were the mescaline analog Structures *cis* and *trans* **12.** These were prepared and tested in rats by Cooper and Walters (40,41). Mescaline-like activity only for the *trans* isomer seems to clearly indicate that mescaline binds to the appropriate receptors with the side chain in a *trans* extended conformation. This finding negated any possibility that hallucinogenic phenethylamines could mimic an indole at the receptor by adopting a cisoid conformation where the side chain amino group corresponded to the indole N(1) atom (213). Aldous et al. (1) prepared the racemic *trans*-2-(2,5-dimethoxy-4-methylphenyl) cyclopropylamine Structure **13.** In three animal models (cat, rat, and rabbit), the racemate showed potent hallucinogen-like effects. This DOM homolog was resolved into its enantiomers (−)-1*R*,2*S*-(**13***R*) and (+)-1*S*,2*R*-(**13***S*). Assays in mice, cats, and rabbits revealed the (−) enantiomer **13***R* to be selectively active (162,167). Subsequently, racemic **13** hydrochloride was found to be a potent hallucinogen in man, with an effective acute oral dosage in the range of 15 to 20 mg (199). As predicted from the animal models, it is the (−) isomer that possesses clinical activity.

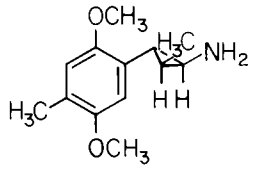
The 2-phenylcyclobutylamines Structures **14** and **15** have also been prepared (161). In contrast to the cyclopropylamine, however, **15** showed no clinical activity following oral administration of a dose up to 25 mg of the racemic hydrochloride (199). The trimethoxy congener **14** has not been tested. The appropriately ring-substituted *trans*-2-phenylcyclopentyl or cyclohexylamines have not been reported. Based on the apparent lack of activity for **15,** as well as the lack of activity for alpha-ethyl phenethylamine derivatives, however, these might be predicted to be inactive.

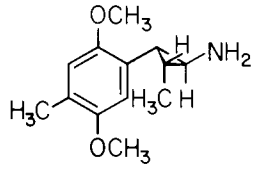
In view of the activity of **13,** but the lack of activity for the alpha-ethyl homolog of DOM, the two isomeric ring-methylated derivatives Structures **16a** and **16b** were recently prepared (114). Neither isomer showed significant activity, either as an agonist in the rat fundus preparation or in a mouse assay, when compared with **13.** It would appear that little bulk can be tolerated near the alpha-carbon, other than a methyl or methylene.

Another series of rigid analogs that have been examined to some degree are the aminotetralins with the general formula of Structure **17.** If, as might be

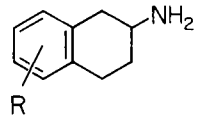


Structures 14: R=2,3,5-$(OCH_3)_3$ and **15:** R=2,5-$(OCH_3)_2$-4-CH_3.





Structure 16a (left) and 16b (right).

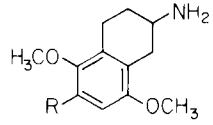


Structure 17. R=OCH_3, R, OH.

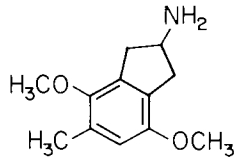
inferred from the data on the 2-phenylcyclopropylamines, the phenethylamine side chain binds in an antiperiplanar conformation, then one might expect to see high activity in such compounds as tetrahydronaphthalenes. The side chain is nearly locked into a conformation that should resemble closely that of the phenethylamines in proposed active binding conformations. Surprisingly, aminotetralins produce sedation in rodents (14,241) and do not elicit behavioral effects that resemble their flexible phenethylamine counterparts.

The aminotetralins have been suggested to represent the A and C rings of LSD as the possible pharmacophoric element, as shown in Fig. 2. Kang and Green (126) noted this possible relationship, which is similar to analogies presented earlier by other workers concerning the oxytocic activity of ergot alkaloids. This view was utilized by several groups (45,156,241). Aminotetralins closely related in structure to highly potent phenethylamines have been prepared (e.g., Structures **18a, 18b,** and **19**).

The tetralins **18a** and **18b** were potent serotonin agonists in dog vascular smooth muscle (33) but did not elicit hallucinogen-like action in a conditioned avoidance response model in rats (156). However, **18b** is a potent pyretic agent in rabbits and produces a rage response in cats (166). Addition of a double bond into the 3,4-position of the tetralins led to decreased serotonin-like action



Structure 18a: R=H, and **18b:** R=CH_3.



Structure 19.

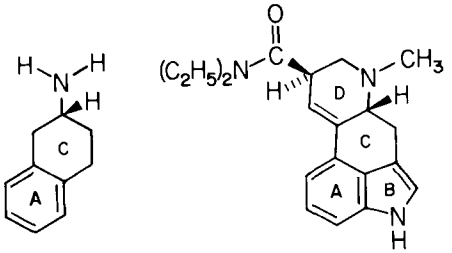


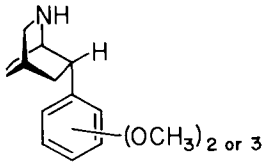
FIG. 2. Possible structural correspondence between aminotetralius and LSD.

in the rat fundus and further attenuation of the *in vivo* activity in the rat serotonin syndrome model (134). Contraction of the six-membered ring of **18b** to the five-membered indan **19** analog did not restore activity (156). Coutts and Malicky (45) did report that high doses of the indan derivative produced a DOM-like effect in a general screen in rats.

Violland et al. (241) examined several methoxy-substituted 2-aminotetralins as hallucinogen analogs. Characterized in mice and dogs, these produced ataxia, sedation, and analgesia.

The lack of clear-cut hallucinogen-type activity for the 2-aminotetralins could be explained in several ways. The known deleterious effect of molecular bulk in the alpha-position would seem to direct attention to the steric effect of the reduced ring of the tetralins as detrimental to activity. In **18b,** however, it has been noted (156) that the 5-methoxy group is forced out of plane by the adjacent 6-methyl and 4-methylene groups. The importance to activity of maintaining the methoxy groups coplanar with the aromatic ring has been emphasized earlier. Both substituent orientation and N-alkylation must also be important to activity, and it may not be realistic to make direct comparisons between the phenethylamines and the 2-aminotetralins.

Several additional analogs that incorporate the side chain into a heterocyclic ring have been prepared and evaluated. Generally, these have been hybrids between the structure of mescaline and phenmetrazine or methylphenidate. Based on the finding that both N-alkylation and α-alkyl groups larger than a methyl are detrimental to activity, it is not surprising to find that none possessed significant activity in animal models (249,250). However, Law and Borne (136) prepared endo and exo isomers of substituted azabicyclooctanes. A screen for



Structure 20.

effects on motor activity in mice revealed the endo isomer Structure **20** to be more active, demonstrating again that structures that incorporate the phenethylamine moiety in an extended *trans* conformation are more active than those with cisoid conformations. This is consistent with the discussions above regarding the cyclopropyl analogs.

Stereochemical Considerations

It has been known for many years that only the 5*R*,8*R*-(+) isomer of LSD is biologically active. Based on ability to produce cross tolerance and similarity of pharmacologic and subjective clinical effects, it has often been suggested that LSD, other hallucinogenic tryptamines, and the phenethylamine hallucinogens share a common or similar component of action. It is possible that this could involve interaction of all these structures at a particular receptor type. Such a possible functional similarity between the tryptamines and the phenethylamines has led to attempts to relate the stereochemistry of the phenethylamines to that of LSD. This relationship was noted by Kang and Green (126) and emphasized by Barfknecht and Nichols (12,157). This analogy, illustrated in Fig. 3 for *R*-(−)-DOM and LSD, correctly predicted that the illustrated *R* isomer of the hallucinogenic phenylisopropylamines would possess highest activity when compared with its *S* enantiomer. This was first confirmed in human assays of the enantiomers of DOM (192) and has been shown to be true for all substituted derivatives that are primary amines, both *in vitro* and *in vivo* (1,15,56,72,88,162,214,251). There is generally a four- to 10-fold difference in potency between the enantiomers.

In Fig. 3, the two molecular faces of LSD can be designated as "beta," in this case the side of the molecule facing the reader, and "alpha," the face of the molecule hidden from the viewer (181). Based on X-ray crystallographic (9) and solution NMR studies (8), the molecule is nearly planar, and the unshared electron pair on N(6) is directed toward the alpha face of the molecule. It is typically assumed that the basic nitrogen atom is an important site for interaction with the receptor. It has also been assumed that the solid state and solution conformation of LSD is the same as the binding conformation at the receptor. That is, there is no present evidence to suggest that the D ring of LSD undergoes a conformational flip which would reorient the N(6) electron pair. It may be inferred, therefore, that the receptor interacts with the alpha face of LSD. Using the analogy presented above, and assuming that LSD and DOM can bind to the same receptor system(s), would lead one to the conclusion that DOM and similarly substituted phenethylamine derivatives also bind to the receptor with their alpha face, the surface of the molecule hidden from the reader. Binding to the alpha face of the more active *R*-(−) enantiomer of DOM in this case would force the alpha-methyl of the side chain into the proposed receptor surface. Similarly, binding of the cyclopropylamine analogue **13R** would direct the C3 methylene of the cyclopropane ring into the binding surface. One could argue that such an interaction may be necessary to elicit the receptor response induced

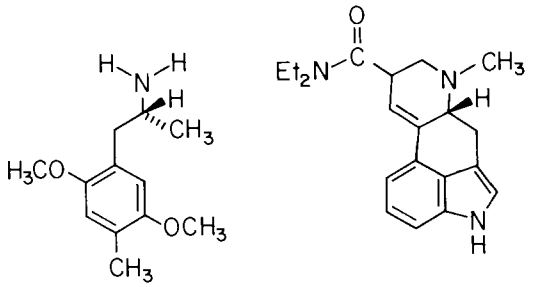


FIG. 3. Possible structural similarity between *R*-(−)-DOM and LSD.

by hallucinogens. An appealing feature of this model is that it might explain the lack of activity for the alpha-ethylphenethylamines. It has been suggested that the alpha-ethyl homologs are inactive as a result of some steric effect at the receptor (47,144,246). If the alpha-alkyl projects into the receptor surface, it seems natural to assume that the receptor would be sensitive to the nature and size of this group. This type of orientation would also be consistent with the observation that it is the *S* enantiomer of alpha-methyltryptamine and the (+)-isomer of 5-methoxy-alpha-methyltryptamine (which presumably has the *S* absolute configuration) which are the most active (72,76).

It is also possible that the beta face of the phenethylamines is the one that is more important for receptor binding. That is, the surface of the molecule that is visible to the reader in Fig. 3 may be the one involved in receptor binding. Thus the binding orientations for *R*-(−)-DOM and **13R** would be as shown in Fig. 4, with the receptor binding to the face of the molecule that is now hidden from the reader. In this orientation, the alpha-methyl in the *R* enantiomer of the amphetamines, or the C3 methylene of the cyclopropylamine with the 1*R*,2*S* configuration, projects away from the binding surface. The inactivity of alpha-ethyl homologs would still be explained as a steric effect. In this case, however, the alpha-alkyl would probably limit access to the receptor. For example, using enzyme active site geometry as a model, the receptor may be more accurately visualized as a groove or cavity in the membrane surface. Although such a receptor might tolerate only limited steric bulk directed toward the alpha face, the beta face of the molecule might be the one that actually interacts with the functional portion of the receptor.

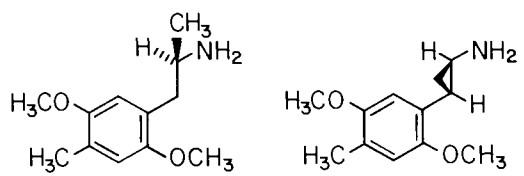


FIG. 4. Binding orientations for *R*-(−)-DOM and **13R**.

This view offers an explanation for the stereoselectivity of the phenylisopropylamines, i.e., the isomer that is more active is the one that presents least interference to the drug-receptor interaction. This idea would be consistent with the observation that the *R* enantiomers of the phenylisopropylamines have receptor affinity similar to their nonalpha-methylated homologs, and that the alpha-methyl of the *S* enantiomer of the amphetamines has a deleterious effect on affinity (72,78). There is no strongly compelling evidence in favor of either of the above hypotheses, however, and either is tenable.

It undoubtedly will be some time before this situation is completely clarified. It may prove to be the case, as suggested by Glennon et al. (79), that the phenethylamines can adopt different binding orientations at the receptor, depending on the nature and orientation of the aromatic substituents.

Pharmacokinetic and Metabolic Effects

Thus far, there has been considerable discussion of structure-activity relationships at the molecular level, or at some hypothetical receptor(s). However, *in vivo* activity must depend on ability to penetrate into the CNS. Furthermore, the duration of action, as well as the overall potency, also must depend on how readily a particular compound is metabolized and removed from the body by excretion. For example, 2,4,5-trimethoxy-β-phenethylamine lacks hallucinogenic activity. Cohen et al. (37) could not detect this material in brain, following administration to rats. The lack of penetration into the CNS could be the reason for the inactivity of this compound, in contrast to mescaline, the 3,4,5-substituted isomer. As these workers emphasize, parameters, such as absorption, metabolism, distribution, excretion, and penetration through the blood-brain barrier, will all be important when considering the potency of the drug in the intact organism. Vogel and Evans (243) have argued that structure-activity relationships should be based on effective drug concentrations in the brain rather than on total administered dose. They have proposed that minimal effective brain levels (MEBLs) be used as the measurement. This suggestion clearly has merit, but no subsequent studies using MEBL have been reported.

Partitioning into the CNS will be important for hallucinogens, as for any drug that acts centrally. Correlation between 1-octanol/water partition coefficients and human activity has been reported (13). Regression analysis of log human activity on log P yielded a parabolic fit with an optimum at log P 3.14. The derived equation accounted for only 62% of the variance but included compounds with a variety of substitution patterns and, presumably, qualitative differences in activity.

No importance of metabolic processes to the mechanism of action has yet been demonstrated. The phenethylamines generally are not good inhibitors of monoamine oxidase (MAO), although more active compounds may not be good substrates for this enzyme (MAO) (36). However, no extensive studies of phenethylamines have been reported, as either inhibitors or substrates of MAO. For

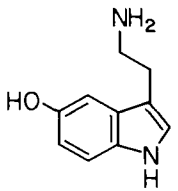
a more detailed discussion of the metabolic fate of phenethylamine hallucinogens, the reader is directed to the recent review by Castagnoli (28).

INDOLEALKYLAMINES

Indolealkylamines constitute a large class of compounds, of which the best known and most studied derivative is the neurotransmitter serotonin (5-hydroxytryptamine; Structure **21**). A number of indolealkylamines are hallucinogenic, and these can be conveniently divided into three basic groups: (a) tryptamine derivatives, (b) beta-carbolines, and (c) lysergic acid derivatives. The pharmacology and structure-activity relationships of hallucinogenic indolealkylamines have been previously reviewed (24,81,106,196,208). As noted above, because clinical evaluation of hallucinogenic agents is relatively restricted, few new human data have been reported since these reviews were published. Nevertheless, this discussion presents an overview of major findings with respect to human activity and attempts to highlight (a) compounds that have previously received limited attention, and (b) the more recent literature. Key references to classic *in vitro* and *in vivo* animal pharmacology are cited. The interested reader is referred to the above reviews and/or to the primary literature for more detailed discussions.

It should be pointed out that much of the data to be discussed is derived from animal studies. Using animals as subjects, greater numbers of compounds and structural modifications can be studied. The reader should be reminded, however, that the relationship between behavioral activity and potency in animals versus man is not yet fully understood or well defined. Furthermore, although many different activities have been measured in animals, these studies have rarely included large series of compounds, making it difficult to formulate structure-activity relationships. Thus an attempt is made to sift through the data and to discuss structure-activity relationships derived from studies employing relatively large numbers of compounds where comparisons can be made with somewhat more confidence. Conversely, studies involving only small numbers of compounds are given less emphasis.

The conformational and quantum chemical properties of indolealkylamines have been investigated (see, e.g., refs. 9,35,61,94–96,112,126–130, and 177), but, to date, such studies have had a limited impact on the understanding of structure-activity relationships. Evidence suggests that the indolealkylamine side



Structure 21.

chain can exist in any of several preferred conformations. These may only be separated by small energy barriers, and one of them roughly corresponds to the indolealkylamine nucleus within LSD. Thus it does not appear to be energetically impossible for indolealkylamines to mimic the aminoethylindole portion of the LSD structure. With respect to electronic properties, no significant relationship to hallucinogenic activity has been demonstrated for an extended series of compounds; however, work in this area continues.

The neurotransmitter serotonin (**21**) has been implicated as playing a role in the mechanism of action of the hallucinogenic indolealkylamines; however, the importance of other neurotransmitters cannot be ruled out at this time. Studies targeted specifically toward the elucidation of the mechanism of action of indolealkylamines are considered in other chapters, and this review is limited to a discussion of structure-activity relationships.

For convenience, the structures discussed in the following sections are listed in Table 3. In many cases, the compounds do not have common or trivial names and are referred to in the text by number.

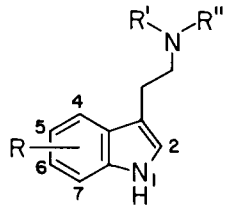
Tryptamines

Primary Amine and Monoalkyl Derivatives

The simplest member of this structural family is tryptamine (**22**). In man, tryptamine increases blood pressure and produces some perceptual distortion (141) but is not generally considered to be hallucinogenic. In animal studies, derivatives of tryptamine have received only scant attention. The 5-hydroxy derivative of tryptamine, serotonin, has not been demonstrated to be hallucinogenic in man or behaviorally active in animals. Comparative clinical evaluations of the isomeric hydroxytryptamines have not been reported. Various tryptamines, including the methoxy derivatives **23–26** (see Table 3), display serotonin agonist (or partial agonist) activity in the isolated rat fundus preparation, guinea pig ileum, or rat uterus (17,63,96,239). 5-Methoxytryptamine has been shown to be more potent than tryptamine or the 6- and 7-monomethoxy isomers **25** and **26,** respectively, in displacing ^{3}H-LSD from rat brain homogenates (95). However, none of these compounds has shown any significant behavioral activity in animal models.

Martin and co-workers (142,143) have found that, in animals, tryptamine produced many of the physiologic effects characteristic of LSD; however, it does not appear to elicit behavioral effects similar to those of LSD. At relatively high doses, 5-methoxytryptamine (**24**) does produce some behavioral effects in rats (66,242) and in nonhuman primates (101). Vogel (242) has suggested that the disruptive effects of 5-methoxytryptamine might be due to the peripheral actions of this agent. Tryptamine had no effect on acquisition of avoidance behavior, whereas 5-methoxytryptamine slightly decreased such behavior (240). Both tryptamine and 5-methoxytryptamine produced discriminative effects in rats

TABLE 3. *Structures of tryptamine derivatives which have been studied for potential hallucinogenic activity*



Structure no.	Designation	R	R′	R″
22	Tryptamine	H	H	H
23		4-OCH_3	H	H
24		5-OCH_3	H	H
25		6-OCH_3	H	H
26		7-OCH_3	H	H
27	N-MeT	H	CH_3	H
28	N-EtT	H	C_2H_5	H
29		H	n-C_3H_7	H
30		H	i-C_3H_7	H
31		H	n-C_4H_9	H
32		H	i-C_4H_9	H
33		H	$CH_2C_6H_5$	H
34	4-OH-N-MeT	4-OH	CH_3	H
35	4-OH-N-EtT	4-OH	C_2H_5	H
36	5-OMe-N-MeT	5-OCH_3	CH_3	H
37	DMT	H	CH_3	CH_3
38	DET	H	C_2H_5	C_2H_5
39	DPT	H	n-C_3H_7	n-C_3H_7
40	DIPT	H	i-C_3H_7	i-C_3H_7
41	DBT	H	n-C_4H_9	n-C_4H_9
42	DHT	H	n-C_6H_{13}	n-C_6H_{13}
43		H	-CH_2CH_2-	
44		H	-$CH_2(CH_2)_2CH_2$-	
45	5-TMT	5-CH_3	CH_3	CH_3
46	6-TMT	6-CH_3	CH_3	CH_3
47	7-TMT	7-CH_3	CH_3	CH_3
48		4-CH_3	CH_3	CH_3
49	Psilocin	4-OH	CH_3	CH_3
50	4-OH-DET	4-OH	C_2H_5	C_2H_5
51		4-OH	CH_3	i-C_3H_7
52	4-OH-DIPT	4-OH	i-C_3H_7	i-C_3H_7
53	Bufotenin	5-OH	CH_3	CH_3
54	5-OAc-DMT	5-$OCOCH_3$	CH_3	CH_3
55	6-OH-DMT	6-OH	CH_3	CH_3
56	6-OH-DET	6-OH	C_2H_5	C_2H_5
57	7-OH-DMT	7-OH	CH_3	CH_3
58	4-OMe-DMT	4-OCH_3	CH_3	CH_3
59	5-OMe-DMT	5-OCH_3	CH_3	CH_3
60	5-OMe-MET	5-OCH_3	CH_3	C_2H_5
61	5-OMe-DET	5-OCH_3	C_2H_5	C_2H_5
62	5-OMe-DPT	5-OCH_3	n-C_3H_7	n-C_3H_7
63	5-OMe-DIPT	5-OCH_3	i-C_3H_7	i-C_3H_7
64		4,5-OCH_2O-	CH_3	CH_3

TABLE 3. (*continued*)

Structure no.	Designation	R	R′	R″
65		4,5-OCH_2O-	i-C_3H_7	i-C_3H_7
66		5,6-OCH_2O-	CH_3	CH_3
67		5,6-OCH_2O-	i-C_3H_7	i-C_3H_7
68	4-SMe-DMT	4-SCH_3	CH_3	CH_3
69	5-SMe-DMT	5-SCH_3	CH_3	CH_3
70	6-SMe-DMT	6-SCH_3	CH_3	CH_3
71	6-OMe-DMT	6-OCH_3	CH_3	CH_3
72	7-OMe-DMT	7-OCH_3	CH_3	CH_3
73		5,7-$(OCH_3)_2$	CH_3	CH_3
74		4,5,6-$(OCH_3)_2$	CH_3	CH_3
75		5,6,7-$(OCH_3)_2$	CH_3	CH_3

that were dissimilar to those of the hallucinogen 5-methoxy-N,N-dimethyltryptamine (5-OMeDMT; **59**). Administration of either **22** or **24** to rats trained to discriminate 5-OMeDMT from saline did not result in stimulus generalization (84). 7-Methoxytryptamine displayed weak behavioral activity in animals (124).

Tryptamines that are unsubstituted on the terminal amine are good substrates for oxidative deamination by MAO. Furthermore, it has been demonstrated that tryptamine and 5-methoxytryptamine cross the blood-brain barrier with great difficulty; administration of 50 mg/kg 5-methoxytryptamine to rats results in a low brain/plasma ratio when measured 15 min postadministration (242).

N-Monoalkyltryptamines are another group of agents that have not received much attention. N-Methyltryptamine (**27**) and its 5-methoxy derivative **36** have been detected as constituents of plant materials used by certain South American Indians as hallucinogenic snuffs (109). Because these plant materials are also known to possess the established hallucinogens N,N-dimethyltryptamine (DMT; **37**) and 5-OMeDMT and since neither N-methyltryptamine (**27**) nor 5-methoxy-N-methyltryptamine (**36**) has been studied in the pure form, the effect of these latter two agents in man is presently unknown.

Like tryptamine, N-methyltryptamine (**27**) had some serotonin agonist activity, as measured using the isolated rat uterus preparation (227); in the rat fundus preparation, however, it possessed one-half the serotonin receptor affinity of tryptamine (75). DeMontigny and Aghajanian (49) compared the effects of microiontophoretic application of 5-methoxytryptamine and 5-OMeDMT (**59**) on the firing of serotonin-containing neurons of the midbrain raphe nucleus and on two postsynaptic brain areas that receive serotonin input from the raphe. Certain similarities were found in that both agents tended to exert more of an effect on the presynaptic neurons. The authors discussed the behavioral implications of these findings.

N-Methyltryptamine (**27**) was found to have no effect on the acquisition of avoidance behavior (240). Brimblecombe (23) compared the behavioral effects of a series of N-monoalkyltryptamines and N,N-dialkyltryptamines using Hall's open-field test. Although there was no clear-cut structure-activity relationship,

the dialkyl derivatives tended to be more active than their monoalkyl counterparts when the alkyl group was small. That is, the monomethyl, ethyl, propyl, and isopropyl derivatives **27–30** were less active than DMT (**37**), DET (**38**), DPT (**39**), and DIPT (**40**), respectively. The opposite was true for N-butyltryptamine (**31**) and N-benzyltryptamine (**33**). In cats, N-benzyltryptamine (**33**) was less active than either DMT or DET in disrupting operant behavior, while administration of N-ethyltryptamine (**28**) produced aggressive behavior (25). Many of the above agents also produced hyperthermia in animals (23). Cerletti and co-workers (29) found that tryptamine inhibited the knee-jerk reflex in spinal cats, while N-methyltryptamine had no effect; 4-hydroxy-N-methyltryptamine (**34**) also inhibited the reflex, while 4-hydroxy-N-ethyltryptamine (**35**), like psilocin (**49**), augmented the reflex response. There was no indication of behavioral disturbance with the 4-hydroxy-N-monoalkyl derivatives.

Misztal (148) prepared 5-methoxy-N-methyltryptamine (5-OMeN-MeT; **36**) for the purpose of pharmacologic evaluation, but no data were reported. Smythies and co-workers (210) reported that 5-OMeN-MeT was much less active than either DMT or 5-OMeDMT in disrupting the conditioned avoidance response in rats. Taborsky and McIsaac (229) also found 5-OMeN-MeT to be less active than 5-OMeDMT. These latter authors further demonstrated that 5-OMeN-MeT was rapidly and nearly quantitatively metabolized by MAO to 5-methoxyindole acetic acid. Julia and Manoury (123) investigated 5-methoxy and 6-methoxy derivatives of N-monoalkyl-substituted tryptamines. Both 5-OMeN-MeT and 5-methoxy-N-isopropyltryptamine (**30**) produced a significant hyperthermic effect in rabbits. N-Cyclopropyltryptamine and its 5-methoxy (248), 7-methoxy (248), 5,6-dimethoxy (34), and 6,7-dimethoxy (34) derivatives have been reported to be inhibitors of MAO, but none of these agents has been evaluated for behavioral activity.

In summary, primary amine and monoalkyl derivatives of tryptamine have not yet been demonstrated to produce hallucinogenic effects in man or to consistently produce profound behavioral effects in animals. Admittedly, relatively few compounds have been examined, and few studies have been conducted. Nevertheless, present evidence suggests that these derivatives, by virtue of their inability to penetrate the blood-brain barrier and/or their rapid metabolism, may not be able to achieve adequate brain levels to elicit effects. In some cases, these factors may lead to masking of potential central effects by peripheral actions of the compounds or their metabolites.

N,N-Dialkyl Derivatives

One of the best studied tryptamine derivatives is DMT (**37**). DMT and 5-OMeDMT (**59**) are probably the active constituents of a variety of South American hallucinogenic snuffs. These and related indolealkylamines have been detected in members of at least five different plant families: Agaricaceae, Leguminosae, Malpighiaceae, Myristicaceae and Rubiaceae (107,109,110,187). In

man, DMT is hallucinogenic at total intramuscular doses of 50 to 100 mg, with the normal dose being approximately 1 mg/kg. Gillin et al. (70) have reviewed human studies with DMT up to 1976; their review included results of trials on more than 150 subjects. While active by parenteral administration or by inhalation (i.e., by smoking or as a snuff), DMT was without activity at a total oral dose of 350 mg (235). The onset of effects after intramuscular administration is usually quite rapid (2–5 min), and the duration of action is relatively brief (about 1 hr). This time course closely follows the blood levels of DMT, with a 50 mg dose resulting in a maximal concentration of 100 ng/ml whole blood (69). There appears to be some question with respect to the minimal effective dose of DMT. Turner and Merlis (235) noted that inhalation of 5 to 20 mg DMT powder was essentially without behavioral effect, and that intravenous administration of 5 to 25 mg led to anxiety and restlessness but not (except for one subject) to disorientation or visual disturbances. On the other hand, Bickel et al. (18) reported that intramuscular doses of less than 20 mg (i.e., 0.25 mg/kg) were capable of producing altered states of consciousness, including hallucinogenic episodes; and Meltzer et al. (147) have recently reported that 50 mg DMT produced psychotomimetic effects. Thus the threshold dose of DMT in man is probably between 20 and 50 mg.

Szara and co-workers (221,223,225) noted psychotomimetic activity for N,N-diethyltryptamine (DET; **38**) at a dose of 1 mg/kg. In at least one study (223), the effects of DET were found to be unpleasant. In a study involving 71 subjects, DET produced behavioral effects at intramuscular doses of approximately 50 mg (0.65 to 0.85 mg/kg) (19). The duration of action of DET was somewhat longer (about 3 hr) than that of DMT. Interestingly, some subjects in the latter study reported, in contrast to Szara's findings, that DET produced a euphoric effect. Szara has suggested that this might be a dose-related phenomenon.

N,N-Dipropyltryptamine (DPT; **39**) is also hallucinogenic in man at 1 mg/kg (222). It has been employed as an adjunct to psychotherapy (97,179,216,217), and, therefore, more information is available concerning dose-effect relationships. The threshold dose for the induction of psychologic effects is in the 10 to 15 mg range, parenterally. There is loss of reality contact with doses greater than 30 mg, although doses of up to 165 mg have been used in psychotherapy (97,217). The onset of effects (5–20 min) is slightly longer than that for DMT, and the duration of action of DPT is dose dependent (1.5–6 hr) (97).

Branching of the propyl groups results in N,N-diisopropyltryptamine (DIPT; **40**), which is orally active at 20 to 50 mg (202). N,N-Dibutyltryptamine (DBT; **41**) and N,N-dihexyltryptamine (DHT; **42**) have been examined only briefly. At 1 mg/kg, DBT produced only slight perceptual, emotional, and thinking disturbances in man, while DHT at the same dose was completely inactive (222).

Although DMT, DET, and DPT are relatively similar in potency, insufficient dose-effect data make it difficult to draw structure-activity conclusions. Additional information can be obtained from animal studies. Szara and co-workers (224)

found that with respect to increasing spontaneous locomotor activity in mice, DPT was slightly more active than DET, which was, in turn, somewhat more active than DMT. Both DBT (**41**) and DHT (**42**) decreased locomotor activity. In producing hyperthermia in rabbits, DPT was more active than DMT or DET, and DBT was the least active of the four compounds.

The compound DMT is capable of producing a hyperactivity syndrome in animals, the head-twitch response in mice (44), limb-flick behavior in cats (119,120), and the "serotonin syndrome" in rats (211). In such assays, tryptamine (**22**) was found to be inactive (119), while DET was approximately twice as active as DMT (210). In a recent drug discrimination study, the effects of DMT, DET, DPT, and DIPT were directly compared in rats. The order of potency was DPT > DIPT > DET > DMT, with ED_{50} values of 7.8, 9.2, 9.6, and 20.2 μmoles/kg, respectively (83,91). Numerous other reports concerning the activity of these agents have not lent themselves to interagent comparisons, or different routes of administration have been employed within a series. Nevertheless, the above results suggest that, with respect to simple dialkyl substitution, the order of potency (on a molar basis), at least in various animal studies, is DPT > DET > DMT. There is probably no more than a two- or threefold difference in potency among this series. As the size of the alkyl groups is increased beyond propyl, activity decreases. Branching of the alkyl groups does not abolish activity and, in the case of DIPT (**40**), may even increase potency. The effect of branching has not been well studied, however, and too few data are available to make any definitive statements.

Cyclic analogs of DMT and DET, i.e., **43** and **44,** respectively, have been synthesized; the aziridine **43** appears to possess activity as a CNS depressant (171), while the pyrrolidine **44** displays some behavioral activity. Compound **44** was active in Hall's open-field test but was less active than DET (**38**) (23). In attempts to measure hyperthermic activity, **44** was found to be rather toxic in rabbits (111). Oddly enough, no cyclic analog has ever shown activity/potency comparable to its acyclic counterpart. Thus, based only on scant animal data, cyclization of the lower dialkyl homologs apparently does not lead to marked behavioral activity.

The complete role of N,N-dialkyl substitution is not fully understood, although it serves to enhance blood-brain barrier permeability and to hinder metabolic inactivation.

Ring-Substituted N,N-Dialkyl Derivatives

N,N-Dialkyltryptamines bearing an alkyl substituent on the aromatic nucleus have not been evaluated in man, and only data from animal studies are available. Taborsky et al. (228) found 1-methylation to have variable effects on behavioral activity. This might reflect blood-brain barrier permeability. Methylation at the N1 position of DMT (**37**), to give 1,N,N-trimethyltryptamine (1-TMT), had

little effect on serotonin receptor affinity, as measured in the rat fundus preparation, but decreased its behavioral activity in rats (73,93). Similarly, 1-methylation of 5-OMeDMT (**59**) also led to decreased behavioral potency (16).

Methylation at the 2-position of a variety of unsubstituted and 5-substituted N,N-dialkyltryptamines afforded agents with weak *in vitro* activity as serotonin antagonists (30), but behavioral activity was not studied. Methylation of the 2-position of DET (**38**) decreased its behavioral activity (20). Both the 5-methyl and 7-methyl derivatives of DMT, i.e., 5-TMT (**45**) and 7-TMT (**47**), respectively, were somewhat more potent than DMT in tests of discriminative control of responding in rats, using 5-OMeDMT as the training drug (93); 6-TMT (**46**) produced saline-like effects at comparable doses (86). Using DOM as the training drug, the order of potency was DET = 4-TMT (**48**) > 7-TMT (**47**) > DMT; 7-methylation of 5-OMeDMT did not adversely affect potency (91,252).

Hydroxylation of N,N-dialkyltryptamines can either increase or decrease hallucinogenic potency, depending on the position of the hydroxyl group. Psilocin (**49**), 4-hydroxy-N,N-dimethyltryptamine, is the best studied of the hydroxylated N,N-dialkyltryptamines. Psilocin and its phosphate ester psilocybin are the active components of several species of hallucinogenic mushrooms. Evidence suggests that Aztec and other Indians may have used such mushrooms (*teonanacatl*) in various ceremonial rituals as long as 3,000 years ago (see refs. 24, 106, 154, and 176 for detailed discussions on psilocin). Psilocin and psilocybin are active in man at oral doses of approximately 8 to 12 mg, with psilocin being somewhat more active than its ester on a weight basis. As such, psilocin is about eight times more potent than DMT. Homologation of psilocin to 4-hydroxy-N,N-diethyltryptamine (4-OH DET; **50**) has little effect on human potency, as does replacement of one of the methyl groups by an isopropyl group (i.e., 4-hydroxy-N-methyl-N-isopropyltryptamine, **51**) (196). Replacement of both methyl groups by isopropyl groups (i.e., 4-hydroxy-N,N-diisopropyltryptamine, **52**) apparently halves activity (196).

Psilocin has also been the object of considerable investigation using animals as subjects. Much of the initial work with psilocin, as well as other 4-hydroxytryptamine derivatives with alterations in the side chain and/or terminal amine, was performed at Sandoz Laboratories in Switzerland (29,245). Subsequent investigations have shown that psilocin produces hyperthermia in rabbits (113), induces the head-twitch in mice (43), disrupts acquisition of avoidance behavior in rats (240), increases startle response magnitudes in rats (68), increases limb-flick behavior in cats (120), and produces discriminative stimulus effects in rats similar to those of 5-OMeDMT (**59**) (93).

The 5-hydroxy derivative of DMT, bufotenine, or N,N-dimethyl-serotonin, is another naturally occurring tryptamine found to occur in South American snuffs. Intravenous administration of bufotenine (**53**) was reported by Fabing and co-workers (59,60) to be hallucinogenic in man. This finding is in conflict with a later report by Turner and Merlis (235). Apparently, due to its low lipid

solubility (65), bufotenine does not readily cross the blood-brain barrier (64,183). The initial observations made by Fabing et al. (59,60) may be the result of peripheral toxic manifestations.

Bufotenine has been found to be behaviorally inactive, or only weakly active, in most animal studies, although at 15 mg/kg, it did produce the head-twitch resonse in mice (43). It was also behaviorally active in experiments in which the blood-brain barrier was bypassed (78). Acylation of the polar hydroxy group of bufotenine increases its lipid solubility (65,74) and apparently enhances its ability to cross the blood-brain barrier (64). For example, 0-acetylbufotenine (5-acetoxy-N,N-dimethyltryptamine; **54**) disrupted conditioned avoidance behavior in rodents (65) and produced tremorigenic activity similar to that elicited by DMT (**37**) or 5-OMeDMT (**59**) when administered to mice (64). In this latter study, a comparison of brain levels of bufotenine after administration of 0-acetylbufotenine with those of DMT and 5-OMeDMT revealed bufotenine to be the most active of the three agents, based on brain concentration. The pivaloyl ester of bufotenine also appears to possess behavioral activity, since stimulus generalization was observed when this agent was administered to animals trained to discriminate 5-OMeDMT from saline (74).

There are only two reports of the human evaluation of a 6-hydroxylated N,N-dialkyltryptamine. Szara and Hearst (223) studied the effects of 6-hydroxy-N,N-diethyltryptamine (6-OH-DET; **56**) in a single subject. Doses of 1 and 2 mg were inactive; a 5-mg dose produced a short-lasting perceptual disturbance; and a 10-mg dose, after 1 hr, produced some psychotomimetic disturbances. Rosenberg et al. (182) compared the activity of DMT with that of 6-OH-DMT (**55**) in five human subjects. While DMT was active, the 6-hydroxy derivative was found to be inactive at intramuscular doses of approximately 50 to 75 mg. At a dose of 10 mg/kg, 6-OH-DMT (**55**) increased spontaneous activity in mice more so than a comparable dose of DMT; 6-OH-DET (**36**) was essentially equiactive with DET in this respect (224). In most other animal studies, however, 6-hydroxylation of DMT has been observed to result in a decrease or complete loss of behavioral activity (228,236–238). The behavioral potency of 5-OMeDMT (**59**) was also reduced by 6-hydroxylation (226). 7-Hydroxy-N,N-dimethyltryptamine (7-OH-DMT; **57**) has not been evaluated in man. At an intraperitoneal dose of 33 μM/kg, 7-OH-DMT displayed no behavioral effects in rats (228). The pharmacologic effects of all four hydroxylated derivatives of DMT, psilocin (**49**), bufotenine (**53**), 6-OH-DMT (**55**), and 7-OH-DMT (**57**) have been compared in studies by Taborsky et al. (228) and by Cerletti et al. (29).

4-Methoxy-N,N-dimethyltryptamine (4-OMeDMT; **58**) has been examined only in animal studies and has shown behavioral activity roughly comparable to that of DMT (65,236,238). It also produced discriminative stimulus effects similar to those of 5-OMeDMT with a potency somewhat less than that of DMT but greater than that of either 6-OMeDMT (**71**) or 7-OMeDMT (**72**) (93). In drug discrimination studies using DOM as the training drug, 4-OMeDMT was more active than DMT but less active than DET (91).

5-Methoxy-N,N-dimethyltryptamine (0-methylbufotenine; **59**) is hallucinogenic in man at a parenteral dose of approximately 6 mg (204). Numerous animal studies have shown that 5-OMeDMT is behaviorally quite active (16,65–67,71,178,184). This compound also produced limb-flick behavior in cats (119) and the "serotonin syndrome" in rats (209). Glennon et al. (85) demonstrated that 5-OMeDMT serves as a discriminative stimulus in rats and have employed rats trained to discriminate 5-OMeDMT from saline to investigate the structure-activity relationships of various substituted N,N-dialkyltryptamine derivatives. The results of these studies have recently been reviewed (84).

In man, 5-methoxy-N,N-diisopropyltryptamine (5-OMeDIPT; **63**) appears to be equipotent with 5-OMeDMT (**59**) and is orally active (202). With the exception of these two agents, no other 5-methoxy-N,N-dialkyltryptamines have been studied in man. Several derivatives, including compounds **60–63,** possess behavioral activity in animals (25,65,93,111). In a drug discrimination study using DOM as the training drug, the following order of potency was reported: 5-OMeDET (**61**) > 5-OMeDIPT (**63**) > 5-OMeDMT (**69**) (91).

Kline et al. (132) have recently prepared the 4,5-methylenedioxy derivatives of DMT and DIPT, **64** and **65,** respectively, as well as the isomeric 5,6-methylenedioxy compounds **66** and **67.** The diisopropyl derivatives **65** and **67** were more active in disruption of behavior than their corresponding dimethyl derivatives. The 4,5-methylenedioxy group conferred higher activity than did the 5,6-methylenedioxy. Kline et al. (132) also evaluated the 4-, 5-, and 6-methylthio derivatives of DMT, **68, 69,** and **70,** respectively, and found 5-SMeDMT (**69**) to be the most active of the three. In a drug discrimination study, Glennon et al. (89) compared 4- and 5-methoxy DMT with their methylthio counterparts and obtained the following ranking of potency: 5-OMeDMT (**59**) > 5-SMeDMT (**69**) > 4-OMeDMT (**58**) > 4-SMeDMT (**68**).

The 6- and 7-methoxy derivatives of DMT, **71** and **72,** respectively, display a low order of behavioral activity in animals (65,86,91,93,124). 5,7-Dimethoxy-N,N-dimethyltryptamine (**73**) was much less active than 5-OMeDMT (**59**) in tests of discriminative control of behavior in rats (86). Nir et al. (170) have reported that 4,5,6- and 5,6,7-trimethoxy DMT, **74** and **75,** respectively, produced unique and long-lasting behavioral effects in rodents.

Side Chain-Altered N,N-Dialkyl Derivatives

Four alterations of the side chain of N,N-dialkyltryptamines have been studied: (a) hydroxylation, (b) shortening, (c) lengthening, and (d) branching. Hydroxylation of the side chain of N,N-dialkyltryptamines ordinarily leads to a decrease in potency (228), as does shortening the chain to one carbon to give the gramines **76** (R = H, n = 1 and R = OMe, n = 1). While these compounds appear to possess some central activity (103), their effects are probably different than those of N,N-dimethyltryptamines. In a recent drug discrimination study, 5-meth-

oxygramine was found to produce effects that were dissimilar to those produced by its homolog 5-OMeDMT (91).

Lengthening of the side chain of DMT by a single methylene group produces N,N-dimethylhomotryptamine (DMHT; **76,** R = H, n = 3), which produced hyperthermia when administered to rabbits (7,232) but was found to be inactive in man (235). Intravenous administration of 5 and 10 mg and intramuscular injection of 20 to 70 mg DMHT was without psychologic effect in 10 human subjects (235). Additional studies on DMHT homologs (i.e., **76,** n = 4–10) did not show any interesting activity (7,232).

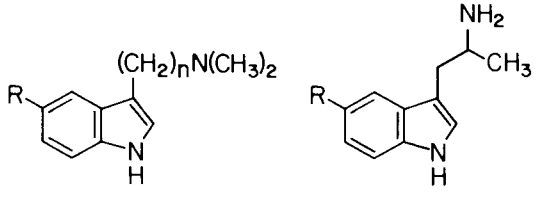
Alpha-methylation of DMT reduced its behavioral activity in animals, while alpha-methylation of N-methyltryptamine (**27**) resulted in an agent with stimulant properties (137,228). Alpha-methyltryptamine (α-MeT; structure 77), however, is hallucinogenic in man at doses of about 30 mg. Thus it is two to three times more active than DMT (for review see refs. 24, 81, and 196). 5-Methoxy-α-methyltryptamine (5-OMe-α-MeT; **78**) was also determined to be twice as active in man as its dialkyl counterpart, 5-OMeDMT. In human trials, 5-OMe-α-MeT produced behavioral effects at about 3 mg (204). A comparison of the activities of the individual isomers of **78** in man has not been reported. However, Glennon and co-workers (76,83,90) found that the (+)-isomers of both α-MeT and 5-OMe-α-MeT are more active than their racemates in tests of discriminative control of behavior in rats. Although (+)-5-OMe-α-MeT was four times more active than its enantiomer, (−)-α-MeT did not produce effects similar to either racemic α-MeT or 5-OMeDMT.

Homologation of the α-methyl group of α-MeT results in compounds with central activity but activity that may be different from that of α-MeT. Alpha-ethyltryptamine, for example, has been used in man as an inhibitor of MAO. However, hallucinogenic activity was not evident (see refs. 24 and 106 for more details).

Structure-Activity Relationship Summary

Based on the foregoing discussion, it is possible to formulate some structure-activity relationships with respect to the behavioral properties of various tryptamine derivatives. It should be noted that these structure-activity relationships are derived from the results of both human and animal studies.

Tryptamine and its N-monoalkyl derivatives are behaviorally inactive, or, at



Structures 76, left; right 77: R=H; **78:** R=OCH_3.

best, only weakly active. This is probably a consequence of their rapid metabolism and/or their inability to penetrate the blood-brain barrier. N,N-dialkyltryptamine derivatives, where the alkyl groups vary from methyl to propyl, are active, with the dipropyl derivative being slightly more active than the dimethyl compound. Branching of the dipropyl groups (i.e., diisopropyl) appears to allow retention of activity. Dialkyl substituents larger than propyl tend to reduce activity.

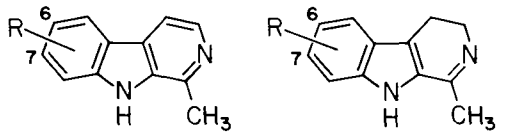
Methylation of N,N-dimethyltryptamines at either the 1-, 2-, or 6-position decreases potency, while methylation at the 5- or 7-position seems to have relatively little effect on activity. The 4-hydroxy derivatives of DMT appear to be the only hydroxy compound to show appreciable activity. The 5-, 6-, and 7-hydroxy isomers are either less active or inactive. Methylation of these hydroxy groups to yield the corresponding methoxy derivatives has different effects, depending on the position of the substituent. Methylation of the 4-hydroxy group decreases potency, while methylation of the 5-hydroxy group increases activity dramatically. The 6- and 7-methoxy derivatives are less active than either the 4- or 5-methoxy isomers.

Both shortening and lengthening of the alkyl side chain result in decreased activity. While alpha-methylation of N,N-dialkyltryptamines reduces activity, alpha-methylation of the primary amines results in agents that are more active than their corresponding N,N-dimethyl counterparts. Further homologation of the alpha-methyl group decreases activity.

Beta-Carbolines

Most discussions of hallucinogens have paid little attention to the beta-carbolines. There are several reasons for this, not the least of which is their relative difficulty of synthesis and consequent general unavailability for detailed study. Furthermore, the effects of the beta-carbolines in man seem to differ qualitatively from that of LSD or mescaline. Nevertheless, a great deal of attention has recently been directed toward beta-carbolines. While most of this renewed interest has been centered on their potential anxiogenic or anxiolytic activity, recent reports have indicated possible pharmacologic similarities between certain beta-carbolines and LSD (38,91,168). Since the pharmacology of hallucinogenic beta-carbolines has not been well characterized, it seemed appropriate to review this class of compounds, which has a long and rich folkloric history.

The beta-carbolines are structurally related to the tryptamines, except that the aminoethyl side chain has been cyclized to form a tricyclic structure. Here again, several members of this class of compounds are naturally occurring. Certain South American Indian tribes prepare a hallucinogenic beverage, variously known as Ayahuasca, Caapi, and Yage, from, principally, the malpighiaceous vine *Banistereopsis caapi* (186). Closely related plants and admixtures have also been employed (2,51,57,108,109,152,153,180,185). Numerous beta-carboline derivatives have been detected and/or isolated from these plants, including harmine (**79**), harmaline (**80**), and tetrahydroharmine (**81**)



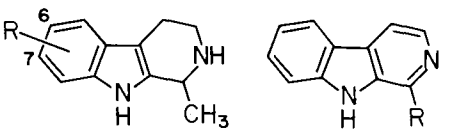
Structure 23. Left: 79: R=7-OCH_3, **84:** R=6-OCH_3; **Right: 80:** R=7-OCH_3; **85:** R=6-OCH_3.

(5,11,109,152,180,185) Structures **23, 24.** Harman (**82**) and norharman (**83**) have been isolated from cigarette smoke (175), and Janiger and deRios (122) have suggested that some of the tobacco-induced altered states reported by South American Indians might be related to the cumulative effects of these beta-carbolines.

A series of early pharmacologic studies on beta-carboline derivatives employing both human and nonhuman subjects was reported by Gunn (99) in 1935. Ho (102) has reviewed the general pharmacology of beta-carbolines, and Buckholtz and Boggan (26) have reviewed their structure-activity relationships as inhibitors of MAO. More recently, Muller et al. (150) have investigated the binding of various beta-carbolines to serotonin, dopamine, opiate, cholinergic, and benzodiazepine binding sites, and Ninan and co-workers (169) have reported that the ethyl ester of beta-carboline-3-carboxylic acid has a high affinity for benzodiazepine receptors in the brain and produces a behavioral syndrome in monkeys that may provide a useful animal model of human anxiety.

A positional isomer of harmaline, 6-methoxyharmalan (**85**), was found to be slightly more active than harmaline in disrupting conditioned avoidance behavior in rats (146). Gryglewski and co-workers (98) found that replacement of the 1-methyl group of 6-methoxytetrahydroharman (**86**) by aryl substituents diminished excitatory behavior and resulted in a series of agents that produced a generalized depressant effect.

In tests of discriminative control of behavior in rats using DOM (1.0 mg/kg) as the training drug, Glennon et al. (83,91) found that administration of harmaline and 6-methoxyharmalan, but not harmine, resulted in stimulus generalization. 6-Methoxyharmalan was somewhat more potent than either its positional isomer **80** or DMT (**37**). The ED_{50} values determined for **85, 80,** and **37** were 5.13, 6.19, and 5.80 mg/kg, respectively. In a similar study using animals trained to discriminate LSD (0.1 mg/kg) from saline, Nielsen et al. (168) found that harman produced saline-like effects at 3 mg/kg, while tetrahydro-beta-carboline (7.1 mg/kg), 6-methoxytetrahydro-beta-carboline (approximately 10 mg/kg), and harmaline (8 mg/kg) produced 69, 70, and 54% LSD-appropriate responding, respectively. The effect of higher doses was not explored.



Structure 24. Left: 81: R=7-OCH_3; **86:** R=6-OCH_3; **Right: 82:** R=CH_3; **83:** R=H.

In a single trial with one human subject, 200 mg harmine (**79**) produced a mild hallucinogenic response that included auditory buzzing and visual distortion (138). In a study employing a larger number of human subjects, it was determined that intravenous administration of harmine produced hallucinogenic effects in five of 11 subjects. The threshold dose was estimated as being 150 to 200 mg (173). Higher doses were not investigated because of the incidence of bradycardia and hypotension. Harmine was inactive when administered orally (up to 960 mg) or subcutaneously (40–70 mg) (173).

Harmaline (**80**) appears to be about twice as active as its fully saturated counterpart harmine (152). Naranjo (151,152) determined that harmaline was effective at intravenous doses of 1 mg/kg and at total oral doses of 300 to 400 mg. In a limited study, tetrahydroharmine (**81**) was found to be approximately one-third as active as harmaline, with an oral dose of 300 mg producing an effect similar to that of 100 mg harmaline (152). Repositioning of the 7-methoxy group of harmaline to the 6-position gives 6-methoxyharmalan (**85**). This compound was active at oral doses of approximately 100 mg (1.5 mg/kg). Reduction to the tetrahydro counterpart, 6-methoxytetrahydroharman (**86**), resulted in a compound with about one-third the potency of the parent 6-methoxyharmalan (152). Rivier and Lindgren (180) have estimated that a 200 ml portion of Ayahuasca contains 30 mg harmine, 10 mg tetrahydroharmine, and 25 mg DMT. Based on the potencies of **79** and **81,** together with the finding that beta-carbolines are inhibitors of MAO, it may be that the effects of such concoctions are due to the presence of DMT as a result of its decreased metabolism by the beta-carbolines. The effects produced by hallucinogenic beverages that contain harmaline may be a direct result of the presence of harmaline. This interesting class of agents certainly warrants additional study.

In summary, based on the results of relatively limited studies, the dihydro beta-carboline, harmaline (**80**), is more active than either its fully unsaturated derivative harmine (**79**) or its reduced derivative tetrahydroharmine (**81**). The positional isomer of harmine, 6-methoxyharmalan (**85**), is slightly more potent than harmaline. Reduction to the tetrahydro derivative **86** reduces potency. Although thorough dose-effect studies have not yet been performed, none of the beta-carboline derivatives has been found to be significantly more potent than DMT (**37**).

Lysergic Acid Derivatives

The most potent of the known hallucinogenic agents is LSD. It is orally active in man at doses of about 0.1 mg (0.05 to 0.25 mg). The vast majority of human studies involving LSD and its structural variants were performed in the 1950s and 1960s and have been reviewed in great detail (24,154,196,208). Therefore, some of the key structure-activity relationships are briefly highlighted here only for the sake of completeness.

Lysergic acid diethylamide possesses two asymmetric centers, one at the 5-position and the other at the 8-position; its absolute configuration is 5*R*, 8*R*. Inversion of the configuration at either of these centers essentially abolishes hallucinogenic activity. From a potency standpoint, LSD can withstand almost no structural variation without at least reduction, if not total loss, of activity. The 1-acetyl derivative of LSD is reportedly equivalent in activity to the parent compound but evidently is readily hydrolyzed *in vivo* to yield LSD. Shortening of the diethylamide to a dimethyl, methyl, ethyl, or monoethyl amide reduces potency by at least 10-fold; lengthening has a similar effect. Cyclization of the diethylamide to a pyrrolidine diminishes activity by an order of magnitude. Reduction of the 2,3-double bond also reduces activity by almost an order of magnitude, while reduction of the 9,10-double bond abolishes activity. The bromination of LSD yields 2-bromo-LSD (BOL). This compound not only lacks hallucinogenic activity but can block the effects of a subsequently administered dose of LSD.

It is surprising that the most potent of all the hallucingens should possess such a rigid structural requirement. Conversely, it may be this rigid requirement that accounts for its unique potency. Relatively little has been reported on the structure-activity relationships of LSD derivatives. This is probably a direct consequence of the difficult task of preparing such compounds.

CONCLUSION

Attempts to discuss the structure-activity relationships of phenylalkylamine and indolealkylamine hallucinogens are stymied by the paucity of human hallucinogenic data. This is further complicated by the subjective nature of the response being measured and by the general lack of good dose-effect studies. On the other hand, discussions of structure-activity relationships may resort to including the results of animal studies, where larger numbers of structural modifications have been examined and where dose-response data are usually collected. However, here exists another problem: Is there any relationship between human hallucinogenic activity/potency and any measure of activity using animals as subjects? Surprisingly enough, there can be considerable qualitative, if not quantitative, agreement between the human data and certain recent animal studies (84). Nevertheless, caution is advised in interpreting structure-activity relationships derived from limited human studies or from animal data.

Taken together, the data presented here show that many phenyl- and indolealkylamines are hallucinogenic in man and behaviorally active in animals. In both series, primary amines penetrate the blood-brain barrier with difficulty, although this seems to be more of a problem with tryptamines (and even N-monoalkyltryptamines) than with phenethylamines. This situation is somewhat alleviated in the presence of an alpha-methyl substituent. The primary amines are also prone to rapid metabolism by oxidative deamination. Metabolism, however, can be impeded by the presence of an alpha-methyl or N-alkyl function.

Compounds such as LSD or the beta-carbolines do not possess a primary amino group, are not rapidly metabolized in comparison to, for example, tryptamine, and enter the brain readily; certain substituent groups can alter this situation. Members of the phenylalkylamine and indolealkylamine families of hallucinogens can produce similar effects in animals but may be capable of producing distinctive effects in man. As yet, there is no satisfactory and comprehensive structure-activity relationship that encompasses both major classes of compounds. This may be due in part to unique metabolic and distributional characteristics associated with the individual ring systems.

From the foregoing discussion, it is apparent that progress is being made in our understanding of these compounds. Nevertheless, a great deal of work remains to be done. While there appear to be correlations between hallucinogenic activity and the ability of tryptamine derivatives to displace [^{3}H]-LSD or serotonin in receptor binding assays, this is not true for phenethylamines. Phenethylamine derivatives generally have low affinity for these sites. Electrophysiologic studies have also failed to identify an anatomic or physiologic basis for the action of phenethylamine-type hallucinogens. Although it is generally believed that the phenethylamines act through a serotonergic mechanism, and this is supported by neurochemical and *in vitro* studies, their locus of action remains obscure. Therefore, continuation of structure-activity studies remains of high importance, particularly for the phenethylamines. Well-designed series of congeners, when the human psychopharmacology is also well defined, will be extremely useful. Such compounds can be studied and their neurochemical effects compared. Their receptor binding properties can be evaluated, and physicochemical and pharmacokinetic parameters can be measured. This information could lead to a much clearer understanding of the relative importance of all these factors and the significance of the various possible component processes in the overall drug effect.

Furthermore, additional work must be done with enantiomers and diastereoisomers in order to completely characterize the stereochemical requirements of the receptor(s) involved. Comparisons between the biologic activities of such isomers, where physicochemical and pharmacokinetic factors are nearly equal, can lead to important insights. Consider, for example, how the knowledge that it is the *R* enantiomer of the hallucinogenic amphetamines that is most active has affected our approach to comparing the structures of the phenethylamines to that of LSD. Furthermore, labeling of such isomers with radionuclides may well help to identify anatomic sites involved in hallucinogenic drug action. One might note that, as of this writing, the simple experiment of comparing the regional brain distribution of the *R* and *S* [^{3}H]-labeled enantiomers of DOM has not even been carried out.

We are still confronted by a list of interesting and important questions that have not been answered. To what extent are dopamine pathways involved in hallucinogenic drug action? What is the relative importance of presynaptic versus postsynaptic serotonergic action? Is the release of endogenous neurotransmitters

an important factor? If so, which transmitters are involved? Given the similarity in structure between mescaline and the catecholamines, is there an as yet unidentified role for norepinephrine receptors in the action of mescaline? With the more sophisticated tools and methods now becoming available to neuropharmacologists, these questions become more amenable to detailed study.

These and many other questions are best answered when one has in hand a series of compounds that differ not only in potency but also in qualitative effect. Only in this way can statistical, theoretical, and modern quantitative and qualitative analytic methods be applied to offer the most meaningful interpretation of the results and to appreciate fully the subtle relationships between molecular structure and biologic effect. Indeed, in this case, we need these compounds to define what is even meant by "biologic effect."

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Common Neurochemical Correlates to the Action of Hallucinogens

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Hallucinogens are defined by their ability to induce distorted auditory, visual, and tactile sensations and hallucinations, i.e., dreamlike episodes in the awake state in humans. In many respects, the symptoms produced by hallucinogens are qualitatively similar to those seen in certain types of psychotic illness, notably schizophrenia. This leads most authors to the postulate that the functional disorders triggered by these drugs are closely related to those occurring in the central nervous system (CNS) of schizophrenic patients. On this basis, investigations on the central biochemical alterations produced by hallucinogens have two main goals: (a) to understand the cellular and molecular mechanisms of action of these drugs and to design appropriate pharmacologic treatments to counteract hallucinogen intoxication in addicts, and (b) to obtain some information regarding the possible functional disorders in the brain of psychotic patients. Limitations to these ambitious goals are obvious, however, since experimental studies concern exclusively animal species, mainly the rat, in which hallucinations are only hypothesized in light of the behavioral disturbances produced by the drugs causing true hallucinations in man. Nevertheless, biochemical investigations in the cerebrospinal fluid (CSF) of schizophrenic patients undergoing hallucinatory episodes and postmortem studies on the brain of psychotic patients support the theory, since the alterations in monoaminergic neurotransmission in these patients are apparently similar to those induced by the administration of hallucinogenic drugs to animals. Such observations confirm that studies on neurotransmitter metabolism in animals treated with these drugs might be a valuable approach to understand the etiology of hallucinations associated with mental illness in man.

Hallucinogens comprise a heterogeneous family of drugs, including indoles [*d*-lysergic acid diethylamide (LSD), 5-methoxy-N,N-dimethyltryptamine (DMT), bufotenine, psilocybin, and derivatives], phenylethylamines [mescaline, 2,5-dimethoxy-4-methylamphetamine (DOM or STP), and other methoxyamphetamines], anticholinergic agents [scopolamine and the glycolate esters ditran and N-methylpiperidyldiphenyl glycolate hydrochloride (A 1111)], opiates interacting with the sigma type of receptors [mainly benzomorphans, such as N-

allylnorcyclazocine (SKF 10,047)], phencyclidine (PCP), cannabinoids [Δ^9-tetrahydrocannabinol (THC) and derivatives] and even a γ-aminobutyric acid (GABA) agonist (muscimol). Efforts to detect a common structural feature in these molecules were largely unsuccessful. The similar behavioral alterations induced by these drugs has led to the suggestion that they share the same target in the CNS. In this chapter, I analyze first the investigations that led to the discovery of neuronal pathways and receptors specifically involved in the action of hallucinogens. In addition, I describe the hallucinogen-induced alterations of neurotransmitter metabolism within these neuronal pathways and discuss whether such changes are directly associated with hallucinations or correspond only to secondary effects of these drugs.

BIOCHEMICAL INVESTIGATIONS ON THE CENTRAL TARGET(S) OF HALLUCINOGENS

Deoxyglucose Studies

Owing to the technique developed by Sokoloff and his colleagues (111), any treatment-induced changes in cerebral glucose utilization can be visualized directly in brain sections. Briefly, this technique consists of an intravenous injection of a labeled, nonmetabolizable analog of glucose, ^{3}H-2-deoxyglucose, 30 to 45 min before death. Animals are then decapitated and their brain frozen and sectioned. Tissue sections are processed for autoradiography, which allows the identification of neuronal structures and pathways that have accumulated the labeled molecule. Since the uptake and retention of ^{3}H-deoxyglucose depend on the metabolic activity of neurons, any qualitative or quantitative change in the autoradiographic image of brain sections indicates an alteration in neuronal activity. The application of this technique to explore the neuronal targets of hallucinogens has been performed notably for PCP. Thus Meibach et al. (76) noted both increases and decreases in glucose consumption in various brain regions following the administration of PCP to rats. A general increase was observed in limbic areas, particularly the molecular layer of the regio superior of the hippocampus, the subicular cortex, the frontal cortex, the cingulate gyrus, and the anteroventral nucleus of the thalamus. In contrast, a marked reduction in glucose consumption was detected in the inferior colliculi. More recently, Crosby et al. (20) and Hammer et al. (43) carried out similar studies with ketamine, an anesthetic agent structurally related to PCP and that also can evoke hallucinations. These authors noted a marked enhancement of ^{3}H-deoxyglucose accumulation in limbic areas (cingulate gyrus, hippocampus) and a reduction in the inferior colliculi and auditory and sensorimotor cortex. Whereas anesthesia is undoubtedly associated with this reduction in auditory and somatosensory areas, the emotional disorders following ketamine administration likely involve the activation of the limbic systems. Indeed, the more pronounced disturbances of thought, perception, and mood induced by PCP

are associated with marked changes in ^{3}H-deoxyglucose accumulation also in these structures (76).

At least for PCP (and ketamine), studies using the ^{3}H-deoxyglucose technique indicate that sensory and limbic areas are involved in the action of hallucinogens. Indeed, limbic structures play a key role in the integration of sensory inputs, so that hallucinogens, disturbing their normal functioning, in fact, induce abnormal sensations. In this respect, it can be concluded that data obtained with the ^{3}H-deoxyglucose technique only confirm the conclusion drawn from previous behavioral and electrophysiologic investigations.

Binding Studies with Labeled Ligands

Recently, considerable progress has been made in the knowledge of neurotransmitter receptors, owing to the use of labeled ligands binding specifically to these receptors either *in vitro*, in brain membranes, or *in vivo* following their peripheral injection. One major extension of these studies consisted of looking for possible specific sites binding radioactive drugs with high affinity in brain membranes. The application of such techniques allowed the discovery of receptors for drugs, such as opiates and benzodiazepines, which do not interact directly with known neurotransmitter receptors. In the case of hallucinogens, binding studies were initially conducted with a view to discovering the single receptor from which these drugs induce their central effects (31). Although binding studies invalidated the naive concept of a unique "hallucinogen receptor," they provided considerable information regarding the likely targets of hallucinogens in the CNS.

^{3}H-LSD

In vitro studies

Using ^{3}H-LSD as the ligand (Table 1), Farrow and Van Vunakis (31) found a specific high affinity site (K_D = 9 nM) only in the cerebral cortex of the rat. Binding of ^{3}H-LSD to cortical fractions was inhibited by high concentrations of numerous hallucinogens (e.g., mescaline, psilocin, DMT, bufotenine) but not by their nonhallucinogenic congeners (e.g., L-LSD and L-isolysergic acid amide). In addition to hallucinogens, serotonin (5-HT) bound also to this site. These findings were confirmed and extended by Bennett and Snyder (9), who reported that, in addition to at least some hallucinogens, 2-bromo-LSD (BOL), a nonhallucinogenic derivative of LSD, was as potent as LSD itself in displacing ^{3}H-LSD specifically bound to brain membranes. Moreover, Lovell and Freedman (72) showed that hallucinogens of other chemical series, such as PCP and THC, did not displace ^{3}H-LSD specifically bound to membranes from the rat forebrain.

Such observations were obviously inconsistent with the original idea (31) of ^{3}H-LSD binding specifically to a receptor for hallucinogens. Comparing the

TABLE 1. *Main characteristics of ^{3}H-LSD- and ^{3}H-PCP-specific binding sites in the rat brain*

Parameter	^{3}H-LSD	^{3}H-PCP
K_D	3–10 nM	46 nM–0.25 μM
Regional distribution[a]	Cerebral cortex ≥ Hippocampus ≥ Striatum	Hippocampus ≥ Cerebral cortex ≥ Striatum
Putative endogenous ligand	5-HT, LDF (?)	Angel dustin (peptide)
Up regulation[b]	Raphe lesion	?[d]
Down regulation[c]	Chronic LSD treatment Chronic amphetamine treatment	?

[a] The three regions indicated for each ligand correspond to those containing the highest densities of related specific binding sites.

[b] Up regulation of ^{3}H-LSD binding (i.e., an increase in the B_{max}) was found in the hippocampus 2 weeks after 5-HT-depleting radiofrequency heat lesions of the midbrain dorsal and median raphe nuclei (103).

[c] Down regulation of ^{3}H-LSD binding (i.e., a decrease in the B_{max}) occurred in the forebrain and brainstem plus spinal cord of rats treated with LSD (100 μg/kg every 6 hr) for 4 days (116). A significant reduction of ^{3}H-LSD binding was noted in the corpus striatum and frontal cortex of rats continuously treated with amphetamine for 5 days (82).

[d] No data are available concerning the possible *in vivo* regulation of ^{3}H-PCP binding sites.

regional distribution of ^{3}H-LSD binding sites to that of ^{3}H-5-HT synaptosomal uptake, Bennett and Snyder (9) reached the conclusion that these sites in fact might correspond to 5-HT receptors. Furthermore, as ^{3}H-LSD binding did not disappear following the degeneration of serotonergic neurons, the authors proposed that ^{3}H-LSD labeled postsynaptic 5-HT receptors.

Numerous investigations using ^{3}H-LSD as a ligand were performed, which extend the initial conclusion of Bennett and Snyder (9). Except in the caudate nucleus, where ^{3}H-LSD also binds to dopamine (DA) receptors (127) and in the cerebral cortex where some binding may occur to β-adrenergic receptors (25), two types of 5-HT sites, called 5-HT_1 and 5-HT_2, seem to be equally labeled by ^{3}H-LSD in most brain areas (87). The 5-HT_1 receptors bind specifically ^{3}H-5-HT with a high affinity (K_D = 1–4 nM) and exhibit generally higher affinities for 5-HT agonists than for antagonists (10,81,87). In contrast, the postsynaptic 5-HT_2 sites, which can be labeled by ^{3}H-antagonists (^{3}H-spiperone, ^{3}H-ketanserin, ^{3}H-mianserin, and ^{3}H-metergoline), have higher affinities for 5-HT antagonists than for 5-HT and related agonists (46,70,87). In the frontal cortex, the total number of ^{3}H-LSD binding sites is equal to the sum of 5-HT_1 and 5-HT_2 receptors.

The selective blockade of 5-HT_1 receptors by 300 nM 5-HT reduces the number of ^{3}H-LSD binding sites to the B_{max} of 5-HT_2 receptors and, conversely, the occupancy of 5-HT_2 receptors by 30 nM of spiperone allows the binding of ^{3}H-LSD to sites qualitatively and quantitatively similar to the 5-HT_1 receptors (87). Because of this specific interaction of LSD with 5-HT receptors, the hallucinogen can be used as a probe for *in vitro* studies on such receptors in various

preparations. Thus Walker et al. (123) reported the successful photoaffinity labeling by ^{3}H-LSD of two proteins (molecular weights, 36 K and 100 K daltons) likely related to 5-HT receptors in fluke membrane fractions exposed to ultraviolet light. The application of the same methodology to rat brain membranes should provide fundamental information on the chemical structure of central 5-HT receptors in mammals.

The ^{3}H-LSD binding sites also can be investigated in brain slices. Briefly, tissue sections are incubated with ^{3}H-LSD, washed to eliminate the radioactivity entrapped in nonspecific sites, dried, and exposed to tritium-sensitive film (77,83). The main advantage of this autoradiographic technique over *in vitro* investigations with brain membranes lies in the more precise anatomic distribution that can be observed. Thus Meibach et al. (77) noted that ^{3}H-LSD binding occurs preferentially in the hippocampus, particularly in the CA_1 area and in the gyrus dentatus, whereas CA_2 and CA_3 regions are sparsely labeled. Another region that was carefully examined is the cerebral cortex (83). Using ^{3}H-LSD as a ligand, Palacios (83) confirmed that the hallucinogenic agent binds to both 5-HT_1 and 5-HT_2 postsynaptic receptors. Furthermore, he found that 5-HT_2 receptors are mainly located in lamina IV of the frontal cortex (and of other DA-rich cortical areas), whereas 5-HT_1 receptors are distributed mainly in the deeper layers V and VI in the entorhinal cortex. In the rat (77), as well as in humans (84), the autoradiographic visualization of brain slices incubated with ^{3}H-LSD revealed that the dorsal raphe nucleus contains a high density of specific binding sites for the hallucinogen. This observation supports numerous electrophysiologic studies which indicate that serotonergic raphe cells are highly sensitive to LSD administration. A marked inhibition of neuronal firing occurs after either the local (intraraphe) application of LSD or after its peripheral administration (42). Even in this region, ^{3}H-LSD apparently does not bind to a specific hallucinogen receptor, since partial pharmacologic investigations suggest that these sites in fact are closely related to 5-HT_1 receptors (*unpublished observations*). Indeed, autoradiographic studies with ^{3}H-5-HT as the labeled ligand provide pictures of the raphe area similar to those obtained with ^{3}H-LSD (12).

In addition to the pharmacologic properties and regional distribution of ^{3}H-LSD binding sites in the CNS, *in vivo*-induced modulations of these sites confirm further that they correspond to functional 5-HT receptors. Thus Seeman et al. (103) reported an increased density of ^{3}H-LSD binding sites in the hippocampus following the rather selective degeneration of serotonergic innervation in raphe lesioned rats. In contrast, a reduction in ^{3}H-LSD binding sites occurs after the chronic administration of LSD (116) or amphetamine (82). Parallel up (103) and down (116) regulations of ^{3}H-5-HT (5-HT_1) binding sites are found under such experimental conditions.

In vivo studies

The regional distribution of LSD after its peripheral administration was examined by Snyder and Reivich (109) in squirrel monkeys. They reported that

20 min after the intravenous infusion of LSD (0.5–2.0 mg/kg), maximal accumulation occurs in the pituitary gland, followed by the visual and auditory areas (lateral geniculate, superior colliculi, medial geniculate, inferior colliculi), hypothalamus, and limbic areas (amygdala, hippocampus). Similar findings were then published by Diab et al. (23). Apart from the choroid plexus, which accumulates the highest concentrations of ^{3}H-LSD, the hippocampus, cerebral cortex, caudate nucleus, and midbrain raphe were found to contain significant accumulations of radioactivity following the intravenous injection of ^{3}H-LSD (23). More recently, Duchemin et al. (27) performed a detailed quantitative analysis of ^{3}H-LSD accumulated in various brain areas of mice treated with the labeled hallucinogen. They noted that the specific *in vivo* binding of ^{3}H-LSD was maximum in the cerebral cortex, followed by the striatum, hippocampus, and hypothalamus. Careful pharmacologic investigations led Duchemin et al. (27) to the conclusion that the binding of ^{3}H-LSD to cortical areas involves 5-HT receptors.

Possible endogenous ligands of ^{3}H-LSD binding sites

In conclusion, *in vitro* as well as *in vivo* studies with ^{3}H-LSD revealed that specific sites which bind the labeled hallucinogen do exist in brain. These sites apparently do not correspond to receptors for hallucinogens but to specific postsynaptic receptors for 5-HT. It can be inferred that serotonergic synapses may be a preferential target for hallucinogens, at least for those of the LSD series. As discussed below, numerous biochemical investigations on brain 5-HT metabolism confirm this hypothesis.

Although 5-HT is undoubtedly a natural ligand of the ^{3}H-LSD specific binding sites, other substances may interact with these sites. This is notably the case for 5-methoxytryptamine, an hallucinogenic indole found in brain under exceptional circumstances (8). In addition, Mehl et al. (75) found other nonidentified substances, called LSD-displacing factors (LDF), in the human CSF which effectively inhibit the specific binding of ^{3}H-LSD to pig brain membranes. The main component of these fractions has a molecular weight of about 500. It is heat stable and resistant to proteolysis (with pronase). In contrast to 5-HT and other indoleamines, possible candidates as endogenous ligands of ^{3}H-LSD binding sites, this compound has acidic characteristics. Since the concentration of LDF in the CSF is higher in unmedicated, acute psychotic patients and hallucinating alcoholics, these molecules may correspond to some endogenous hallucinogens (75). Their interaction with ^{3}H-LSD sites is complex, since they exert a noncompetitive inhibition of the ligand binding. Similar observations have been made by Fillion et al. (32) with respect to the LSD-5-HT interactions: the hallucinogen noncompetitively inhibits ^{3}H-5-HT binding; reciprocally, 5-HT is a noncompetitive inhibitor of ^{3}H-LSD binding to rat brain membranes. Such data suggest that ^{3}H-LSD binds to specific sites undergoing possible allosteric modulations by closely related accessory sites. Whether a particular conformation

of ^{3}H-LSD binding sites is selectively involved in the hallucinogenic action of this drug deserves further investigation.

^{3}H-PCP

In vitro studies

Whereas large doses of PCP (Table 1) produce anesthesia in humans (this drug was initially proposed as an anesthetic), low doses induce a drugged state associated with auditory hallucinations (50). When emerging from anesthesia, patients describe a confusional state, vivid dreaming, and hallucinations, i.e., symptoms typical of schizophrenia. Furthermore, in contrast to LSD, PCP greatly exacerbates schizophrenic symptoms for up to several weeks (50). Because of the wide use of PCP by addicts (the common name of PCP is "angel dust") and of the close similarity between PCP-induced behavioral disturbances and schizophrenia, numerous studies were conducted recently in order to explore the central mechanism of action of this drug. With respect to LSD, investigators looked for a putative receptor of hallucinogens using ^{3}H-PCP as a ligand.

Two groups succeeded in the identification of specific binding sites for ^{3}H-PCP in the rat brain (121,130). According to these authors, the whole brain contains specific ^{3}H-PCP binding sites characterized by a K_D of 0.15 to 0.25 μM and a B_{max} of 1.5 to 2.4 pmoles/mg membrane protein. Although different regional distributions have been described by Vincent et al. (121) and Zukin and Zukin (130), both groups mentioned that the cerebral cortex, striatum, and hippocampus were among those regions containing higher densities of ^{3}H-PCP binding sites. In contrast, the brainstem, cerebellum, and spinal cord are relatively poor in ^{3}H-PCP binding sites. Difficulties in examining the pharmacologic properties of these sites arose from the fact that ^{3}H-PCP showed high adsorbance to almost any surface, notably the GF/B filters used for binding assays. Indeed, Maayani and Weinstein (73) detected a specific binding site for ^{3}H-PCP in these filters having a K_D of 0.28 μM and the same apparent properties as those found in brain membranes. Nevertheless, several groups managed to eliminate this artifact and could identify reliably central PCP receptors (47,121a). In particular, they could distinguish clearly these sites from those found in the periphery (121a). Affinities of the central binding site for PCP derivatives but not those of the peripheral site are correlated with the efficacies of these drugs to induce ataxia, as measured with the rotarod test (121a). However, the final demonstration of the existence of central ^{3}H-PCP specific sites was achieved when Quirion et al. (94) confirmed that the labeled drug binds differently to various brain areas, as visualized directly on the autoradiographic images of brain slices previously incubated with the ligand. As observed with membranes, Quirion et al. (94) noted that ^{3}H-PCP binds most densely to cortical areas, diffusely in neocortex, and somewhat heterogeneously in the laminae of the hippocampal formation and dentate gyrus. The highest levels of specific ^{3}H-PCP binding in the rat brain

were found in the zone superficial to the pyramidal and granule cell layers of the hippocampus (94).

In addition to providing detailed information on the regional distribution of ^{3}H-PCP specific sites, autoradiographic studies on brain slices incubated with the labeled ligand offer the advantage of exploring the actual pharmacologic characteristics of these sites. Since filtration (of membranes) is not used for these investigations, the results allow the definition of the pharmacologic profile of purely central ^{3}H-PCP binding sites with no artifactual contamination by some ligand binding to glass fiber filters. In addition to PCP analogs, including ketamine, three classes of drugs effectively inhibit ^{3}H-PCP binding to central sites: (a) muscarinic agonists and antagonists [oxotremorine, scopolamine, atropine, (94)], sigma opiate ligands [N-allylnorcyclazocine or SKF-10,047, cyclazocine, and, to a lesser extent, metazocine and pentazocine (94)], and calcium antagonists (29,95). To which of these series could the actual ligand of ^{3}H-PCP binding sites belong?

The effects of muscarinic drugs are not surprising, since PCP itself possesses muscarinic antagonist properties (64). This is not the only action of PCP regarding cholinergic neurotransmission; Eldefrawi et al. (28–30) also demonstrated that PCP blocks the ionic channel coupled to nicotinic receptor. However, the apparent affinity of ^{3}H-PCP binding sites is relatively low for cholinergic ligands [the lowest IC_{50} is that of oxotremorine: 9 μM, a value 10^2 times higher than that of PCP (94)]. Furthermore, PCP is far more potent than muscarinic antagonists, such as scopolamine and atropine, in evoking hallucinations; the reverse is true when considering the anticholinergic properties. A recent study by Johnson (60) established that even after a large systemic dose, PCP does not reach sufficiently high levels in the brain to inhibit muscarinic receptors. Accordingly, the hallucinogenic action of PCP cannot derive simply from its antagonistic action on cholinergic neurotransmission.

In contrast, the possibility that ^{3}H-PCP binding sites in fact correspond to sigma opiate receptors is more substantiated (131). Of a large number of opiates tested, cyclazocine-like compounds are the most potent in inhibiting ^{3}H-PCP binding. In addition, PCP and its derivatives can displace ^{3}H-cyclazocine bound to its lowest affinity (K_D = 70 nM) sigma site. Behavioral data also support the hypothesis that PCP can interact with sigma opiate receptors; Holtzman (53) found that rats trained to respond to PCP in a discriminative stimulus paradigm generalize not only to ketamine but also to cyclazocine and SKF-10,047, two known agonists at sigma opiate receptors. These observations led to the conclusion that PCP triggers hallucinations by interacting with the sigma opiate receptor. Indeed, other sigma agonists also exert strong hallucinogenic effects (131).

Recently, two groups (29,95) reported that Ca^{2+} antagonists (D 600, cinnarizine, verapamil) inhibit ^{3}H-PCP binding to its specific sites with K_I ranging between 0.1 and 2 μM. Furthermore, the cations La^{3+} and Co^{2+}, which are known blockers of the Ca^{2+} channel, also inhibit the specific binding of

^{3}H-PCP, with IC_{50} lower than 1 mM (29). Therefore, ^{3}H-PCP binding sites might be functionally related to a Ca^{2+} channel. Although further investigations will be necessary to prove this relationship, it must be emphasized that some pharmacologic effects of PCP are efficiently counteracted by Ca^{2+} antagonists. Thus the potent contractile responses produced by PCP on isolated basilar and middle cerebral arteries can be completely prevented by a low dose (1 μM) of verapamil (4). Since the similar cerebrovasospasm induced by other hallucinogens of the indole (LSD) and phenylethylamine (mescaline) series is also prevented by verapamil (4), changes in the Ca^{2+} fluxes through cell membranes might correspond to pharmacologic effects common to most if not all hallucinogens.

Possible endogenous ligands of ^{3}H-PCP binding sites

Following the reasoning made for opiates and for benzodiazepines, the discovery of specific binding sites for an exogenous molecule, PCP, led to speculation about the existence of endogenous PCP-like compounds in brain. Such binding sites may be accessory allosteric sites and not true receptors, thereby questioning the requirement for endogenous ligands. This criticism is particularly relevant to PCP binding sites, since data indicate they have properties similar to those of the allosteric site coupled to the nicotinic receptor. Indeed, drugs interacting with this accessory site, such as phenothiazines and local anesthetics, are potent inhibitors of ^{3}H-PCP binding to synaptic membranes (1,2,30,120). Nevertheless, Pert et al. (90) reported the successful extraction from the porcine hippocampus of a peptide called "angel dustin," which displaces bound ^{3}H-PCP in a dose-dependent manner. Its regional distribution is closely parallel to that of ^{3}H-PCP binding sites (hippocampus > cerebellum > striatum > brainstem). Furthermore, the unilateral injection of this peptide into the rat substantia nigra induces PCP-like rotational behavior (90). Careful examination of the pharmacologic properties of angel dustin should determine whether the putative endogenous ligand of PCP binding sites is in fact a sigma opiate ligand and/or a compound that interacts specifically with Ca^{2+} channels.

In conclusion, the respective regional distributions, pharmacologic properties, and putative endogenous ligands of PCP and LSD binding sites (Table 1) clearly demonstrate that these sites are completely distinct. Indeed, PCP does not inhibit ^{3}H-LSD binding (72), and LSD does not interact with ^{3}H-PCP-specific sites (131). Therefore, the extensive binding studies using ^{3}H-LSD and ^{3}H-PCP as the labeled ligands indicate unequivocally that hallucinations do not involve the interaction of psychotomimetic drugs with a unique class of receptors in brain.

Other Labeled Hallucinogens

Amphetamines

Although amphetamine itself is not a hallucinogen after acute administration, it provokes a syndrome analogous to schizophrenia, including pseudohallucin-

atory episodes during chronic intoxication. Furthermore, methoxy derivatives of amphetamine are well-known hallucinogenic drugs (mescaline, DOM). Recently, binding studies with two related labeled ligands—^{3}H-amphetamine itself (85) and ^{3}H-β-phenylethylamine (49)—showed the presence of specific sites for these drugs in brain membranes. The regional distributions of these two categories of sites are clearly distinct from those binding ^{3}H-LSD or ^{3}H-PCP, since maximal binding of ^{3}H-amphetamine and ^{3}H-β-phenylethylamine occurs in the hypothalamus and brainstem. Pharmacologic investigations indicated that the low affinity site for ^{3}H-amphetamine (K_D = 300 nM) recognizes anorexic agents and, therefore, would mediate the anorexic activity of amphetamine (85). Whether the high affinity sites for ^{3}H-amphetamine (K_D = 93 nM) and ^{3}H-β-phenylethylamine (K_D = 55 nM) are involved in the psychotomimetic action of some amphetamine derivatives remains to be explored.

In vivo studies on the brain accumulation of ^{3}H-2,5-dimethoxy-4-methylamphetamine (^{3}H-DOM) following its intravenous injection to adult cats also revealed marked regional differences. Interestingly, ^{3}H-DOM was particularly concentrated in the hippocampus, amygdala, hypothalamus, medial and lateral geniculate bodies (57). These regions involved in the transfer (geniculate bodies) and processing (hippocampus) of sensory messages are also those exhibiting significant modifications in ^{3}H-2-deoxyglucose accumulation following the administration of hallucinogens.

Cannabis derivatives

A few studies have been conducted on cannabis and its derivatives. Alozie et al. (3) measured the radioactivity accumulated in various brain areas following the intravenous injection of ^{3}H-THC, ^{3}H-cannabinol, and ^{3}H-cannabidiol to adult male rats. Five minutes after injection, these three labeled compounds exhibited a homogeneous distribution in brain, suggesting that no specific binding occurred. Such studies must be completed by examining the time course of the evolution of ^{3}H-cannabis derivatives in various brain areas before any firm conclusion can be drawn.

Muscimol

In contrast to the two preceding classes of hallucinogens, muscimol, a constituent of the mushroom *Amanita muscaria,* has been the subject of abundant literature directly related to its interaction with brain membranes. *In vitro* binding studies with ^{3}H-muscimol revealed the presence of specific sites having a regional distribution (cerebellum > cerebral cortex > hippocampus) completely different from those of ^{3}H-LSD and ^{3}H-PCP binding sites but closely related to GABAergic innervation (21). Indeed, muscimol is a potent GABA agonist, and its tritiated derivative is an appropriate ligand to label central GABA receptors (17,18). Determinations of the respective numbers of specific sites labeled with ^{3}H-GABA and ^{3}H-muscimol revealed that the latter ligand binds to more numerous sites than ^{3}H-GABA in the rat brain. Although biochemical studies confirmed that some relationships exist between the central action of hallucinogens and GABAergic systems (67–69,86), one wonders whether these extra sites, besides GABA receptors, are involved in the hallucinogenic action of muscimol.

Conclusion

In vitro and *in vivo* binding studies with ^{3}H-labeled hallucinogens showed the existence of specific binding sites for these drugs in the CNS of animals and humans. No relationship can be found, however, between the respective sites for ^{3}H-LSD, ^{3}H-PCP, and ^{3}H-muscimol. In contrast to the hypothesis proposed by neurobiologists in the early 1970s, the psychotomimetic action cannot result from the interaction of hallucinogens with a putative unique "hallucinogen" receptor.

Careful analyses of the pharmacologic properties of ^{3}H-hallucinogen binding sites indicated that they may correspond to 5-HT receptors (in the case of ^{3}H-LSD), sigma opiate receptors (in the case of ^{3}H-PCP), or even GABA receptors (in the case of ^{3}H-muscimol). Such data recall that hallucinogens should interfere markedly with the metabolism of neurotransmitters in the CNS. These hallucinogen-induced alterations of neurotransmitter metabolism and functions are summarized below.

EFFECTS OF HALLUCINOGENS ON THE METABOLISM AND FUNCTIONS OF NEUROTRANSMITTERS IN THE CNS

Although hallucinogens have several primary targets (as shown by binding studies with ^{3}H-derivatives of these drugs), their common pharmacologic properties might result from a similar action on a given neuronal circuit more or less distant from this primary site. Studies on hallucinogen-induced changes in neurotransmitter metabolism in various brain regions should be particularly relevant for identifying this neuronal circuit. The measurement of the turnover rates of neurotransmitters in hallucinogen-treated rats has led to convergent hypotheses regarding, first, the neuronal populations that are selectively affected by hallucinogens and, second, the neurochemical alterations produced by most if not all of these drugs.

Effects of Hallucinogens on Nonmonoaminergic Systems

As discussed, PCP, ditran, and scopolamine exert anticholinergic action. This property apparently is not linked to the hallucinogenic action of these molecules, however, since other hallucinogens, such as LSD and mescaline, do not affect cholinergic systems in doses sufficient to provoke hallucinatory-like behaviors in animals (67). Nevertheless, Revuelta et al. (96) noted a decreased turnover

of acetylcholine in the hippocampus following the administration of low doses of THC to rats; accordingly, a reduction in the central cholinergic tone may be involved in the action of at least some hallucinogens.

The story of the possible involvement of histamine in the hallucinogenic action of drugs began with the discovery, 20 years ago, by Siva Sankar et al. (105) that LSD increases the levels of this amine in the 12,000 × *g* pellet (crude synaptosomal pellet) of isotonic homogenates of the rabbit cerebrum. In contrast, Leonard and Tonge (69) noted that PCP treatment does not change histamine levels in the rat brain. Despite such differential effects of drugs belonging to distinct chemical series, a possible link between histamine and most hallucinogens has been postulated in the CNS. Thus Green et al. (40) reported that LSD inhibits competitively the histamine H_2 receptors coupled to adenylate cyclase in the hippocampus and cerebral cortex of guinea pigs. More recently, Fredrickson and Richelson (33) found that not only LSD but also mescaline, DOM, psilocybin, bufotenine, and DMT are more potent antagonists of histamine H_1 than of H_2 receptors. However, other observations deny any correlation between the histamine-antagonist properties and hallucinogenic potency. Green et al. (40) noted that BOL, a nonhallucinogenic ergot compound, is 10 times more potent than LSD itself as an antagonist of H_2 receptors. Furthermore, well-known hallucinogens, such as psilocin (up to 10^{-4} M) and mescaline (up to 10^{-3} M) do not block H_2 receptors in brain. More generally, it can be concluded that the blockade of histamine receptors is not typical of hallucinogens, since other drugs, such as most antidepressants, also exhibit marked antihistamine properties (44). Histamine antagonism, therefore, is a secondary effect of some of these drugs, which is clearly unrelated to their hallucinogenic action.

Since muscimol is a potent GABA agonist (21), one may infer that GABAergic neurotransmission plays some role in the central effects of hallucinogens. A reduction in GABA levels has been noted in the whole brain 30 and 60 min after the administration of a large dose of PCP (10 mg/kg i.p.) to rats (69). Regional studies on glutamic acid decarboxylase (GAD) revealed that the subacute administration to rats of large doses of PCP (5–10 mg/kg i.p.) induces a slight decrease (−20%) in the GABA-synthesizing enzyme activity only in the cerebellum (86). Such fragmentary data obviously are not sufficient to draw conclusions about the possible participation of GABAergic processes in the central action of hallucinogens. Similarly, the fact that muscimol exacerbates psychotic symptoms in schizophrenic patients (113) is not enough to conclude that hallucinatory episodes involve GABAergic neurotransmission in those patients. Indeed, muscimol is rapidly catabolized *in vivo,* leading to the formation of active compounds possibly not acting on GABA receptors (21). Accordingly, the possible involvement of GABAergic neurons in hallucinations deserves further investigation.

As shown by binding studies with ^{3}H-PCP, some relationship exists between the hallucinogenic action of this drug and the sigma class of opiate receptors (131). Indeed, sigma opiates of the cyclazocine series are themselves potent

hallucinogens. This led to the postulate that hallucinatory episodes may involve endogenous opiates in psychotic patients. In support of this assumption, Watson et al. (124,125) and Gunne et al. (41) observed that naloxone, a potent opiate antagonist, produced decreases in auditory hallucinations in some schizophrenic patients. Other investigators, measuring CSF by radioimmunoassay, have shown increased levels of β-endorphin-like material in paranoid schizophrenic subjects with auditory hallucinations (26). These observations lend some support to a dysfunctioning of endogenous opiate mechanisms in hallucinating patients. This conclusion should also apply to animals, since the chronic administration of antipsychotics, such as haloperidol, has been shown to increase immunoreactive met-enkephalin (55) and β-endorphin (52) levels in several brain areas in rats. In contrast, the acute administration of PCP induced a significant reduction in met-enkephalin levels in the medulla oblongata/pons and the midbrain of mice (79). Such modifications did not occur after the chronic administration of the drug (10 mg/kg i.p. daily for 6–7 days); instead, a 42% increase in met-enkephalin levels was noted in the striatum of PCP-treated mice (80). Whether such changes were related to the psychotomimetic action of PCP treatment seems improbable, since another drug producing hallucinatory-like episodes under chronic conditions, e.g., amphetamine (4.5 mg/kg per day for 5 days), did not affect met-enkephalin levels in various brain areas (cerebral cortex, striatum, hippocampus, hypothalamus, brainstem) in rats (48). Obviously, further neurochemical investigations are required to assess the possible role of endogenous opiates in the mechanism of action of hallucinogens.

Effects of Hallucinogens on Monoaminergic Systems

Because experimental studies are still fragmentary and inconclusive, no clear functional relationship can yet be deduced regarding the effects of hallucinogens on nonmonoaminergic neurons. In contrast, numerous investigations have been devoted to hallucinogen-induced alterations of monoaminergic neurotransmission, thereby providing a greater opportunity for a typical pattern to emerge. Whether this pattern involving exclusively monoaminergic neurons is enough to account for the hallucinogenic action of most if not all hallucinogens will remain an unsolved question until appropriate studies on nonmonoaminergic systems are performed.

Effects of LSD on Serotonergic Neurons

The possible effects of hallucinogens on central monoaminergic neurons were first explored by Freedman (34), who discovered that a single injection of LSD increases 5-HT levels in the rat brain, whereas its inactive congener BOL fails to affect brain 5-HT. Since this change is associated with a decrease in the concentration of the main metabolite of 5-HT, 5-hydroxyindole acetic acid (5-HIAA) (Fig. 1), Rosecrans et al. (98) postulated that LSD administration in

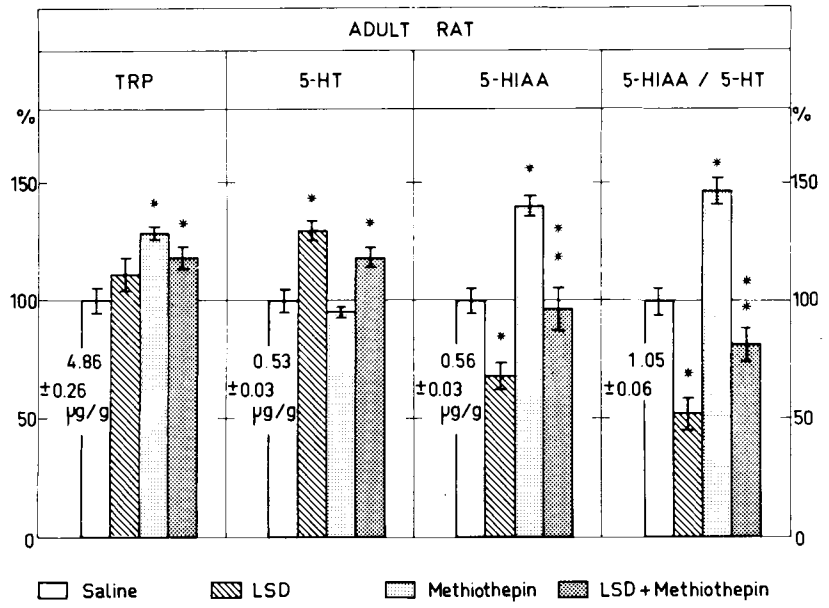

FIG. 1. Reversal by a 5-HT antagonist (methiothepin) of changes induced by LSD administration on indole levels in the whole brain of adult rats. LSD alone (2 × 1 mg/kg i.p. 120 and 100 min before death) induced a significant reduction of the 5-HIAA/5-HT ratio, indicating a marked decrease in 5-HT turnover. This effect was almost entirely suppressed by the combined treatment with the potent 5-HT antagonist methiothepin (20 mg/kg i.p. 110 min before death). Therefore, 5-hydroxyindole alterations due to LSD involve the direct stimulation of 5-HT receptors by the hallucinogen. *Bar*, mean ± SEM of six determinations. * $p < 0.05$ when compared with saline-treated rats; ** $p < 0.05$ when compared with rats treated with LSD alone.

fact induces a slowing down of 5-HT turnover in the CNS. These results were confirmed by various neurochemical approaches. Thus LSD treatment has been shown to reduce the rate of 5-hydroxytryptophan (5-HTP) accumulation in various brain areas following the blockade of aromatic amino acid decarboxylase (AAD) by benserazid (15). This effect, indicative of a partial inhibition of 5-HT synthesis by LSD, was also found by several authors (71,101,104) who demonstrated that the conversion of ^{3}H-tryptophan into ^{3}H-5-HT in brain is significantly delayed following the acute administration of the drug to rats.

Furthermore, LSD reduces the rate of 5-HT disappearance following 5-HT synthesis inhibition by parachlorophenylalanine or alpha-propyldopacetamide (5). More direct investigations revealed that LSD administration induces a decrease in the *in vivo* release of ^{3}H-5-HT synthesized *in situ* from ^{3}H-tryptophan (36,51). Owing to a highly sensitive radioenzymatic microassay, Ternaux et al. (114) succeeded in measuring endogenous 5-HT released from the caudate nucleus in cats and proved that LSD exerts a direct inhibitory effect on the *in vivo* release of the indoleamine.

These findings corroborate electrophysiologic data which indicate that LSD triggers a selective inhibition of neuronal firing within 5-HT-containing cells in the anterior raphe nuclei (42). Accordingly, *in vivo*-induced changes in 5-HT turnover might be considered to be the consequence of the direct neuronal inhibition exerted by LSD acting on serotonergic cell bodies (and dendrites). Several observations do not fit with this interpretation, however. Pieri et al. (92) noted that the direct infusion of LSD into the medial and dorsal raphe nuclei of rats does not affect 5-HT turnover in the forebrain; in addition, Díaz and Huttunen (24) reported that the behavioral tolerance produced by repeated LSD administration to rats is associated with a persistent increase in brain 5-HT turnover, whereas Trulson et al. (115) found a depressant effect of LSD on 5-HT cell firing within the anterior raphe nuclei even after chronic treatment with the hallucinogen. Therefore, the 5-HT receptor involved in the LSD-induced reduction in 5-HT synthesis (Fig. 1) is not that mediating the cessation of nerve impulse flow within serotonergic neurons. Since the *in vitro* addition of 1 μM LSD does not affect the conversion of ^{3}H-tryptophan into ^{3}H-5-HT by hippocampal and striatal slices (45), the hallucinogen-induced change in 5-HT synthesis cannot result from some interaction of the drug with presynaptic autoreceptors located on 5-HT terminals. It can be postulated, therefore, that LSD-induced reduction in 5-HT synthesis involves a long negative feed-back loop triggered by postsynaptic 5-HT receptors. This would explain why LSD treatment does not affect 5-HT synthesis in the rat forebrain when neuronal circuits are either immature at birth (15) or destroyed by a cerebral transsection (63).

In the case of ^{3}H-5-HT release, the reduction noted in LSD-treated rats probably results from a direct effect of the drug on 5-HT terminals, since *in vitro* experiments with brain slices have shown that the addition of LSD (≥0.01 μM) to the incubating medium produces a significant decrease in the K^+- or electrically induced release of the labeled neurotransmitter [either newly synthesized from ^{3}H-tryptophan (see Fig. 2) or previously taken up into 5-HT terminals] (14,15,45,62,65). This effect probably results from an interaction of LSD with a specific receptor, since the nonpsychotomimetic isomer *l*-LSD does not affect the Ca^{2+}-dependent release of ^{3}H-5-HT from serotonergic terminals (14). As noted for the interaction of LSD at the postsynaptic level, the receptor involved is probably serotonergic, since 5-HT antagonists, such as methiothepin and metergoline, counteract the action of LSD on ^{3}H-5-HT release (14,15). Recently, we succeeded in labeling the presynaptic 5-HT autoreceptor using ^{3}H-8-hydroxy-N,N-dipropyl-2-aminotetralin (^{3}H-PAT) as a ligand (39). We observed that LSD concentrations required to displace the ligand bound to this receptor (Fig. 3) were in the same range as those inhibiting significantly the release of ^{3}H-5-HT from brain slices (*unpublished observations*).

In conclusion, LSD reduces the rate of 5-HT synthesis and release by stimulating 5-HT receptors. Those controlling 5-HT synthesis are probably post-

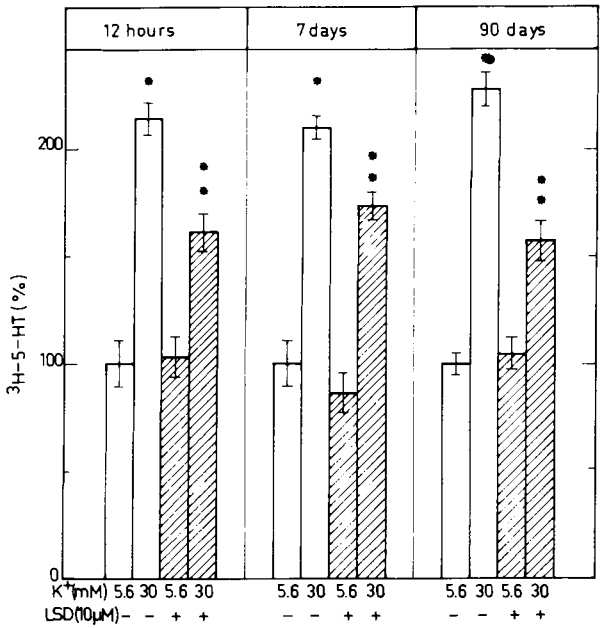

FIG. 2. Effects of LSD on the spontaneous and K^+-induced release of newly synthesized ^{3}H-5-HT in brainstem slices of 12-hr-, 7-day-, or 90-day-old rats. At the end of a 30 min incubation with ^{3}H-tryptophan (0.56 μM) under conditions indicated in the abscissa, ^{3}H-5-HT was measured separately in tissues and medium. The ratio (^{3}H-5-HT%) of ^{3}H-5-HT found in medium over that in tissues is expressed in percentage of that calculated for brainstem slices incubated in normal Krebs-Henseleit medium (K^+ = 5.6 mM) in the absence of LSD. *Bar,* mean ± SEM of six to eight separate determinations. * $p < 0.05$ when compared with control values (K^+ = 5.6 mM, no LSD); ** $p < 0.05$ when compared with values found with slices incubated in K^+-enriched medium in the absence of LSD.

synaptic whereas the presynaptic autoreceptors are involved in the LSD effects on 5-HT release. These neurochemical changes seem to be correlated with the hallucinogenic action since behavioral tolerance to LSD is associated with alterations in 5-HT receptors (116) and metabolism (24) making 5-HT synapses much less sensitive to the drug. Furthermore, behavioral studies demonstrated that LSD effects in rats are undoubtedly mediated by serotonergic processes (106).

Effects of LSD on Catecholaminergic Neurons

The serotonergic system is not the only monoaminergic neuronal population affected by LSD; numerous reports also mention that the turnover of catecholamines is significantly altered in LSD-treated rats. Thus a decrease in cerebral norepinephrine (NE) levels was first reported by Freedman (35) in rats treated acutely with LSD. Tolerance to this action develops rapidly, since LSD no longer

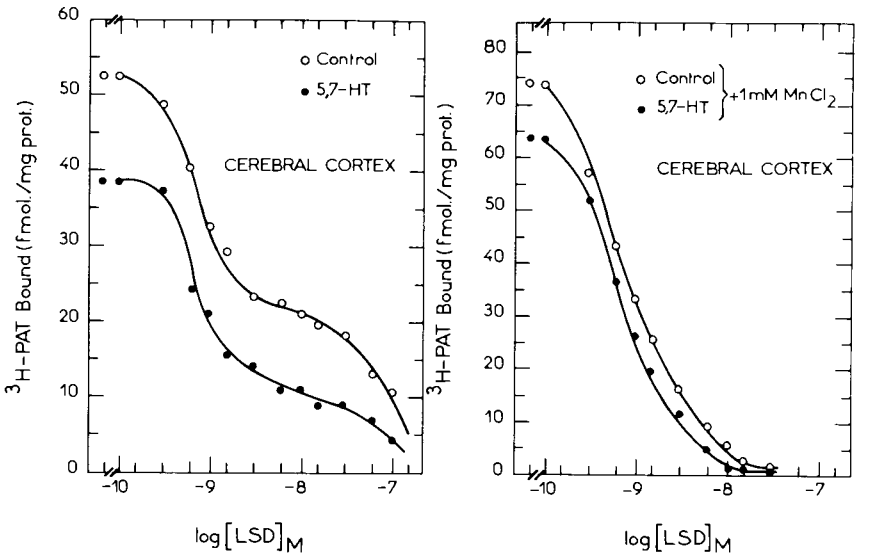

FIG. 3. Direct evidence for LSD binding to both post- and presynaptic 5-HT receptors in the rat cerebral cortex. ^{3}H-PAT is a direct agonist, which binds to both postsynaptic 5-HT$_1$ receptors and presynaptic 5-HT autoreceptors (39). The displacement by LSD of ^{3}H-PAT specifically bound to cortical membranes is biphasic, with the low affinity component (with LSD concentrations ranging between 5 and 100 nM) being markedly reduced (*left panel*) following the selective degeneration of 5-HT terminals by intracerebral 5,7-dihydroxytryptamine administration. The addition of 1 mM $MnCl_2$ to the binding assay mixture (*right panel*) suppresses the low affinity component; LSD displacement of ^{3}H-PAT bound to the high affinity sites is not significantly different in control and in 5,7-HT-treated rats. Such experiments illustrate that the postsynaptic 5-HT$_1$ receptor has a higher affinity for LSD (IC_{50} # 0.8 nM) than the presynaptic 5-HT autoreceptor (IC_{50} # 0.1 μM).

affects NE levels following daily injections of the drug for 1 week (107). Peters and Tang (91), who also studied the effects of chronic administration of LSD (100 μg/kg for 14 days) to rats, reported a reduction of NE levels associated with an enhanced tyrosine hydroxylase activity, suggesting a persistent acceleration of NE turnover following such treatment (at least in the brainstem and the cerebral cortex). Whether the reduction in NE levels occurring acutely is also associated with an increased turnover is open to question, since the depletion of brain NE induced by the administration of the tyrosine hydroxylase inhibitor alpha-methylparatyrosine is unaltered in LSD-treated rats (67). At the postsynaptic level, LSD interacts with NE neurotransmission. Dolphin et al. (25) noted that the specific binding of ^{3}H-dihydroalprenolol to β-receptors is inhibited by LSD in the cerebral cortex of rats (K_I = 0.1 μM). Furthermore, LSD reduces the stimulation of cortical adenylate cyclase by isoproterenol (K_I = 0.16 μM).

Numerous investigations were carried out on the LSD-induced alterations of central dopaminergic systems. Persson (88,89) reported that LSD administration increases both the concentration of DOPAC and the rate of DOPA accumulation

in the striatum following the blockade of AAD by NSD 1015. Recently, Bowers and Salomonsson (16) confirmed the LSD-induced acceleration of DA turnover by measuring homovanillic acid (HVA). A marked increase in the levels of this DA metabolite occurs in the rat striatum 1.5 hr after a small dose of LSD (25 μg/kg). Similar alterations take place in extrastriatal areas, notably the prefrontal cortex, where HVA levels are also enhanced under such pharmacologic conditions (16). Since dopaminergic terminals in the prefrontal cortex apparently lack autoreceptors, the LSD-induced acceleration of DA turnover is not likely the consequence of some interaction of the hallucinogen with such receptors, as it was originally proposed for the striatum (88,89). In the latter structure, LSD behaves as a partial agonist of DA; LSD stimulates directly DA-sensitive adenylate cyclase but to a lesser extent than DA. Furthermore, the drug reduces significantly the maximal activation of striatal adenylate cyclase by DA (122).

In conclusion, extensive studies on LSD-induced alterations of monoaminergic neurotransmission have shown that the typical hallucinogen (a) reduces the turnover of 5-HT in most brain areas, (b) accelerates DA turnover in striatal and extrastriatal regions, and (c) accelerates NE turnover notably in the cerebral cortex and brainstem.

Effects of Other Hallucinogens on Monoaminergic Neurons

If the LSD-induced changes in 5-HT and catecholamine turnover are functionally related to the hallucinogenic action of the drug, they should occur also following the administration of other hallucinogens. In agreement with this proposal, a decrease in 5-HT turnover has been noted in rats treated with other indole hallucinogens, such as DMT and psilocybin (5), with psychotomimetic phenylethylamines, such as *p*-methoxyamphetamine and DOM (6,68), and with PCP (59) or ketamine (74). Furthermore, although acute amphetamine administration increases 5-HT synthesis via a primary action on brain tryptophan (102), chronic amphetamine treatment, under conditions resembling those provoking psychosis with auditory hallucinations in man, elicits a marked reduction of 5-HT turnover in the cat CNS (117).

Evidence for a negative influence of GABAergic processes on 5-HT turnover and release in various brain areas has been reported in the rat (100) and cat (112). Further investigations are necessary, however, to demonstrate that the hallucinogenic action of muscimol involves a reduction in 5-HT turnover via the stimulation of GABA receptors.

In the case of cannabis hallucinogens, Holtzman et al. (54) first reported that the acute injection of a large dose of THC (10 mg/kg i.p.) produces a small (20–25%) but significant increase in 5-HT levels in the whole brain of mice. These results were confirmed by several groups (110,126). According to Sofia et al. (110), this change is associated with a marked reduction (−50%) of 5-HT turnover after the administration of 20 mg/kg THC to rats. Using much lower doses (5.5 mg/kg i.p. and 1.0 mg/kg i.v.), Gallager et al. (37) failed to detect

any alteration in brain 5-HT turnover, although treated animals exhibited behavioral signs typical of hallucinogens (e.g., hyperreactivity to tactile and auditory stimuli). The problem becomes even more complex with the report by Johnson and Dewey (61) that high doses (10–30 mg/kg s.c.) of THC increase the rate of 5-HT synthesis in the mouse brain.

In conclusion, most hallucinogens, in addition to LSD, significantly reduce 5-HT turnover in brain. In the case of indole and phenylethylamine compounds, this effect results from negative feedback processes triggered by the direct interaction of these drugs with 5-HT receptors (5,6,22). However, further investigations are necessary before converting this relationship between hallucinogens and serotonergic systems into a general rule. This is particularly obvious for drugs, such as THC, that are still controversial.

Clear similarities exist between the effects of LSD and those of other hallucinogens on catecholaminergic systems. Andén et al. (5) noted that psilocybin and DMT accelerate NE turnover in the rat brain. Hallucinogens of other chemical series, notably methoxyamphetamines (e.g., DOM) (68) and THC (13), also increase the rate of synthesis and utilization of NE in brain. The increase due to THC probably involves a direct action of the drug, since an enhanced conversion of ^{3}H-tyrosine into ^{3}H-NE was found in synaptosomes incubated in the presence of 3 to 10 μM THC (13).

Like LSD, THC increases the synthesis and utilization rates of DA in the mouse brain (13). This also applies to muscimol. Chéramy et al. (19) reported that the intrastriatal injection of this drug (1 μM) enhances the local release of DA in the cat. Furthermore, the application of muscimol onto DA cell bodies in the substantia nigra also increases the release of DA in the ipsilateral caudate nucleus (19). Clear activation of dopaminergic neurotransmission also occurs in PCP-treated animals. *In vitro* experiments suggest that this effect results from both the inhibition of DA reuptake (38,108) and the stimulation of DA synthesis and release (7,118,119). Indeed, PCP administration has been shown to increase the *in vivo* release of DA in the cat striatum (56). As shown after the administration of DA agonists, the activation of dopaminergic neurotransmission resulting from PCP treatment is associated with a reduction in circulating prolactin levels in rats (99). Long-term experiments also confirmed that PCP enhances the stimulation of specific receptors by DA, since chronic treatment with this drug induces a DA subsensitivity associated with a reduction in the number of ^{3}H-spiperone binding sites in the rat striatum (97). The same change occurs after the chronic administration of amphetamine, a DA releaser (11), under conditions close to those producing a psychotic-like syndrome in humans (97).

In addition to PCP, other sigma opiate agonists, particularly SKF 10,047, accelerate striatal DA turnover. A small (+15%) but significant elevation of DOPAC levels occurs in the striatum of SKF 10,047-treated rats (128).

In conclusion, measurements of monoamine turnover following treatments with various classes of hallucinogens reveal that most of these drugs decrease the activity of 5-HT synapses and increase that of dopaminergic systems in

brain. Interestingly, such changes likely occur during schizophrenia, since indirect evidence suggests that DA neurotransmission is exaggerated (66), whereas the activity of serotonergic systems is reduced (93) in the CNS of acute psychotic patients. As expected from such endogenous alterations, treatments facilitating DA neurotransmission (L-DOPA, amphetamine) worsen the psychotic illness (78), whereas those stimulating 5-HT neurotransmission (tryptophan, 5-HTP) produce some clinical improvement (129). Such observations provide further support for the existence of close similarities between the central effects of hallucinogens and the functional disorders associated with schizophrenia.

CONCLUSION

The remarkable observation that minute amounts of LSD and related indole hallucinogens induce a dramatic reduction in the nerve impulse flow of 5-HT-containing neurons within anterior raphe nuclei (42) led to the postulate that hallucinations may in fact result from this primary effect. Indeed, a marked decrease in the nerve impulse flow of serotonergic neurons occurs during paradoxical sleep, i.e., when the brain is dreaming and therefore undergoes hallucinatory-like processes (58). However, examination of the electrophysiologic effects of other hallucinogens, such as phenylethylamine derivatives (methoxyamphetamines, mescaline) and PCP, failed to confirm that a reduction in the firing of 5-HT neurons is the common action of all hallucinogens, since these compounds do not affect the 5-HT cell population in anterior raphe nuclei (58). Furthermore, the lack of a direct relationship between the behavioral and electrophysiologic effects of LSD has been emphasized by Trulson et al. (115). The authors mentioned that the behavioral tolerance to repeated injections of the hallucinogenic drug is not associated with any sign of tolerance to the depressant effect of LSD on the nerve impulse flow of serotonergic raphe cells. Nevertheless, electrophysiologic findings (42,58) focused the attention of pharmacologists on serotonergic systems. Thus LSD and most other hallucinogens were found to decrease the turnover rate of 5-HT in brain. Obviously, all drugs that reduce 5-HT turnover in brain are not hallucinogenic, and this is only one of the multiple actions required for making a given compound hallucinogenic. Another biochemical alteration produced by most hallucinogens concerns the central dopaminergic systems: LSD, indole and phenylethylamine hallucinogens, and PCP increase dopaminergic neurotransmission, which results in an enhanced turnover rate of DA in mesocorticolimbic and nigrostriatal dopaminergic neurons. Therefore, a decrease in 5-HT neurotransmission associated with an enhanced dopaminergic neurotransmission probably is a prerequisite for evoking hallucinations.

As mentioned herein, other neurotransmitters are affected by hallucinogens. Accordingly, the opposite changes in 5-HT and DA neurotransmission produced by these drugs seem necessary but insufficient to evoke hallucinations. Current studies on the effects of hallucinogens on recently detected neuroactive compounds (notably neuropeptides, including angel dustin) could end with the discovery of another neurochemical correlate of hallucinations. This would be of considerable interest for a better knowledge of the endogenous mechanisms involved in hallucinatory episodes in schizophrenic patients.

Hallucinogens are a heterogeneous family of drugs, including those, like LSD, that produce almost exclusively visual hallucinations, and PCP and methoxyamphetamines, which evoke mainly auditory hallucinations. Therefore, in addition to altering 5-HT and DA neurotransmission in various brain areas, hallucinogens act on central structures specifically involved in the transfer of visual, auditory, and tactile messages. Such inference has been confirmed by autoradiographic studies using either radioactive hallucinogens or radioactive deoxyglucose to identify the targets of these drugs. Thus intense labeling is generally found in geniculate bodies and colliculi.

In conclusion, hallucinations probably result from a dual action of these drugs on the specific circuits involved in the transfer of sensory messages and on the neuronal processes integrating these messages, notably in the limbic areas. The biochemical alterations identified so far, i.e., a reduction in 5-HT turnover associated with an acceleration of DA turnover, involve exclusively the integrative processes, since monoamines behave as neurohormones modulating the activity of most central neurons without insuring the transmission of specific messages (except in rare cases). Further improvements in the autoradiographic technique using radioactive hallucinogens would be helpful in precisely determining the specific targets of these drugs in sensory pathways. Biochemical investigations at these levels should provide crucial information about the as yet unknown mechanisms of action of the various families of hallucinogens on the specific sensory pathways.

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LSD and Serotonergic Dorsal Raphe Neurons: Intracellular Studies *In Vivo* and *In Vitro*

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Single cell studies on the central effects of *d*-lysergic acid diethylamide (LSD) and other hallucinogenic drugs were begun more than 15 years ago. It is now well established that these drugs can have dramatic effects on neuronal firing patterns in a number of identified brain systems in both anesthetized (1) and behaving (32) animals. The studies described in the latter reviews, however, have for the most part employed extracellular recording techniques, and the underlying membrane mechanisms through which hallucinogenic drugs alter neuronal activity are not well understood. The purpose of this chapter is to consider newly emerging intracellular data on the action of hallucinogenic drugs. Since most of this work deals with the effects of LSD on serotonergic neurons in the dorsal raphe nucleus of the rat, results obtained from this region are emphasized. The intracellular effects of LSD are viewed against the background of the known properties of dorsal raphe neurons.

BASIC PROPERTIES OF SEROTONERGIC DORSAL RAPHE NEURONS

Identification

The location of serotonin-containing neuronal perikarya (23), terminals (6,26), and pathways (13,50) was mapped originally by means of the formaldehyde condensation histochemical method of Falck and Hillarp (25) applied to freeze-dried brain tissue (22). More recently, serotonergic neurons have been localized successfully by immunocytochemical methods (46). Both methods show that the perikarya of serotonergic neurons are located mostly in the brainstem raphe nuclei. Serotonergic fibers project from the raphe nuclei to innervate other parts of the brainstem, the spinal cord, and the forebrain. The prominent clustering of serotonergic neurons in the dorsal raphe nucleus of the midbrain makes it practical to conduct single unit recordings from identified serotonergic neurons

in this area. Serotonergic neurons in the dorsal raphe nucleus have been tentatively identified by their slow rate of firing (about 1–2 spikes/sec) and regular rhythm. Neurons with these characteristics have been inferred to be serotonergic, since they can be activated antidromically from the serotonergic pathway as it traverses the ventromedial midbrain tegmentum (53). Recently, an intracellular double labeling procedure has provided a definitive identification of serotonergic neurons: an intracellularly injected red fluorescing dye (ethidium bromide) has been colocalized with the formaldehyde-induced yellow fluorescence of serotonin (9). By this method, slow, rhythmically firing neurons of the dorsal raphe nucleus have been confirmed to be serotonergic in nature.

A slow, rhythmic firing pattern is characteristic of dorsal raphe neurons in many different preparations, including the anesthetized (2,3,20,42) and cerveau isolé (54) rat, the awake, unrestrained cat (49), and even *in vitro* in midbrain slices from rat (43,51) and mouse (31,48). Although dorsal raphe neurons in awake animals generally have a higher mean rate of firing during periods of behavioral arousal than during slow wave sleep, a regular rhythm pervades, except when the animal is perturbed by certain sensory stimuli (49). Dorsal raphe units become totally silent only during periods of rapid eye movement (REM) sleep. The fact that serotonergic neurons of the dorsal raphe nucleus maintain their slow, rhythmic firing pattern under a wide variety of conditions and in a number of different species has suggested that they possess intrinsic pacemaker properties (11,43).

Pacemaker Activity *In Vivo*

Recent intracellular recordings have been made *in vivo* from serotonergic neurons in the rat dorsal raphe nucleus to elucidate the membrane events underlying the apparent tonic pacemaker properties of these cells (8). These experiments have shown that typical rhythmic dorsal raphe cells exhibit a large postspike hyperpolarization, followed by a gradual interspike depolarization (Fig. 1). Spikes arise from such depolarizing ramps rather than from excitatory postsynaptic potentials (EPSPs). When serotonergic neurons are stimulated by

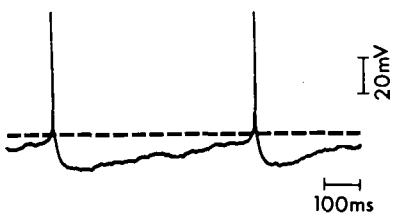

FIG. 1. Intracellular recording from a serotonergic dorsal raphe neuron *in vivo*. Experimental preparation: chloral hydrate anesthetized rat; intracellular recording performed according to the method of Aghajanian and VanderMaelen (8). Note the large (~20 mV) afterhyperpolarization and gradual interspike depolarizations leading to threshold (*dotted line*) and the triggering of successive spikes. Also note lack of EPSPs, which would indicate that pacemaker potentials rather than discrete, phasic extrinsic influences are responsible for the regular firing pattern of serotonergic dorsal raphe neurons. (On-line storage oscilloscope trace provided by G. K. Aghajanian.)

intracellular pulses to produce a train of spikes, they show even more prominent afterhyperpolarizations (and poststimulus inhibitions) proportional to the number of preceding evoked spikes. Voltage deflections produced by hyperpolarizing test pulses are reduced in amplitude during periods of poststimulus afterhyperpolarization, indicating that the hyperpolarization results from an increase in membrane conductance.

The rhythmically firing neurons of the dorsal raphe nucleus exhibit several characteristics of the pacemaker potential; the latter has been defined as the gradual depolarization of a cell during the interspike interval (33,35). The occurrence of pacemaker potentials in dorsal raphe neurons could explain why spontaneous activity is retained in midbrain slices *in vitro* (31,43,48,51; however, see below). The initial feature of the pacemaker potential is the postspike hyperpolarization (afterhyperpolarization). Qualitatively, the afterhyperpolarization of dorsal raphe neurons resembles that of motoneurons (19,36,37) and hippocampal pyramidal cells (12,30,45), which are thought to be mediated by a Ca^{2+}-dependent K^+ conductance. One explanation for spontaneous repetitive firing, or automaticity, is that as net K^+ conductance decays during the latter part of the interspike interval, there is a slow depolarization which, when coupled with a reactivation of an inward current mechanism, leads to the succeeding spike. In certain molluscan neurons with a low rate of repetitive firing, the major influence on interspike interval has been shown to be a Ca^{2+}-activated K^+ conductance (44). The reason this mechanism may be particularly critical for regulating cells with slow rates of discharge is that Ca^{2+} diffusion and sequestration are relatively slow processes compared to changes in voltage-dependent K^+ channels. If such a mechanism holds for serotonergic neurons of the dorsal raphe nucleus, then both slow firing rate and automaticity could be explained, at least in part, by a slow decay in a Ca^{2+}-activated K^+ conductance.

Pacemaker Activity *In Vitro*

Recently, we conducted intracellular recordings from serotonergic dorsal raphe neurons in the rat brain slice preparation (51). In most respects, we find the properties of serotonergic dorsal raphe neurons *in vitro* to be identical to those recorded *in vivo* from anesthetized rats. For example, we encounter at least some spontaneously firing serotonergic dorsal raphe neurons in our brain slice preparation. This is in agreement with the initial study by Mosko and Jacobs (43), who also recorded from rat brain slices, and the recent report by Howell et al. (31), in which mouse brain slices were used. In contrast to the situation *in vivo,* however, in which the majority of serotonergic dorsal raphe neurons are spontaneously active (11), we found that more than 75% of viable dorsal raphe neurons are silent in the slice. This finding is in agreement with the earlier study of Mosko and Jacobs (43), who found a total of only 21 spontaneously active units in 21 rats. Although early technical difficulties associated with the brain slice preparation could account for the low yield of cells in the latter study,

it is possible that many healthy but silent dorsal raphe neurons were present but went undetected. A possible explanation for the relative lack of spontaneous activity *in vitro* is that excitatory afferents to the nucleus, which originate outside the slice, have been cut. The noradrenergic system, which has been shown to make direct synaptic contacts onto serotonergic dorsal raphe neurons of the rat brain (16), may represent one such afferent system. Interestingly, exogenous norepinephrine excites silent as well as active serotonergic dorsal raphe neurons in the brain slice (see below). Since a reduction or blockade of the noradrenergic input to these neurons in the anesthetized animal *in vivo* results in a decrease in spontaneous activity (14,15,17,39,41,47), it is possible that the relative lack of spontaneous activity of presumed serotonergic dorsal raphe neurons in our studies was caused in large part by a disfacilitation due to the loss of tonic noradrenergic input.

The fact that most serotonergic dorsal raphe neurons are dependent on extrinsic excitatory or facilitatory inputs to express their characteristic spontaneous activity may seem to contradict previous studies suggesting that these neurons may function as autonomous pacemakers (42) with an endogenous rhythm (31) attributable to the presence of pacemaker potentials (8). Such a contradiction exists only if one insists that endogenous rhythms and pacemaker potentials must, by definition, be totally autonomous, i.e., completely independent of all extrinsic synaptic or neurohumoral influences. Such a definition would seem too restrictive in view of the fact that some invertebrate neurons display pacemaker potentials only when certain afferent fibers are stimulated (38) or when exposed to certain neurohumoral substances (18,28).

Thus, based on our recent observations in brain slices as well as previous intracellular (8) and extracellular (31,42) experiments, it appears that serotonergic neurons do possess pacemaker potentials, but its expression is dependent on the presence of adequate tonic excitatory influences. These influences may be provided by noradrenergic (14,15,17) or other excitatory inputs. For example, intracellularly recorded serotonergic dorsal raphe neurons, which are quiescent in the slice, can be made to fire in a slow and regular fashion by injecting a continuous, low amplitude depolarizing current. In unanesthetized, freely moving cats, some spontaneous activity is present in the dorsal raphe nucleus even after administration of high doses of α-adrenoceptor-blocking drugs, especially when the animal is aroused by sensory stimulation (29). In unanesthetized animals, a variety of excitatory or facilitatory influences can maintain spontaneous activity, or at least temporarily restore it, even after pharmacologic blockade of the noradrenergic input to serotonergic dorsal raphe neurons (28a,29).

In brain slices, even though no anesthesia is present, there is a reduction in both noradrenergic and other inputs to these cells (e.g., from sensory systems); thus most of these neurons become silent. Consistent with this interpretation is the fact that all presumed serotonergic neurons we have tested in the brain slice are uniformly activated by norepinephrine or the α_1-agonist phenylephrine, applied either iontophoretically or in the perfusion medium (51). Similarly, *in vivo,* most serotonergic dorsal raphe neurons can be activated by low currents of iontophoretically applied norepinephrine (15). *In vitro,* as *in vivo,* the activation of dorsal raphe neurons by phenylephrine or norepinephrine can be blocked by nonselective α-adrenoceptor antagonists, such as phentolamine and thymoxamine, as well as by the selective α_1-antagonist prazosin. Thus the noradrenergic activation of serotonergic dorsal raphe neurons in the brain slice preparation would seem to be via an α_1-adrenergic receptor, as has previously been found *in vivo* (15,39,41).

Preliminary intracellular data suggest that the noradrenergic activations of serotonergic neurons are probably not caused primarily by a norepinephrine-induced decrease in Ca^{2+} conductance (51). If there were a decrease in Ca^{2+} conductance, a corresponding decrease in Ca^{2+}-activated K^+ conductance should occur. Such a decrease in the Ca^{2+}-activated K^+ conductance would be evident as a decrease in the peak amplitude of spike afterhyperpolarizations. Despite an increased rate of interspike depolarization, however, such decreases in the initial amplitude of afterhyperpolarizations were not observed. Conceivably, norepinephrine could also affect a Ca^{2+}-activated K^+ conductance by accelerating the rate of intracellular Ca^{2+} sequestration (such as occurs with epinephrine in the heart) (34). This mechanism would accelerate the decay of the afterhyperpolarization, thereby shortening the interspike interval. Alternatively, α_1-adrenoceptor stimulation could activate serotonergic neurons by causing an increase in net inward current. Recent intracellular studies in the brain slice support this latter possibility. Phenylephrine induces a depolarization of serotonergic neurons even when they are silent and concomitantly causes an increase in input resistance (7). This combination of effects can be explained by a decrease in net outward K^+ current, which would be equivalent to increasing net inward current.

LSD AND SEROTONERGIC DORSAL RAPHE NEURONS

LSD and Serotonin Autoreceptors

Serotonin suppresses the firing of serotonergic neurons in the dorsal raphe nucleus when it is applied directly by microiontophoresis (5,21,27). It has been proposed that serotonin may exert its inhibitory effect by acting on autoreceptors located in the somatodendritic region of serotonergic neurons (the term autoreceptor denotes receptors mediating the response of a neuron to its own transmitter). LSD, which possesses the indole nucleus of serotonin, also has a powerful inhibitory effect on dorsal raphe neurons when it is given in small intravenous doses (2,3) or when it is applied by microiontophoresis (5,21). The inhibition of serotonergic neurons by LSD is much more pronounced than the inhibitory effect of LSD on nonserotonergic postsynaptic neurons even in brain areas that have an identified serotonergic input (24,27). In contrast, serotonin itself shows no such preferential activity. Three simple indoleamine hallucinogenic drugs—

4-hydroxy-N,N-dimethyltryptamine (psilocin), N,N-dimethyltryptamine (DMT), and 5-methoxy-N,N-dimethyltryptamine—also have a preferential inhibitory action on serotonergic neurons (4,24), suggesting that their hallucinogenic effects may be related to their selective action on autoreceptors. This selectivity serves to define the serotonergic autoreceptor in terms of a traditional pharmacologic rank ordering of agonists (4).

LSD: Intracellular Studies

Intracellular recordings from serotonergic neurons show that the systemic administration of LSD bitartrate (50 μg/kg i.p.) produces a hyperpolarization, a cessation of spontaneous firing, and a reduction in membrane input resistance (Fig. 2) (8). As cell firing decelerates following the injection of LSD, there is a progressive decrease in the slope of interspike depolarization. Finally, interspike depolarization is totally blocked, and there is a sustained hyperpolarization. LSD appears to cause a sustained hyperpolarization and a loss in repetitive firing by blocking the usual decay in postspike afterhyperpolarization. From these data alone, it cannot be known whether this effect of LSD on membrane potential is caused by a failure of a Ca^{2+}-dependent K^+ conductance to decay or whether some other conductance is altered during the interspike interval. It

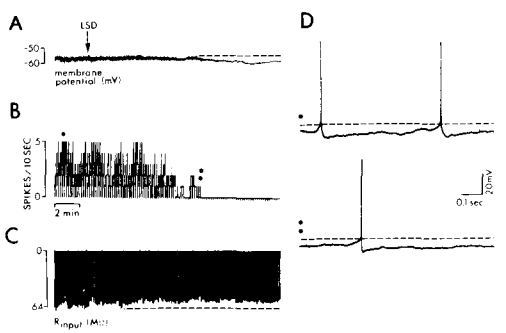

FIG. 2. Simultaneous polygraph recordings from a serotonergic dorsal raphe neuron showing the effects of LSD on membrane potential, firing rate, and neuronal input resistance. **A:** Low pass filtered DC trace showing hyperpolarization of a dorsal raphe neuron after the injection of LSD (50 μg/kg i.p.). The thickness of the initial portion of the trace reflects the slow interspike fluctuations in membrane potential. After LSD, membrane potential no longer fluctuates markedly and remains at a level of 4 to 6 mV below the most negative excursions prior to injection. **B:** Average rate record showing a gradual inhibition of firing of the same cell after injection of LSD. Note that the counter resets to zero every 10 sec, giving rate in terms of spikes/10 sec. **C:** Input resistance decreases after LSD. Resistance values were calculated by Ohm's law, using isolated voltage deflections induced by periodic constant current hyperpolarizing pulses (0.2 nA, 0.2 Hz). **D:** *Upper trace,* spontaneous spikes prior to LSD taken from point shown on the average rate record by a single asterisk; *lower trace,* last spontaneous firing of this cell preceding complete inhibition by LSD; taken from point shown on average rate record by a double asterisk. Note that the usual interspike depolarization fails to occur following this spike. (From ref. 8.)

is conceivable that LSD could act by causing a sustained increase in intracellular Ca^{2+} levels; alternatively, LSD could act through a Ca^{2+}-independent mechanism.

Intracellular studies in the brain slice preparation are now in progress to explore the ionic mechanisms underlying the hyperpolarizing effect of LSD on serotonergic dorsal raphe neurons (10). As a first step in this inquiry, the reversal potential for the LSD-induced hyperpolarization has been determined. The reversal potential can be defined as the point at which diffusional potential of the ionic species involved is equal and opposite to the potential difference across the cell membrane. In the present situation, this was ascertained by plotting current-voltage (IV) curves in the presence and absence of LSD (Fig. 3). As can be seen in Fig. 3, the IV curve for LSD intersects the control curve in the deeply hyperpolarized region (approximately −98 mV). Such a negative reversal potential would indicate that an increase in K^+ rather than Cl^- conductance is responsible for the hyperpolarizing effect of LSD. This interpretation is supported by the fact that when recording electrodes contained 3 M KCl, reversal potentials did not shift in the depolarizing direction, despite a presumed increase in intracellular Cl^- concentrations.

Reversal potentials for LSD were also determined over a range of external K^+ concentrations. According to the Nernst equation, reversal potentials should shift approximately 60 mV per 10-fold shift in K^+ concentration if K^+ were the ionic species involved in a conductance change. Reversal potentials of LSD were found to shift almost exactly to the extent predicted by the Nernst equation for a K^+-dependent potential. Of course, there are several different types of K^+ conductances that could be activated by LSD, including the Ca^{2+}-dependent outward current. To evaluate the latter possibility, midbrain slices were exposed

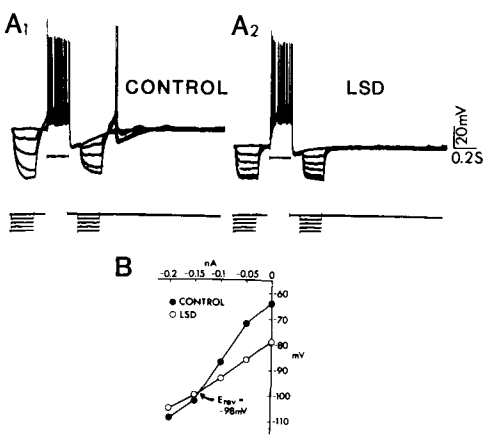

FIG. 3. Current-voltage (IV) relationships in a serotonergic dorsal raphe neuron in a brain slice preparation before and after the infusion of LSD (80 nM). In **A,** superimposed voltage deflections (*upper traces*) in response to gradual constant current pulses (*lower traces*) are shown before and after a burst of spikes elicited by depolarizing pulses. In **A1,** note the reduced voltage deflections during the postburst afterhyperpolarization, which is indicative of the Ca^{2+}-activated K^+ conductance in these cells. In **A2,** during LSD infusion, a hyperpolarization occurs in association with a decrease in voltage deflections elicited by the same intensity constant current pulses as in **A1.** In **B,** the above IV data have been plotted to determine the reversal potential for the LSD-induced change in ionic conductance. (Figure provided by G. K. Aghajanian.)

to zero Ca^{2+} solutions, a treatment that causes a marked activation of firing of serotonergic dorsal raphe neurons (52). Despite the absence of Ca^{2+}, LSD was still able to inhibit serotonergic cell firing and produce a hyperpolarization. This result suggests that LSD increases K^+ conductance through a Ca^{2+}-independent mechanism.

In most respects, the membrane effects of serotonin were found to be similar to those just described for LSD. For example, serotonin-induced hyperpolarizations have deeply negative reversal potentials, which shift with changes in external K^+ concentration in accordance with the Nernst equation. These similarities might be expected from the fact that LSD and serotonin have similar inhibitory extracellular actions via serotonin autoreceptors. An unanticipated difference between LSD and serotonin has emerged recently from our intracellular brain slice experiments (10). Whereas serotonin induces a rapid hyperpolarization (accompanied by a decrease in input resistance), which reaches a maximum within 5 to 10 min of perfusion, the effect of LSD is progressive over prolonged periods (30–60 min) of perfusion, reaching levels beyond maximal serotonin effects. Since the effects of LSD continue to increase well beyond the period required for simple drug equilibration in the slice chamber, it appears that another time-dependent process may be involved. It is possible that LSD slowly induces a recruitment of additional K^+ channels, which are not directly accessible to serotonin itself. This may be another instance of a modulatory rather than serotonin-like effect of LSD (e.g., the sensitizing effect of LSD described for facial motoneuron) (40).

CONCLUSIONS

Traditionally, serotonergic dorsal raphe neurons have been identified by their slow, rhythmic discharge patterns *in vivo*. Intracellular studies now show that pacemaker-like potentials rather than EPSPs underlie this regularity. The pacemaker potential begins with a large postspike hyperpolarization (afterhyperpolarization) that slowly decays during the interspike interval. The occurrence of a spike at the end of the depolarizing ramp reinitiates the cycle. The afterhyperpolarization, which is prominent in the early phase of the pacemaker cycle, is produced by a Ca^{2+}-dependent K^+ current; voltage-dependent inward currents may be involved in later phases of the pacemaker potential. While most serotonergic neurons *in vivo* exhibit spontaneous activity, most serotonergic neurons are silent *in vitro;* this may be due to a loss of excitatory afferents in the largely deafferented slice. Norepinephrine or the α_1-adrenoceptor agonist phenylephrine can restore normal pacemaker activity in the slice; this may occur through a shutting off of K^+ channels, which would have the effect of increasing net inward current.

Pacemaker activity can be blocked by LSD, which produces a hyperpolarization and a decrease in input resistance. Intracellular studies in the brain slice show that an increase in K^+ conductance accounts for these changes. However, LSD does not seem to act simply as a serotonin autoreceptor agonist. Serotonin itself rapidly produces a maximal change in K^+ conductance, whereas LSD slowly enhances this conductance to supramaximal levels (i.e., above maximal serotonin effects). This phenomenon may be indicative of an allosteric effect of LSD, which is not shared by serotonin. The possibility must now be considered that such receptor modulatory effects of LSD may be more relevant for the hallucinogenic effects of this drug than any simple agonist (or antagonist) action, as has been traditionally assumed.

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Postsynaptic Serotonergic Action of Hallucinogens

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Evidence from a variety of different experimental approaches leads to the conclusion that an alteration(s) in serotonergic neurotransmission plays a critical role in mediating the action of "LSD-like" hallucinogenic drugs. This phrase refers to those drugs whose psychologic and behavioral effects in humans mimic those of lysergic acid diethylamide (LSD) and whose effects in humans show at least unidirectional cross tolerance with LSD [e.g., psilocin, N,N-dimethyltryptamine (DMT), mescaline, 2,5-dimethoxy-4-methylamphetamine (DOM), and their derivatives]. This conclusion, regarding serotonin and hallucinogenesis, is amply supported by data presented in many of the chapters in this volume, e.g., those describing studies employing receptor binding, structure-activity relationships, behavioral pharmacology, and electrophysiology. It is also evident, however, that the precise site and nature of this critical interaction between hallucinogenic drugs and the brain serotonergic system is not known. Thus these drugs may modify serotonergic neurotransmission by acting at some or all of the following sites: soma-dendrite of serotonergic neurons, axon terminal of serotonergic neurons, or target neurons postsynaptic to serotonergic neurons. Furthermore, their action at these various sites may be that of agonist, antagonist, releaser, or blocker of reuptake. Despite the fact that we can directly point to a crucial role for brain serotonergic neurons in the action of hallucinogenic drugs, we are far from having a complete appreciation of the exact nature of this interaction.

In this chapter, I focus on our studies investigating the behavioral effects of hallucinogenic drugs while concurrently recording the single unit activity of brain serotonergic neurons in unrestrained and unanesthetized animals. In addition to the obvious advantages that derive from being able to examine brain single unit activity directly in conjunction with the behavior, these studies also afforded the opportunity of testing the hypothesis that the critical site of action of hallucinogenic drugs was on the serotonergic neuron soma-dendrite (the presynaptic hypothesis). Our results indicate that although the action of hallucinogenic drugs at this site may contribute to hallucinogenesis, it does not seem to be crucial for mediating these effects. At present, we favor the hypothesis

that the important action of hallucinogens is exerted directly at postsynaptic serotonergic receptors (the postsynaptic hypothesis). This chapter reviews these two hypotheses and presents evidence from behavioral pharmacology studies in animals and humans that support the postsynaptic hypothesis.

PRESYNAPTIC HYPOTHESIS

Based on neurochemical data indicating that LSD and related hallucinogens decreased the turnover rate of brain serotonin (33,73), Aghajanian and co-workers hypothesized that this might be mediated by a decrease in unit activity of serotonergic neurons (4). The direct examination of this issue was made possible by the pioneering fluorescence histochemical studies of Dahlstrom and Fuxe (27), who provided a detailed map of the localization of serotonergic neurons within the brainstem of the rat. Most were found in groups on or near the midline, from the caudal medulla to the mesencephalon. In many cases, these clusters of serotonergic neurons corresponded closely to the raphe nuclei, as defined by classic anatomic methods (raphe and serotonergic are used interchangeably throughout this chapter). With this information in hand, Aghajanian and co-workers directed microelectrodes toward the mesencephalic dorsal and median raphe nuclei of chloral hydrate-anesthetized rats (4). These two groups of cells represent the densest aggregation of serotonergic neurons in the rat brain and also give rise to virtually all the serotonergic axon terminals innervating the forebrain.

The activity of mesencephalic serotonergic neurons recorded in chloral hydrate-anesthetized rats is characterized by a slow (1–2 spikes/sec) and regular discharge pattern. When low doses of LSD (25–50 μg/kg; 12.5 μg/kg in later studies) were administered intravenously, they produced a complete and immediate depression of the discharge rate of these neurons (4). This supported the original hypothesis regarding the mechanism of action of LSD. In a subsequent study, the same group (5) reported that the activity of nonserotonergic neurons in a variety of brain areas was typically unaffected or slightly increased by LSD. These investigators also went on to test the effects of a variety of psychoactive drugs, including some classic hallucinogens, on the activity of serotonergic neurons in chloral hydrate-anesthetized rats. It was found that DMT produced an effect similar to that of LSD but at significantly higher doses. Interestingly, mescaline and DOM depressed the activity of only a subgroup of mesencephalic serotonergic neurons in the ventral portion of the dorsal raphe nucleus. Atropine, 2-bromo-LSD, scopolamine, phencyclidine, and chlorpromazine were without effect on raphe unit activity. Aghajanian's group (32) also reported that psilocin was effective in depressing raphe unit activity, whereas amphetamine consistently increased the activity of these cells. Consistent with these results, an experiment in my laboratory demonstrated that low doses of the hallucinogen 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) exerted a potent depressant effect on the activity of serotonergic neurons (66).

Once it was determined that LSD-like hallucinogens did indeed exert a strong depressant action on brain serotonergic neurons, the next issue was to determine how this was mediated. Was their action a direct one on serotonergic neurons, or was it exerted via some type of feedback loop, such as that known to influence brain dopamine neurons? Since the serotonergic neurons found in the dorsal and median raphe nuclei send their axons primarily rostrally, into the forebrain, it seemed reasonable to assume that hallucinogens might exert their effect on these neurons indirectly, by means of a negative feedback consequent to their action on forebrain target neurons.

This concept was tested in two ways. First, LSD (40) and 5-MeODMT (66) were administered systemically to animals that had complete transections of the neuraxis, immediately rostral to the mesencephalon, thus precluding any significant feedback influence from the forebrain. In both studies, the compounds were equally effective in depressing the activity of raphe neurons in the intact and transected groups of animals. A second approach involved the direct application of LSD, psilocin, DMT, 5-MeODMT, and mescaline onto neurons in the area of the dorsal raphe nucleus by means of microiontophoresis (6,31,39). Except for the experiments with mescaline, which may act indirectly, the iontophoretic application of the other hallucinogenic drugs produced a profound suppression of serotonergic unit activity at low ejection currents.

These results provided support for the hypothesis that the effect of hallucinogenic drugs is mediated by a direct action on serotonergic neurons, possibly one mediated by serotonin receptors. This is consistent with data indicating that raphe neurons receive inputs from other raphe neurons and thus, presumably, contain serotonin receptors on their somata and/or dendrites (65).

Another important issue remained to be resolved. If the action of hallucinogenic drugs is mediated by a depressant action on serotonin-containing neurons, why are compounds, such as *l*-5-hydroxytryptophan (*l*-5-HTP) and *l*-tryptophan, both of which depress raphe unit activity (2,87), not hallucinogenic? The answer, at least in the context of this theoretical framework, is provided by two elegant experiments (39,40). When serotonin is iontophoretically applied onto serotonergic neurons in the raphe nuclei or onto their postsynaptic target neurons in the ventral lateral geniculate or amygdala, it is approximately equipotent in depressing unit activity at these various pre- and postsynaptic sites. In contrast, when the effects of LSD or psilocin are tested in the same manner, they have a much more profound influence on serotonergic cells than on their target neurons. In other words, hallucinogenic drugs have an action that appears to be preferential for serotonin-containing neurons. Thus, it is reasoned, when brain levels of serotonin are elevated by administration of its precursors *l*-5-HTP or *l*-tryptophan (or any of a variety of other pharmacologic means), raphe unit activity is depressed; but simultaneously, so is the activity of target neurons receiving serotonergic inputs. On the other hand, when LSD is administered systemically, it depresses raphe unit activity, while having little direct effect on target neurons. Because much of the effect of serotonin on target

neurons in the forebrain is inhibitory (40), it was hypothesized that the consequence of the preferentially depressant action of LSD on raphe neurons was to produce a disinhibition of forebrain target neurons, precisely the opposite of the depression produced by elevated synaptic levels of serotonin.

This presynaptic serotonergic model of hallucinogenic drug action is based on several assumptions: (a) All hallucinogenic drugs strongly depress the activity of at least some serotonergic neurons; (b) the synaptic action of serotonin in the forebrain is exclusively inhibitory; (c) hallucinogenic drugs exert little direct effect on postsynaptic serotonergic receptors; and (d) only hallucinogenic drugs have a depressant action that is strongly preferential for serotonergic neurons, as compared to their action on postsynaptic neurons.

The first assumption is examined in the next section, where we describe the effects of these drugs on the activity of serotonergic neurons recorded in freely moving cats. The second assumption of this model, that the action of serotonin in the forebrain is inhibitory, is based on studies of subcortical sites in the rat brain that receive a dense and uniform serotonergic input. Thus, in areas such as the ventral lateral geniculate and amygdala, the iontophoretic application of serotonin exerts an exclusively depressant effect (40). However, there is also a good deal of evidence to indicate that in other brain regions serotonin may exert excitatory effects on postsynaptic neurons. For example, Bradley and Wolstencroft (18) reported that 40% of brainstem neurons were excited by iontophoretic application of serotonin; and Roberts and Straughan (72) found that serotonin produced excitation in 30% of the cortical neurons on which it was tested in acute decerebrate cats. More recently, in light of anatomic evidence that serotonergic input to the cortex of the rat is dense and fairly uniform throughout all cortical layers (59), Olpe (68) has reported that in some cortical areas, at least 20% of the cells were excited by serotonin applied iontophoretically.

Given that serotonin can exert excitatory effects in some brain areas, we can now reexamine the third assumption, that hallucinogens exert little direct effect on postsynaptic serotonergic receptors. Even in those subcortical brain areas where the action of serotonin is strictly inhibitory, hallucinogens do exert some direct effect; it is not as strong as that exerted directly on serotonergic neurons, but, nonetheless, it is a significant effect. For example, Aghajanian and Haigler (6) reported that the amount of iontophoretically applied LSD necessary to produce a complete suppression of raphe unit activity produced a 30 to 40% suppression of activity in the lateral geniculate and amygdala. Similarly, the amount of psilocin needed to completely suppress the activity of raphe neurons produced a 40 to 50% suppression of activity in these latter two subcortical sites.

We now can examine the effects of hallucinogenic drugs at those sites where serotonin exerts excitatory actions. Roberts and Straughan (72) reported that the excitatory effects of iontophoretically applied serotonin on cortical neurons in acute decerebrate cats were effectively blocked by LSD in more than 60% of

the cells tested. Boakes et al. (15) reported that LSD exerted similar blocking effects on the excitatory action of serotonin on brainstem reticular formation neurons. In this same study, LSD did not block the excitatory effects of either *l*-norepinephrine or acetylcholine, nor did it block the inhibitory effects of serotonin. In an important extension of these results, Boakes et al. (16) reported that brom-LSD was considerably less effective than LSD in blocking serotonergic excitation. Finally, Bradley and Briggs (17) demonstrated the generality of these effects when they reported that both DMT and 5-MeODMT antagonized the excitatory neuronal effects of serotonin in the brainstem of anesthetized rats and cats, but that 5-methoxytryptamine, a structurally related nonhallucinogen, showed no antagonism.

Several classic serotonin antagonists were also tested and found to be effective in blocking these excitatory effects of serotonin (72). This has since been confirmed by a number of other investigators (16,41,68). Both Roberts and Straughan (72) and Haigler and Aghajanian (41) reported that these antagonists failed to block the inhibitory effects of serotonin on neurons in cortical and subcortical sites. Thus it appears that where serotonin exerts inhibitory effects, neither the hallucinogens nor the classic antagonists block these actions, whereas where serotonin exerts excitatory effects, both the hallucinogens and the serotonin antagonists block these actions. However, there may be some exceptions to this general rule (68,80).

Aghajanian has recently described another synaptic action for serotonin and another related, and direct, neuronal effect of the hallucinogens. The action of serotonin on brainstem motoneurons in the facial nucleus appears to be facilitatory (63). Thus, the iontophoretic application of serotonin produced neither excitation nor inhibition of the unit activity of facial nucleus neurons; when applied in combination with an excitatory input, however, it greatly facilitated the excitatory effect. A similar facilitatory effect was observed for norepinephrine. The serotonin antagonist methysergide blocked the facilitatory effects of serotonin but not those of norepinephrine. In a continuation of this line of investigation, McCall and Aghajanian (64) reported that LSD, mescaline, and psilocin had no effect themselves on facial nucleus motoneurons but potentiated the response of these neurons to serotonin and norepinephrine. In a sense, then, the hallucinogens appear to facilitate the excitatory effects of serotonin and norepinephrine in this brainstem site. The serotonin antagonist metergoline blocked the facilitatory effect of mescaline on the action of serotonin but not of norepinephrine.

A recent experiment by Blier and de Montigny (14) directly questions the fourth assumption and, therefore, the basic validity of the presynaptic model of hallucinogenic drug action. These investigators reported that quipazine, a drug that apparently has little or no hallucinogenic potency in humans, had exactly the same preferential presynaptic serotonergic action as LSD when examined in iontophoretic studies in rats. Like hallucinogenic drugs, quipazine

would be expected to produce disinhibition of serotonergic target neurons in various forebrain sites. Whether quipazine in the dose levels employed in this study is indeed nonhallucinogenic remains to be determined.

A review of the various known central nervous system (CNS) synaptic actions of serotonin, serotonin agonists and antagonists, and hallucinogens follows: (a) Both serotonin and the hallucinogens depress the activity of serotonergic neurons; these effects are not blocked by serotonin antagonists (41,52). This is the so-called presynaptic action of the hallucinogens. (b) Serotonin exerts inhibitory effects on postsynaptic neurons in a variety of brain areas, especially those in forebrain subcortical regions. These effects do not appear to be effectively blocked by the classic serotonin antagonists. The hallucinogens display a moderate serotonin agonist effect at these sites. (c) Serotonin exerts excitatory effects on postsynaptic neurons in a variety of brain areas, especially those in the cerebral cortex and brainstem. These effects are potently blocked by both the serotonin antagonists and the hallucinogens. (d) In brainstem and spinal cord (96), areas receiving a direct serotonergic input, serotonin exerts a facilitatory effect on excitatory inputs to these target cells. This facilitation is potentiated (or facilitated) by the hallucinogens and blocked by the serotonin antagonists. It is presumably this action of serotonin that is responsible for the serotonin behavioral syndrome (see below). Considering as a whole the variety of sites at which serotonin acts, it is clear that the hallucinogens exert a mixed serotonin agonist-antagonist effect, which is not paralleled by either serotonin or its antagonists. How this constellation of synaptic effects exerted by hallucinogenic drugs differs from that exerted by multiaction compounds, such as quipazine, remains to be determined.

Finally, I briefly review the effects of hallucinogenic drugs on monoamine-containing neurons other than serotonin. As mentioned above, mescaline, LSD, and psilocin potentiate the facilitatory effects of norepinephrine on neurons in the facial nucleus. Aghajanian (3) has reported that parenteral administration of both LSD and mescaline depressed the spontaneous activity of noradrenergic neurons localized in the locus ceruleus of the rat but potentiated the response of these neurons to a peripheral input. We have studied the effects of LSD on identified dopamine-containing neurons in the pars compacta of the substantia nigra (A-9) and on cells in the adjacent A-10 area in chloral hydrate-anesthetized rats (22). Intravenous injections of LSD (20–50 μg/kg) produced significant decreases in the discharge rate of these cells, an effect attributable to a dopamine agonist action of LSD. This dopamine agonist action of LSD probably is not critical for its hallucinogenic properties, however, because 5-MeODMT, another potent hallucinogen, was devoid of dopamine agonist action. Instead, 5-MeODMT increased the activity of A-9 and A-10 cells through a disinhibition most likely mediated by a depression of midbrain serotonergic unit activity.

Qualitatively similar effects of LSD on dopaminergic neurons, but of a lesser magnitude, have been reported by Bunney (20). This picture has become complicated by the results of our more recent experiments examining the effects of LSD on the activity of A-9 and A-10 cells in freely moving cats. Under these conditions, LSD (50 μg/kg i.p.) consistently increases the activity of dopaminergic neurons (G. F. Steinfels and B. L. Jacobs, *unpublished observations*); 5-MeODMT (50 or 250 μg/kg i.m.) did not mimic this effect. This LSD response is qualitatively as well as quantitatively similar to that produced by dopamine antagonist drugs, such as haloperidol. LSD is known to exert both dopamine agonist and antagonist effects. Thus our data suggest that when studied under physiologic conditions, LSD may manifest a dopamine antagonist effect. The dopaminergic actions of hallucinogenic drugs may relate more to their secondary properties, such as potency or development of tolerance, than to their basic ability to elicit hallucinations.

In summary, however, we do not have a sufficient amount of consistent electrophysiologic data to draw any definitive conclusions concerning the effects of hallucinogenic drugs on either noradrenergic or dopaminergic neurons.

POSTSYNAPTIC HYPOTHESIS

The electrophysiologic experiments described in the preceding section were conducted in anesthetized and/or immobilized animals. We have recently reported that the response of serotonergic neurons to brain stimulation, peripheral sensory input, or drug administration is dramatically altered by anesthetization with chloral hydrate (45). Furthermore, it is obvious that acute electrophysiologic studies of hallucinogenic drugs cannot directly be tied to changes in behavior. Such analyses are imperative if our ultimate goal is to draw conclusions about functional relationships. A combined behavioral-electrophysiologic approach is one of the ways to begin sorting out the relative importance of the four or more different effects exerted by the hallucinogens on the brain serotonin system.

To analyze the behavioral effects of the hallucinogens, we employed an observational method of scoring changes in the spontaneous occurrence of specific response categories in the cat. When cats were administered LSD parenterally, we observed the emergence of several behaviors that were rarely if ever seen in saline-injected animals (55,56). These responses included limb flicking, abortive grooming, investigatory behavior, and hallucinatory-like behavior. The peak behavioral response occurred at an LSD dose of 50 μg/kg, where 40 to 50 limb flicks per hour were elicited, but significant effects were produced by doses as low as 2.5 and 10 μg/kg. Other hallucinogens, such as psilocin, mescaline, DMT, and DOM, also produced these responses, but not a variety of nonhallucinogens: saline, Δ^9-tetrahydrocannabinol, amphetamine, chlorpheniramine, caffeine, and atropine (54,56). Brom-LSD and methysergide, both of which produce mildly hallucinogenic effects in humans, produced small but significant increases in responses such as the limb flick. These results may be of more general interest, since similar behavioral effects have been reported to be produced by various hallucinogens in rats (67) and monkeys (78,79,93).

On the basis of these data, we proposed that emergence of this group of

behaviors, but especially the limb flick and abortive groom responses (the two that were most reliable and robust), could be used as an animal behavior model for the actions of hallucinogenic drugs. More recently, we and others (62,84,85,94) have found that several drugs not typically assumed to be hallucinogens also evoke these responses, for example, lisuride, quipazine, apomorphine, and pilocarpine. However, the doses of these drugs that are necessary to produce these effects in cats are far in excess of those that are administered to humans. Therefore, these drugs might well be "LSD-like" if given to human subjects at these high dose levels. Despite the presumed lack of complete specificity of these effects for hallucinogenic drugs, they have been helpful in the study of this class of drugs.

In order to record the activity of single units in freely moving cats, we have utilized a technique that employs movable bundles of flexible, large-tipped microwires (32 or 64 μm in diameter) rather than the traditional small-tipped, high-impedance metal or glass microelectrodes (48,51). Thus we recorded the activity of serotonergic units in various raphe nuclei of the cat brainstem (e.g., dorsalis, centralis superior, magnus, and pallidus). This technique also allows us to "hold" cells for long periods of time (from several hours to several days), despite vigorous movements on the part of the cat.

First, I describe our experiments with 5-MeODMT, which has a molecularly more simple structure than LSD and which produced more clear-cut data. We were particularly interested in the temporal correlations between the onset, peak, and offset of the behavioral and unit data and whether or not the behavioral and unit data would have a correlated dose dependency. In order to examine these issues, we administered 5-MeODMT in doses of 10, 25, 50, 100, or 250 μg/kg i.m. and monitored the activity of serotonin-containing neurons in the dorsal raphe nucleus in conjunction with any gross behavioral effects (88). Under baseline conditions, serotonergic neurons in the awake, freely moving cat discharge with the same characteristic slow, rhythmic activity seen in the anesthetized rat. Following injections of 5-MeODMT, raphe unit activity was rapidly depressed in a dose-dependent manner; and dose-dependent increases were observed in the rate of limb flicking and abortive grooming. Furthermore, the onset, peak, and offset of the behavioral effects were temporally correlated with the onset, peak, and offset of changes in unit activity. By directly correlating behavioral changes with changes in the activity of serotonin-containing neurons, this study provided some of the strongest direct evidence in favor of the presynaptic serotonin hypothesis of hallucinogenic drug action.

We then extended this approach to the study of LSD. The results were generally similar to those seen with 5-MeODMT but with two critical differences (89). First, a 50 μg/kg dose of LSD produced a depression of raphe unit activity lasting, on the average, 3 to 4 hr, while the behavioral effects lasted for at least 6 to 8 hr. Second, when the 50 μg/kg dose was readministered 24 hr later, it produced little or no behavioral effect (tolerance), but the effect on raphe unit activity was as large as that seen on the previous day. Based on those two

dissociations of unit activity and behavior, we began to question the validity of the presynaptic hypothesis. Our skepticism was reinforced by later experiments with DOM, mescaline, and psilocin (86). With all three drugs, we observed the same temporal dissociations of serotonergic unit activity and behavior as observed with LSD. In addition, a low dose of psilocin (25 μg/kg i.p.) produced no significant decrease in serotonergic unit activity in any of the cells tested; however, it did produce significant behavioral effects. Mescaline (5 mg/kg i.p.) produced no overall significant change in unit activity but did produce large behavioral effects. Similarly, a low dose of DOM (50 μg/kg i.p.) did not significantly affect any of the serotonergic units tested but did have a significant behavioral effect. The highest dose of DOM (1 mg/kg) produced only increases in serotonergic unit activity but nonetheless elicited significant behavioral changes. Furthermore, cells in the ventral portion of the dorsal raphe nucleus did not appear to be preferentially sensitive to either mescaline or DOM.

We have also attempted to examine the generality of these dissociations between the effects of hallucinogenic drugs on behavior and their effects on the activity of raphe neurons by studying single unit activity in other groups of raphe neurons. The overall pattern of results with LSD for serotonergic neurons in nucleus centralis superior (K. Rasmussen, J. Heym, and B. L. Jacobs, *unpublished observations*) was similar to the dissociations described above for studies in the dorsal raphe nucleus. In addition, we examined the effects of LSD on unit activity of neurons in nucleus raphe pallidus, the most caudal group of serotonergic neurons in the cat brainstem. Somewhat surprisingly, the majority of neurons examined were almost completely unresponsive to doses of LSD (50 μg/kg i.p.) and 5-MeODMT (50 μg/kg i.m.) that produced potent behavioral effects (43,44). To account for these data, we hypothesized that the magnitude of the response of serotonergic neurons to hallucinogenic drugs may be related to the density of autoreceptors in the soma/dendritic area (44,50). Thus serotonergic neurons in nucleus raphe pallidus would be assumed to have relatively fewer autoreceptors than serotonergic neurons in nucleus raphe dorsalis. This relative paucity of autoreceptors on pallidus neurons might also explain why they display a high level of spontaneous activity.

Finally, a recent study from my laboratory provides perhaps the most damaging evidence to the presynaptic serotonergic hypothesis of hallucinogenic drug action (J. Heym, K. Rasmussen, and B. L. Jacobs, *submitted for publication;* 52). As described above, when cats are administered LSD (50 μg/kg i.p. in this case), they display a number of characteristic behaviors, such as limb flicking. If the cats are given any of a variety of serotonin antagonist drugs (e.g., ketanserin, mianserin, or metergoline) prior to the administration of LSD, the behavioral effects of LSD will be blocked in a dose-dependent manner. This was not attributable to nonspecific sedative or cataleptic actions of these drugs; when given alone, they did not significantly depress spontaneous locomotor activity. Furthermore, they did not block the behavioral effects of the nonhallucinogen apomorphine, but they did block the behavioral effects of DOM.

The main goal of this experiment was to examine whether pretreatment with the serotonin antagonist mianserin would also block the depressant effects of LSD on serotonergic neurons in the dorsal raphe nucleus of the cat. If it did, these combined behavioral and electrophysiologic data would support the presynaptic hypothesis. The results were unequivocal. Pretreatment with a dose of mianserin (1 mg/kg i.p.) that produced a complete blockade of the behavioral effects of LSD exerted no statistically significant blocking effect on the typical suppression (40–60% below baseline) of raphe unit activity induced by LSD. Similar results were obtained in experiments on serotonergic neurons in nucleus centralis superior and in experiments utilizing the serotonin antagonist ketanserin. These data support a postsynaptic serotonergic action as being important in mediating the effects of LSD and related hallucinogens.

BEHAVIORAL PHARMACOLOGY

This section is a selective review of behavioral pharmacology studies in animals and humans that are consistent with a postsynaptic serotonergic action of LSD-like hallucinogens. (See also the chapters by Davis et al., Appel and Rosecrans, and Nichols and Glennon, *this volume.*)

Experiments in which LSD increased the magnitude of the hindlimb extensor reflex in spinal rats were among the first to suggest that LSD exerted a serotonin agonist effect in the CNS, since this motor response is also produced by a variety of manipulations known to elevate central serotonergic neurotransmission (8). Andén et al. (7) later reported that similar effects were produced by psilocybin and DMT. Evidence that these were direct effects is provided by experiments that show that prior depletion of endogenous stores of CNS serotonin has no effect on the ability of LSD to influence the extensor reflex (7,8). Most important for our thinking was the fact that these effects of LSD were blocked with classic serotonin antagonist drugs (61).

We extended this type of analysis by employing a response with greater neurochemical specificity than the extensor reflex and examined the ability of LSD to elicit the "serotonin syndrome." This syndrome is considered a behavioral assay for increased activity in serotonin-mediated synapses (36,47). The syndrome is observed in rats and other species and consists most conspicuously of tremor, rigidity, Straub tail, hindlimb abduction, reciprocal forepaw treading, and lateral head weaving. Evidence that the presence of this constellation of behavioral signs reflects increased central serotonergic transmission is detailed in a review by Jacobs (47). We reported that intraperitoneal administration of LSD effectively produced this syndrome in rats (ED_{50} = 600 μg/kg) (91). This line of investigation has been continued more recently by Sloviter et al. (82), who reported that unlike LSD, brom-LSD did not elicit the syndrome, even in very high doses. In fact, pretreatment with brom-LSD had a significant blocking effect on the response to LSD. These authors also reported that classic serotonin antagonist drugs, such as methysergide, metergoline, and mianserin, blocked the serotonin

syndrome induced by the short-acting hallucinogen 5-MeODMT. Finally, in an important extension of this line of investigation, the same authors (82) found that the direct serotonin agonist actions of indole nucleus hallucinogens also generalized to phenylethylamine hallucinogens. Both mescaline and DOM produced the syndrome, and these effects were not blocked by prior depletion of endogenous stores of brain serotonin.

Two other sets of experiments that have employed the serotonin syndrome in the study of hallucinogenic drugs deserve mention. We reported that the repeated daily administration of LSD leads to a dramatic tolerance to the behavioral response to this drug: day 1 ED_{50} = 600 μg/kg, day 5 ED_{50} = 1,860 μg/kg (91). Thus we demonstrated that LSD had not only a direct postsynaptic serotonergic action, but that tolerance to the syndrome response might also be mediated postsynaptically. This is of particular interest since we also reported (89,92) that tolerance to LSD is not mediated by an altered presynaptic response (i.e., a change in the sensitivity of raphe neurons to LSD). In an attempt to directly examine whether tolerance to the serotonin syndrome-inducing effects of LSD was mediated by an alteration of postsynaptic receptor sensitivity, we carried out an experiment employing receptor binding. Repeated administration of LSD to rats (100 μg/kg every 6 hr for 4 days) resulted in significant decreases in the number of binding sites for both (^{3}H)-serotonin and (^{3}H)-LSD in both the forebrain and brainstem (90). This effect was not produced by a single injection of LSD nor by repeated injections of brom-LSD. These receptor binding data support the hypothesis that tolerance to at least some behavioral effects of LSD is mediated by an alteration in sensitivity of postsynaptic serotonin receptors.

Savage et al. (76) reported that chronic administration of monoamine oxidase inhibitors (MAOIs) to rats for 4 to 16 days produced a significant decrease in the number of binding sites for (^{3}H)-serotonin. This decrease in receptor sites was not seen after a single injection of a MAOI. The effect was assumed to be due to the increased long-term build-up of synaptic levels of serotonin that are known to be produced by MAOIs, since the effect was blocked by the coadministration of a serotonin-depleting agent. Peroutka and Snyder (69) reported that MAOIs decreased the availability of both serotonin agonist and antagonist binding sites, whereas tricyclic antidepressants selectively decreased the availability of serotonin antagonist binding sites. In a follow-up study examining the functional importance of these results, Lucki and Frazer (60) reported that the serotonin syndrome normally elicited by the hallucinogens 5-MeODMT and LSD was completely blocked by the chronic administration of a MAOI but not by chronic administration of tricyclic antidepressants. Furthermore, the authors suggested that the important action may be occurring at the serotonin agonist binding site.

We recently extended this line of research to include cat behavior (J. Heym and B. L. Jacobs, *unpublished observations*). Cats were given a daily injection of nialamide (5 mg/kg i.p.) for 1 week and then tested with LSD, DOM, or apomorphine at various times after the drug was withdrawn. The behavioral

response to LSD (50 μg/kg i.p.) or DOM (250 μg/kg i.p.) was almost totally blocked for the first week, showed a small amount of recovery during the second week, and returned to approximately baseline levels by the third or fourth week. To examine whether this suppression was due to nonspecific factors, such as malaise or debilitation, animals were tested with the nonhallucinogen apomorphine. At no time following nialamide withdrawal was there any significant depression of the response to apomorphine. Furthermore, chronic administration of the tricyclic antidepressant amitryptyline had no blocking action on the behavioral effects of LSD. These results from animal studies have a remarkable parallel in the human literature. Grof and Dytrych (38) reported that chronic treatment of patients with the same MAOI, nialamide, resulted in a partial or total blockade of the effects of LSD in doses as high as 400 to 500 μg. Further paralleling the animal studies was their report that this blockade of the effect of LSD persisted for at least 2 weeks after withdrawal of nialamide.

Direct evidence is also available from functional studies that LSD can act as a serotonin antagonist. Anderson (9) has reviewed experiments on spinal reflexes conducted in acute spinal cats in which stimulation of the dorsal roots elicits monosynaptic, polysynaptic, and dorsal root reflexes. Increases in CNS levels of serotonin increased the size of the monosynaptic reflex and decreased the size of the polysynaptic and dorsal root reflexes. The increase in magnitude of the monosynaptic reflex induced by serotonin was blocked by a variety of classic serotonin antagonist drugs; in addition, it was blocked by the systemic administration of LSD. Decreases in the other two types of spinal reflexes were unaffected by LSD and the serotonin antagonists.

A simple approach to examining the role of serotonin in the behavioral effects of hallucinogens involves comparing the effects of these drugs with the effects of decreasing brain serotonin levels. Destruction of serotonergic neurons in the midbrain of rats produces an augmentation of the acoustic startle response (29), which is similar to that produced by LSD (30). The augmented startle response produced by 5-MeODMT is blocked by pretreatment with the serotonin antagonists cinanserin and cyproheptadine (28). Another approach involves the direct manipulation of CNS serotonin and examination of the effect on the actions of hallucinogenic drugs. Studies by Appel and his colleagues (10,12,13) have shown that prior serotonin depletion, either by means of destruction of serotonin-containing neurons (13) or by pharmacologic means (10,12), potentiates the effectiveness of LSD in suppressing a bar press response for food in rats. Similarly, the suppressant effects of DOM, mescaline, and psilocybin were also potentiated by prior serotonin depletion (11,24). We discuss this "pause"-inducing effect of hallucinogens more fully below.

Results of studies on the role of serotonin in the action of LSD, which were conducted on human subjects, may be more easily interpreted because they directly examined the hallucinogenic effects of LSD. Prior depletion of brain serotonin with reserpine accentuated the effects of LSD (34,71). As described above, prior treatment with a MAOI attenuated the effects of LSD (38,70) and

DMT (75). Other studies in humans also lend support to the concept that hallucinogens act by means of an effect on the brain serotonin system and further suggest that the drugs may act specifically on postsynaptic receptors. A number of reports state that methysergide can elicit mildly hallucinogenic effects (1,42). Furthermore, Sai-Halasz (74) has reported that the effects of DMT were potentiated by methysergide. In this context, it is important to keep in mind that methysergide, like LSD, has mixed serotonin agonist-antagonist properties. This combined action may be a critical pharmacologic feature of drugs displaying hallucinogenic potency.

One of the characteristic effects of hallucinogenic drugs, discussed above, is to produce a pause in the responding of a rat trained to press a bar for either a food or water reward or to avoid a shock (12,83). Rats given a drug such as LSD will abruptly stop bar pressing for a period of 10 to 20 min and will then abruptly resume responding at the predrug rate. The early studies in this field demonstrated that the depressant effects of hallucinogens on response rate were potentiated by serotonin depletion (10–13). Such enhanced disruptiveness is difficult to interpret with any degree of specificity, since it may occur as a result of nonspecific factors. On the other hand, manipulations that block the disruptive effects of hallucinogens would provide more powerful information, since an increase in a specific behavior is less likely to be attributable to nonspecific drug actions.

A series of such studies has recently been completed. Commissaris et al. (26) reported that the responding of rats trained to press a bar 40 times in order to obtain a small food pellet was disrupted for long periods by DOM. This effect was blocked by pretreatment with the serotonin antagonist cinanserin but not by the dopamine antagonists haloperidol and chlorpromazine. In a subsequent study employing the same paradigm, Commissaris et al. (25) reported that the response suppressant effects of LSD, DOM, DMT, and mescaline were blocked by pretreatment with the serotonin antagonist metergoline. In control studies, the authors also demonstrated that the suppressant effects of amphetamine and phenobarbital were not blocked by metergoline, a finding that strengthens the argument that the effect of the hallucinogens is mediated by an action on serotonergic receptors.

Drug discrimination is another experimental paradigm that has proved to be useful in the study of hallucinogenic drugs. This approach has become increasingly popular in recent years (for a more extensive review of this topic, see the chapters in *this volume* by Nichols and Glennon, and Appel and Rosecrans). Basically, a rat is deprived of food (or water) and is then trained that pressing one of two bars will produce food if it has been previously administered a particular drug (e.g., LSD), while pressing the other bar will produce food if it has been previously administered another compound (e.g., saline or amphetamine). When rats have been highly trained on such a discrimination (i.e., if injected with LSD, they choose the left bar; if injected with amphetamine, they choose the right bar), they can be used in a variety of experiments. For example,

the rat can be given a third compound, such as DMT or cocaine, and then observed for its choice of a bar. If the drug has properties that make it "LSD-like," the rat would choose the left bar; if the drug was "amphetamine-like," it would choose the right bar; if the drug had none of these properties, or both of these properties equally, the choice would be somewhat random.

The blocking effects of one drug on the actions of another can also effectively be tested in this paradigm. A positive feature of this type of analysis is that it is often sensitive to low drug doses (e.g., 5 μg/kg LSD) (37). A limitation that this paradigm shares with other behavioral approaches to studying drug action is its lack of complete specificity. For example, Winter (97) reported that rats trained to discriminate mescaline generalized to 2,3,4-trimethoxyphenylethylamine, a nonhallucinogen. In a subsequent study (101), he demonstrated that rats trained to discriminate LSD generalized to 2,5-dimethoxy-4-methyl-α-ethylphenethylamine, a nonhallucinogen. Furthermore, Koerner and Appel (57) recently reported that the psilocybin cue did not generalize to mescaline.

The first experiment in this area was the demonstration that the systemic administration of either LSD or mescaline to rats could function as a discriminative stimulus (46). Several studies have reported that animals trained to discriminate a high dose of a hallucinogen, such as mescaline or LSD, will show a moderate degree of generalization to a low dose of the same drug (19,21,95). When this experiment is repeated in animals whose CNS stores of serotonin are depleted, the amount of generalization is increased, implying that at least some aspect of the effect of the hallucinogenic drug is mimicked by decreased serotonergic neurotransmission.

This approach has also been used to demonstrate that the cue properties across hallucinogenic drugs are similar. For example, rats trained to discriminate 5-MeODMT generalized to DOM, DMT, and mescaline (35); those trained to discriminate mescaline generalized to DOM (81); rats trained on LSD transfer to mescaline and psilocybin, but not amphetamine (77); and those trained on DOM generalized to mescaline but not to amphetamine or cocaine (98). In one of the most interesting studies in this series, Colpaert et al. (23) reported that rats trained to discriminate LSD showed partial generalization to the serotonin antagonists cyproheptadine, methysergide, and mianserin. This may imply that some aspect of the effect of LSD is mimicked by serotonin receptor blockade.

Of critical importance for this discussion are those studies that have attempted to block the discriminative properties of the hallucinogens. Several studies have examined one or more of the classic serotonin antagonist drugs (cinanserin, cyproheptadine, methysergide, and/or metitepine) and found them to be effective in blocking the discriminative stimulus properties of one or more of the hallucinogens (mescaline, DOM, and/or LSD) (19,58,81,99,100). Silverman and Ho (81) further reported that although cinanserin and methysergide, but not haloperidol, blocked the cue properties of DOM, they did not block those of methylphenidate or amphetamine, implying some degree of specificity of action. Furthermore, Kuhn et al. (58) have reported that although several serotonin antagonists blocked the discriminative stimulus properties of LSD, a variety of other drugs, such as antagonists of dopamine, acetylcholine, histamine, and α- and β-adrenergic receptors, did not exert a blocking action on the cue properties of LSD.

The material presented in this section suggests that the behavioral effects of a variety of hallucinogenic drugs, in both animals and humans, are heavily dependent on an action on the brain serotonin system. The exact nature of this interaction between hallucinogen and the serotonin system is not completely understood, but it may involve a combined agonist-antagonist action, and one that may be exerted primarily on postsynaptic serotonergic receptors. It is also worth pointing out that in a number of the studies described above, the serotonergic presynaptic action of the hallucinogen was precluded or at least strongly compromised by either synthesis inhibition or nerve terminal destruction, yet the behavioral effectiveness of the drug was either undiminished or enhanced. This also argues against a critical role for the presynaptic serotonergic action of hallucinogenic drugs.

SUMMARY AND OUTSTANDING ISSUES

LSD and related hallucinogens, such as psilocin, DMT, mescaline, and DOM, produce similar phenomenologic effects in humans and also display cross tolerance in their action. The most parsimonious explanation for these similarities is that these drugs share, at least to some extent, a common biological action. This chapter surveyed the evidence from behavioral studies in both animals and humans that the effect of these hallucinogenic drugs is mediated via an action on the brain serotonergic system. Electrophysiologic evidence that supports the hypothesis that this action is exerted postsynaptically (on the target neurons of serotonergic neurons) rather than presynaptically (on the serotonergic neuron itself) was reviewed. The major question that now confronts us is to provide a precise description of the nature of this postsynaptic action. This remains a difficult issue both because of the multifaceted action of drugs such as LSD and the inherent complexity of the synaptic action of serotonin (for review, see ref. 49).

In a review similar to the present one published several years ago (53), we listed the outstanding issues, as we saw them, regarding the action of hallucinogenic drugs. To date, many have remained unanswered, and new ones have now arisen. Therefore, I end this chapter by listing some issues, old and new, that remain unresolved:

1. Perhaps the most important question is whether highly specific serotonin antagonist drugs, such as ketanserin, would block drug-induced hallucinogenesis in humans. What other classes of pharmacologic agent would exert a similar blocking action?
2. As discussed above, what is the exact nature of the interaction between hallucinogenic drugs and serotonin neurotransmission? Is this effect characteristic

of all LSD-like hallucinogens? Does this action vary according to brain area (e.g., cortex versus brainstem)?

3. What, if anything, does the presynaptic serotonergic action of hallucinogenic drugs contribute to hallucinogenesis? For example, is the postsynaptic serotonergic effect altered because of a concomitant presynaptic serotonergic effect?

4. Is the dopaminergic action of LSD, on balance, an antagonist one? Is this action shared by all LSD-like hallucinogens? If not, what additional properties does this dopaminergic action confer upon those drugs that manifest it?

5. What is the critical difference between the action of LSD and quipazine on the CNS? When given in the dose levels employed in animal studies, is quipazine hallucinogenic in humans?

6. What are the precise synaptic mechanisms that mediate tolerance and cross tolerance to LSD? Are they different than the basic processes that mediate the acute actions of these drugs?

7. What is the significance of the differential inter- (dorsalis versus pallidus) and intraraphe (within dorsalis) neuronal sensitivity to hallucinogenic drugs?

8. Most studies to date have focused on monoamine systems; therefore, it would be of interest to examine the effects of hallucinogenic drugs on the neurochemistry, specific receptor binding, and electrophysiology of other putative neurotransmitter and peptide systems, such as γ-aminobutyric acid, glycine, acetylcholine, enkephalin, and substance P.

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LSD: The Bridge from Human to Animal

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Having personally paced the bridge from human to animal for almost 30 years, and often finding ultimate explanatory destinations as a mirage—intensely visible, salient to the moment's needs, but aggravatingly elusive to grasp—I hesitate to expose an unseemly reach. While a view from the bridge calls for perspective, too often one has the sense of suturing fleeting clouds. If one focuses solely on the striking array of effects of lysergic acid diethylamide (LSD) and related psychoactive indoles and phenylethylamines, a number of different explanatory syntheses have been attempted. These start with different observations—experiential, clinical, anthropologic, ethologic, biochemical, behavioral, neurophysiologic—and often with different purposes in mind. These drugs, then, generate inquiry across a range of phenomena in which biobehavioral correlates of the fact or structure of human subjective experience might be at issue.

Some seek to illumine the nature of mind and mysticism, to gain insight into (or access to) creativity or new learning, or a new therapeutics; others aim to understand the schizophrenias, or to find the clue to an endogenous psychotoxin unique to these disorders; and more commonly there are those who would discover etiologic or (preferably) mediating neurobehavioral and biologic mechanisms which might or might not be directly relevant to events in the clinic or meditative retreat. While others see an opportunity to study the psychobiology of perceptual mechanisms, many seem, often simplistically, to search for a unitary cause of hallucinations. Still others focus on "the meaning of amines" or a possible compellingly psychotomimetic configuration at the molecular or submolecular level. In this melange of purpose—observation, sporadic or systematic experiment, anecdote, and inference—it is not surprising that adjudicated fact, careful assessment of evidence, and systematic search for the contradictory (let alone the confirmatory) are too often missing, in either conclusory assertions, ascriptive discourse, or ad hoc assumptions underlying various experimental approaches.

What is encouraging for keeping watch on the bridge is the renewed pace, relevance, and even rigor with which components of the effects of LSD are being pursued in a range of research paradigms. If the bridge from human to animal is stipulated in the framework of biobehavioral sciences, the obvious

purpose is to understand how it is that human behavior and experience can occur as it does (requiring its accurate description, analysis, and test), and to discover mechanisms, processes, or leads in animals that might be tested to that end in man. It is in one sense a preposterous query, clearly one that ultimately awaits discoveries in neurobiology and human psychology by which brain operations and their parameters can be soundly linked to physiologic and behavioral processes. A part of the grand agenda of the life sciences is to find the essential element or parameter of an adaptive sequence or behavioral variable (whether dependent or independent) for which neuronal operations might be relevant. Thus molecular biology would hope to move from gene to phenotypic expression and appreciate the multiple complex paths to a phenotype. Nor, in retrospect, would there be apologies that, in the search for designs by which organizations are achieved and evolve, such banal witnesses as garden peas, fruit flies, yeast, bacteria, and fossils provided a bridge.

On this bridge, we need not apologize for assuming that biophysical and biochemical events reflect not only cellular changes but changes in the integration and control of small or large components of an organ, the function of which creates the links of the behaving mind and body. One would have to suppose that, at bottom, this is what actuates our interest, whether we work with snails or humans. Clearly, in neurobiology, aspects of sensitization and habituation (and perhaps of learning)—in terms of the effect of a signal on membrane processes and temporal interactions with ongoing action potentials—are now elegantly discerned (44). In both animals and humans, mnemonic, motivational, and affective components of subjectively vivid or strange experience (and behavior) apparently require limbic brain function as a substrate (38). Different roughly defined classes of psychotropic drugs differentially affect transmission, transmitters, and receptors. While detailed charts are few, there are occasional landmarks. Simply making a journey can expose new rules of the road and new territory. Elegance in linking a sequence of mechanism and actions to effect is rare, from whichever end of the bridge one takes his vantage. Yet there is reason to believe that persistent research into the mode of action of hallucinogenic drugs can lead to dissections and discoveries congruent with the grand design.

Whether we look at biopsychology, neurobiology, or psychiatry, different paths of inquiry and their languages are difficult to integrate and to keep conceptually clear. This is intrinsically difficult. We know we are dealing with an ongoing system and, in a sense, with five brains: neuroanatomic, electrophysiologic, monoaminergic, and peptidergic—if not ionic and molecular—and neurobehavioral. Thus, having reviewed aspects of LSD at least a dozen times since 1965 (3,23,25–28,30–34,36), I could regrettably create a catalog of carelessness (my own and others), dangling findings awaiting new knowledge before significance can be gained, observations uncoupled to function, or simply mislabeled as to process or mechanism, and hence missed opportunities for systematic investigation in both human and animal research.

Even in the simplistic sense, disturbed perceptual mechanisms, illusions, and hallucinatory vividness are not a clinical diagnosis, occur via many routes and contexts, and, along with the deployment of attention, arousal, thought, and affective processes, comprise a part of the picture of mental function. No more than an antihistamine can be thought of as solely antihistaminic, can we be trapped by labels—ascriptions of convenience—whether we speak of amine blockers or "hallucinogens," the psychotomimetics, psychedelics, or mysticomimetics. Every drug has patterns of action and effect that will differ in minor or major ways from congeners, and these complexities need not distract one if operational precision is kept in mind.

To improve traffic, let alone firm the bridge's bipolar anchors, we all, I suppose, could strive for precision, providing operational referents, whether speaking of human experience or the range of particular receptors linked to particular processes (and organisms, from cockroach to goats and humans) under current study. Thus I briefly review the basis of some of my own observations, then some essentials of the experience with the drug in humans useful for biologic and animal investigations, and, finally, some overall tactics or approaches that might be useful at each end of the bridge.

BRIEF RETROSPECT

In investigating LSD or hallucinogens, it would be useful to keep in focus what feature of pharmacologic or neurobehavioral interest is being sought. One could simply want to know about a drug—its pharmacodynamics, sites of action, and array of effects. One could also use a drug to know about something—a tool to investigate biologic systems, a probe to elicit fundamental regulatory mechanisms in cells and cellular systems, and in human or rat investigations to determine what aspects of a dysfunction are repaired or aspects of normal function are dissociated or altered (which in turn leads to a new perspective on the capacity of the organism and questions of underlying mechanisms). Both have, in fact, been done.

This is noted since the intense flurry of studies of LSD in humans had occurred between 1947 and 1957, at a time when biochemistry of the major psychoses offered no lead that could rationally command pursuit, and central nervous system (CNS) pharmacology was rudimentary. The presence of acetylcholine, norepinephrine (NE), and serotonin (5-HT) in brain came to be known within that decade, but not their localization, link to cellular organizations, or function. The useful effects of reserpine in schizophrenia had most strikingly stipulated a link of brain amines and behavior only when concomitant sedative and 5-HT-releasing effects were later discovered in 1955. By 1957, monoamine oxidase inhibitors (MAOIs) as "psychic energizers" were linked to an elevation of brain amines and their possible utility as antidepressants. Exciting knowledge of how the brain, operating as more than a switchboard, might produce graded states of consciousness and intensity in affective and cognitive function, derived from discoveries including the ascending and descending reticular systems. There

were also demonstrations through ablation and implanted depth electrodes of the role of subcortical and limbic systems in pleasure and pain, and appetitive, sexual, and aggressive dimensions of behavior. While mescaline had been noted to be structurally linked to NE, the search for biotransformations into putative endogenous psychotogens (adrenochrome) was fruitless. For the wrong reasons, the right investigations into the enzymatic mechanisms regulating synthesis and catabolism (and, later, nerve ending mechanisms regulating catecholaminergic function) were indeed stimulated, and advances in fundamental knowledge, led by Axelrod and others, ensued.

For LSD, by 1957 some of the essential behavioral effects in humans had been roughly delineated in clinical reports and systematic human psychopharmacologic studies largely pursued by Abramson and Jarvik, Kornetsky, and Isbell (26,60). Taken together, one could extract from these reports a rough map of the basic phenomena in man, although gropings with such strange phenomena as initially observed in unsystematic clinical studies led to an expectably florid range of assertion and inference. Nor have we entirely escaped their residue in either animal or human study as, in the 1970s and 1980s, human investigations especially have lagged. This, in part, is because of a major lack of systematic questions (pharmacologic, psychopathologic, and psychophysiologic), in part because of an ascendancy of "fringe" as well as therapeutic interests difficult to put into designed research, and in part because of the difficult social problems in conducting orderly, safe, and sober inquiry. Between 1957 and 1968, the major emphasis in human investigation sharply tapered off to a few systematic studies of therapeutic efficacy of different uses of LSD. These were eventually largely suspended as the abuse of LSD and psychiatric consequences of lay experimentation became a subject matter in their own right.

In 1957, then, at one end of the bridge were mollusks, uterine fundi, liver fluke, and gut, from which classic pharmacology could deduce drug action and receptor linked function, and at the other, an array of clinical puzzles, of dissociated behaviors, and a pattern of effects (in humans, spiders, fish, and important structure-activity relationships of ergots in rabbit) that had yet to be linked to any biochemically mediated process in brain. Animal experimentation had shown dehabituation (the familiar becomes novel), and fundamentally that the drug facilitated reactivity of reticular systems to environmental input. Differential changes in optic and auditory pathways were deduced from animal experiments, low dose LSD enhancing certain sensory systems and simultaneously inhibiting the responsiveness of various cortical systems and inhibitory effects of LSD and 5-HT on human and animal cortical cells. The general picture was of a behavioral state in which there was enhanced input with diminished and more variable control. The structural similarities of LSD and 5-HT, while physiologically borne out in *in vitro* studies, had yielded no link in brain, and the lack of psychotomimetic effect of the potently anti-5-HT LSD congener 2-brom-LSD (BOL) (and other ergot congeners) was widely taken as an indication that there was none.

My bias, then, reinforced by gifted students, was that the potency and reliability of LSD were too unique to ignore, and that both ends of the bridge required some systematic focus for useful traffic. Furthermore, it did not seem that genetic or biochemical change—if these actually existed in clinical disorder—produce a diagnosis, but rather shifts in neuronal systems, such that the range of signals and thresholds for different components of interlinked brain operations (and hence behavioral dimensions and effects) would be altered. Thus the use of LSD as a "model" was selected not because of any evident immediate or future clinical relevance, but rather because the drug reliably created periods of neurochemical and physiologic change—a chemically determined package of time (23)—during which sequences of subjective effects unfolded. Components of these effects could be readily observed in a range of acute psychotic and prepsychotic states, and in the case of LSD, a chemical trigger to events was undeniable. For both the brain biochemical and behavioral effects, LSD should provide a reliable way of tracing a sequence of effects and mechanisms and sites for them. A systematic study should yield evidence of mechanisms that could occur in nature, and expanded knowledge of brain function might be a useful spin-off. There were admittedly idiosyncratic motives as well—one beyond querying the dominant thesis of the day—that psychopathology was solely explained by learning. Having focused on CNS mechanisms in psychosis and allergy and the central actions of antihistamines, I had an illogical and certainly a hubristic hope that "tolerance" could be usefully investigated. Clinical work with families at high risk for schizophrenia, and offspring who did not develop the disorder, made any mechanism by which a psychotogen could "turn itself off" attractive to pursue.

Mechanisms of tolerance (for both morphine and LSD) remain elusive, but it was perhaps a fortunate beginning with respect to subsequent findings. Tolerance is a decrement of effect contingent on dosage schedule, and its analysis requires sorting out an array of reliable physiologic and behavioral effects and careful attention to temporal parameters. Thus with the general notion of studying periods of drug-induced biochemical changes and concomitant sequences of behavioral changes, we began a series of studies at Yale which branched off to a variety of systematic inquiries. Beginning with rewarded rope climbing behavior and later fixed ratio schedules of reinforcement in the rat, time parameters for the sequence of aminergic events, neurophysiologic changes, drug pharmacodynamics, behavioral effects, and characteristics of tolerance and cross tolerance were investigated. While commencing rat behavioral projects (19,20), I was able to systematically study both tolerance and acute tolerance in volunteer subjects at the National Institute of Mental Health (NIMH). More important, with various dosage schedules repeated in the same set of collaborative informers (prior to the period of frenetic psychedelic expectancies), one could remap the essential sequence of effects over a 10-month period and appreciate the environmental and personality sources of variability as well. Thus it was possible to test the regularity of the sequence of probable states in both schizophrenic

(21,26) and postdelirium tremens volunteers in observing the peyote ceremonial and, later, respectively, in studies of the aftereffects in lay experimenters (12,26,54).

When periods of acute behavioral change in rats were precisely coupled with brain biochemical measures, it was possible, by 1960, to establish a direct, stereospecific effect of LSD and psychoactive congeners on brain 5-HT levels (21a). The LSD effect was originally characterized as enhancing the binding of newly formed 5-HT to intracellular storage sites, and without direct effects on 5-HT enzymes. Fixed ratio schedules in rat met the criteria for a threshold dose and for tolerance and cross tolerance, with similar time parameters as in man. By 1963, it appeared to be simple (22): LSD and psychoactive congeners produced a unique pattern of small elevations of 5-HT and decrease in NE during a period of change in an array of electroencephalographic (EEG) (23), autonomic, and behavioral effects; furthermore, nonpharmacologic "stress" produced a similar pattern (6,22). Both an environmental and molecular signal appeared to converge in a common pattern of CNS aminergic response. The mechanisms for these changes are now, of course, differentiated. Nevertheless, changes in amine binding and release seemed to be related to a factor of intensity in both human and animal behavior, the amines appearing to modulate ongoing neurobehavioral regulations (23). The mirage of some unity in brain-mediated response to stress and molecules did spur further brain biochemical, behavioral, and electrophysiologic studies differentiating key processes. Unfortunately, this promising yield left time for only a terse report to the NIMH on human acute tolerance studies; and by 1966 (when I moved to Chicago), the feasibility of managing focused human investigations accountably and responsibly was minimal.

This is not the place to document what students, colleagues, and collaborators of that decade, as well as many others, have independently assembled and learned. Looking back, one sees striking advances in neuroanatomy and physiology in the ability to deduce important receptor or aminergic functions from behavioral analyses (67), a far better grasp of the link of aminergic function to component behavioral effects, a focus both on perikaryal and nerve ending events, and, while lagging, postsynaptic events as well. In the mid-1960s, Aghajanian and I (3) noted the recurrent difficulty of estimating the significance of biochemical findings viewed in isolation from the cellular systems that link chemical events to physiologic and behavioral effects. It is now clear, however, that the logic of how the CNS is built from dorsal root to cortex, and the arrangement of aminergic source cells at the raphe pacemaker and at cortical nerve endings that can facilitate or inhibit major afferent input, as well as the different 5-HT-LSD binding sites (and new systems of behavioral analysis relevant to them), can provide the text for future biobehavioral research. The focus on LSD has had utility. With general advances in biopsychology, one can no longer assume that arrays of known behaviors are started or stopped by an amine; rather, we can appreciate the interacting influences on any component system,

depending in part on the prior state of one or another significant variable. For LSD, the logic of coupling sequences of behavioral change and periods of biochemical and neurophysiologic change is evident and nicely demonstrated in the recent combined electrophysiologic, behavioral, and biochemical studies of LSD and tolerance in the freely moving cat (64). Thus we can turn to the question of what observations in man may require of and suggest for animal investigations and, occasionally, vice versa.

RELEVANT PARAMETERS OF LSD EFFECTS IN HUMANS

Without doubt, LSD compelled attention because of its stereospecificity, high potency, and reliability in producing a time-limited period of uniquely altered psychedelic mental functioning, as well as the striking structural and physiologic links to 5-HT systems. Less than one-billionth of a gram per gram of brain will signal a sequence: a march or train of multiple effects. While variably embellished, these effects are reliable in terms of basic periods of altered perceptual, affective, and mental functioning. However we describe the pattern and characteristics of the "trip," the enhanced clarity of consciousness in the presence of the diminished importance of reality, we must contrast the reliability of a single dose of LSD (and far less potent related drugs) with the amnestic and confusional effects of the cholinolytic deliriants and the dissociative anesthetics with neurologic and neurosensory effects. All these drugs differ from the uncertain psychotomimetic effects of single doses of amphetamine (especially in naive subjects) and the variability of mental response produced by enzyme inhibitors and amine precursors.

Onset and Offset of Effects

First we note that a threshold dose is necessary for the psychedelic sequence to be triggered; a dose of between 25 and 50 μg by mouth or intravenously is necessary. We lack systematic observations of subthreshold dosages. What is striking is that once begun, the trip unfolds through an acute phase (about 4 hr in man) and a 4- to 6-hr second phase. During the second 6 hr, the "TV show in the head" no longer compels interest; subjects think often that the effect is over but fairly regularly report (at, perhaps, 10 hr after an initial dose) that they had been at the least self-centered, and usually suspicious, with ideas of reference or even paranoid convictions. This LSD effect continues to go unstudied and unnoted in discourse on, or research design for, psychotomimetic and hallucinogenic studies.

With an increase in dosage, the total duration of effect is some minutes longer, but what is most marked is an increased intensity of effects and diminished control or regard for, or valuation of, the banal real world and its immediate requirements. I cannot, with any certainty, describe toxic doses in terms of temporal parameters (although these might be gleaned from sporadic reports).

Whether subthreshold doses in animals can produce any animal neurobehavioral component of the "loosening" of inhibition and inner-directed attention sought for by some clinicians in using less potent drugs for a kind of "psychosynthesis" is uncertain. Sensitization and habituation studies implicate raphe function but not in any simple way (32), and pavlovian studies show very low dose effects on sensory processing (39,43).

Route of administration may be an important variable to apply to animal research. Early fragmentarily reported investigations in humans indicate an onset after oral ingestion of early effects at about 30 to 40 min, with a more rapid onset with intramuscular injection, and even more rapid with intravenous injections; the latter, in my experience, when given slowly over a 2-min period, show an onset at around 20 min. As later noted, accelerating the rate of intravenous injection can bring on a brief, immediate effect. In two individuals receiving intrathecal injection, the onset noted by Paul Hoch (at Columbia University) was 1 to 2 min. The question is whether one can deduce something about the brain areas affected and perhaps specific receptors within the mass of different key brain areas that might be essential for the unique pattern of effects and the switching of attention from exterior to interior.

Thus it is clear, in both animals and man, that the clearance of drug is related to the period of acute effects, with plasma half-life values signaling their termination; for the human, this takes about five times as long as for the rat. The plasma half-life also signals a shift from the first phase of rat brain 5-HT, and 5-hydroxyindoleacetic acid (5-HIAA) changes [the point at which I have deduced that postsynaptic or feedback-induced inhibition of synthesis of 5-HT occurs (32–34); the presynaptic nerve ending signal for reducing tryptophan hydroxylase activity or blocking methiothepin stimulation of the enzyme occurs early in the course of events (9,42)]. The peak vesicular (or, after reserpine, juxtavesicular) retention of 5-HT occurs at this point (41,50,58), as drug appears to leave a particulate fraction (24,58) and be cleared from brain. In the rat, we know that brain concentrations of the drug peak within 1 or 2 min following intravenous injection (58); that gross behavioral effects of the drug (nose twitches, generalized piloerection, tachypnea, atactic hind limbs, periods of hypersensitivity to noise) occur sooner with the intravenous as compared to intraperitoneal route, and the duration of behavioral effects was somewhat shorter, correlating with slightly shorter half-life and shorter period of 5-HT-5-HIAA effects (58). We know, too, that plasma values are generally about 1,000-fold greater than brain values, and that clearance from different brain areas in which drug had been preferentially taken up closely follows the plasma half-life of LSD. We had some evidence (24) that there may be different clearance rates in a few regions, perhaps the anterior hippocampus being slightly slower. The role of the choroid is apparently important in drug clearance, with residual drug binding noted in autoradiography (18); the recent studies by Meibach et al. (55), elegantly demonstrating cellular aggregates and regional differences in the binding of drug, are interestingly discussed in terms of possible functional significance.

Thus there are regional and even subcellular aspects of the uptake and clearance of drug, with subsequent shifts in the regulation of 5-HT metabolism which may relate to function. In man, the period of drug clearance may be somehow accountable for the "march" of unfolding effects. In acute tolerance studies, one could observe events characteristic of the first 2 hr (i.e., the perception that something new was happening and perceptual illusions enhanced) when a second dose was given at 3 hr; the acute effects were briefer and the total duration of effects of doses so spaced was longer but not additive (26).

When the drug was given by rapid intravenous injection, rather than slowly over 1 or 2 min, subjects reported a different onset. Usually about 20 min after slow intravenous administration, there is a sudden and surprising shift in consciousness. This is described in terms of visual perception as a sudden awareness that what is at the periphery of the visual field is as important as that at the center; there are also odd feelings referred to the muscles or body, and occasionally slight dizziness and even nausea. Acute observers found, and others confirmed, an "oops, here we go" feeling in the pit of the stomach, or "like a roller coaster." One sees a facial flush most regularly, pupil size increasing, some perceptual illusory phenomena, and build-up of tension relieved by giggling. The initial shifts in attention may involve a sudden appreciation of the grain in wood, rather than the door itself; for several minutes, the change of state is what is impressive, with visual aspects and emotional lability gaining in intensity and frequency after the first hour and for the subsequent two. This may later be followed by laughing or crying in the second hour. At that time, there is an increasing absorption in internal feelings or in the distortion of objects in which adaptive perceptual behavior is diminished: aspects rather than the functions of objects dominate perceptual behavior. Elemental feelings—fear and exhilaration—coexist (26).

With rapid intravenous injection, it was as if the subsequent $3\frac{1}{2}$ hr were rehearsed as a preview of coming attractions. In brief, the intensity of visual illusions and quasihallucinatory experiences seemed initially to flick rapidly by for 2 or 3 min (as if they were clips of a movie); then the pace slows, and the initial effects (or adaptations to them) seemed to follow the usual sequence. Recalling that intensity and vividness of subjective effects in all its components—affective and visual—are characteristic of this enhancement of "highlights" with rapid injection, one wonders whether there are any leads or leverage with dose effects and rate parameters in determining critical sites of action. Pharmacodynamics in the human should account for the 20-min lag after slow intravenous injection; obviously, the onset can be pushed closer to time zero by controlling administration rate and route, but the unfolding of events appears related to clearance from brain tissues. Perhaps rapid access to tissue creates a brief dysequilibrium of drug content; but after equilibration, clearance of drug then regularly commences. Both events could produce "signals" of the characteristic drug effects. Animal study focused on these phenomena might clarify the issues.

Mydriasis and Phases of Drug Effects

A remarkable concomitant mydriasis appears to signal the triggering of the sequence of psychotomimetic effects. This is a dose-dependent response in both magnitude and duration of effect. Known to be centrally mediated, the neurobiologic study of this effect requires further scrutiny. Indeed, in studying the offset of effects—by asking when the human was no longer reacting to drug (the termination of the "second phase")—the time of the return of pupil size to normal seemed to reliably signal the subject's consensus (and retrospective consensus) as to the end of the trip. Mydriasis begins to decline at about 4 to 5 hr post-LSD, returning to normal at 8 to 10 hr after doses of 100 to 200 μg.

The course of post-LSD pupillary changes, with respect to dosage schedule and intensity and duration of effects, is a valuable tool. Pupil size 3 hr after the initial dose responded to the second dose of LSD and was an obvious measure to track in acute tolerance studies in humans. Given the number of rat studies in which this would be useful to monitor, the problem lies in determining rat mydriasis (easy in other animals); while a computerized pupillometer (developed by Martin Adler at Temple University) was informally tried by us once with LSD, systematic studies have not been done.

Mydriasis is also relevant to an underlying theme, that of "phases of effects." An overlooked effect in the human is important to note. In a study of chronically schizophrenic women (in whom typical LSD psychologic and behavioral effects, not an exacerbation of disorder, was noted), there was apparently a 24-hr effect: a matinal rebound increase in pupil size (21). Thus after the first dose, usual pupillary increases were noted (although I, unfortunately, do not recall precisely measuring the offset of effect in these subjects, pupil size had clearly begun to show the expected decrease at 4 to 5 hr). What was surprising was that if one measured pupil size 24 hr after each of three daily doses, the 9:00 a.m. pupil size was increased but showed tolerance with daily dosage. Tolerance during the first 6 hr after each dose was expectedly present (less mydriasis and shorter duration), but the 24-hr effect was unexpected. These women later received a large dose of reserpine; after 48 hr, when behavioral effects of reserpine had subsided, they were again studied with LSD for tolerance development. The subjects themselves had readily detected tolerance, and did so with LSD after the reserpine pretreatment; the usual mydriatic response to LSD and to the tolerance dosage regimen was also observed. When the 24-hr pupil size was examined, a different picture emerged. Reserpine alone had produced a matinal miosis which, in controlled studies, seemed to disappear after 7 days. After LSD, the matinal miosis was increased and did not show tolerance. We speculated that LSD might exhaust available stores of adrenergic mediators leading to an unmasking of the parasympathomimetic effects (too long ignored in LSD research), either of LSD or of reserpine, or of an effect of amine-depleted nerve endings on parasympathetic function. Since the effect of LSD at adequate time periods after reserpine-induced depletion is to enhance retention of 5-HT in a

juxtavesicular fraction in the nerve ending (32), and since we do not, to my knowledge, know the postreserpine effects of LSD on nerve ending catecholamines (as we do for indoleamines), there are obvious studies ahead. Further discussion of "compensatory" shifts at time periods after the initial dose is relevant to tolerance.

Tolerance

The third criterion that animal systems should demonstrate with respect to the psychedelic trip in man is the observed tolerance to both the mental effects and mydriasis. This appears to be complete after several daily doses and to be lost after 4 days without LSD. With respect to biologic mechanisms, occurrence of acute tolerance in both man and animals (20) poses a problem. Whether tachyphylactic or other processes are entailed remains to be defined.

In the rat, multiple low doses of LSD over days or weeks produce changes in 5-HT and NE turnover rates, but with measures taken many hours after the final dose (32–34). After a single dose, the initial changes (in the first 60 min where our behavioral and biochemical correlations have been focused) of nerve ending amine distribution are followed over the next 2 hr by longer lasting changes, such as the inhibition of conversion of 5-HT from labeled tryptophan and other indices of slowed turnover. This may be similar to the feedback inhibition induced by chlorimipramine (CMI) and its blockade of reuptake. With CMI, Halaris and I (32) saw an initial (30-min) increase of 5-HT (not in the juxtavesicular fraction) and decrease of 5-HIAA, followed for 2 hr by parallel decreases of 5-HT and 5-HIAA, congruent with 5HT-induced, postsynaptically mediated, or feedback inhibition. How the LSD sequence of changes are signaled requires investigation. Effects after a single dose in animals at time points throughout the 24-hr period following the initial LSD dose and similar time course studies after tolerance are needed. What is clear is that the effects during the first 60 min of LSD on brain tryptophan, 5-HT, and 5-HIAA [as well as brain tyrosine and dopamine (62) and plasma corticosterone (40)] show tolerance: there is an earlier termination of 5-HT effects and a diminished magnitude of 5-HIAA effects. Behaviorally, perhaps parasympathetically mediated effects, such as salivation and bradycardia, and other effects (diminished grooming) were noted as long as 90 min after injection (23). Biochemical correlates are not yet established, nor has tolerance been carefully studied for these effects.

In rats, we know that tolerance does not occur to parasympathomimetic effects of LSD at a time when sympathomimetically mediated and behavioral effects show tolerance. Apart from the postreserpine LSD-induced pupillary changes, such differential effects in man are not known. We know also that the bradycardia in unrestrained rats (19) converts readily to a tachycardia, and assertions that LSD elevates blood pressure or pulse in man should be viewed as reactivity rather than a direct effect.

With respect to the biochemical effects in animals and the behavioral effects

in man, tolerance is characterized not only by a decrement in specific effects but by a decreased intensity and magnitude and duration of effects. Thus by the third daily dose of LSD, the schizophrenic volunteers complained that they were not having the exciting effects of the first dose, and normal volunteers had noted that, even with the second dose, the "roller coaster effect" was regularly absent. There is, then, a shift to the left on any dose- or time-response curve with respect to tolerance and components of intensity that are blunted. How the initial "it's like adrenalin, but it isn't" (according to one experienced volunteer) effect is mediated is intriguing. How to determine the real basis for this, I cannot presently suggest. Fancifully, viewing the shift of all effects to the left, it is as if some initial effect occurs but is quickly compensated and some possible contingent subsequent effects are also diminished; i.e., there is a "minireaction" shortened in duration. If the phenomena were in any way linked to speeded up compensatory effects of 5-HT or NE systems (such as the increased 5-HT turnover 18 to 24 hr after multiple daily doses), animal studies over appropriate intervals will be needed. Furthermore, if 5-HT or catechol-mediated effects of LSD can influence the intensity of LSD effects, these may be obvious areas to pursue for characterizing the neurobiology underlying tolerance.

In our animal studies, it is apparent that one had to await the offset of the first 45 min of behavioral effects—perhaps 25 min more—before acute tolerance on rope climbing could be observed. If the second dose occurs during acute effects, there appears to be an enhancement of ongoing impairments. I speak only to the exquisite importance of temporal factors in producing a clear picture of tolerance. When these factors were appreciated, the long postponed demonstration of behavioral tolerance to dimethyltryptamine (DMT) in animals (49) was achieved. Half-life of drugs are somehow entailed; why, after short-acting drugs, the next dose must be sooner than 24 hr requires explanation.

Animal observations also point to a dimension of effects that have not been studied in humans. Thus in general, behaviors maintained by noxious reinforcement do not show tolerance; to my knowledge, this has not been searched for after daily doses in man. Nor has the cyclicity of tolerance with high dose been much investigated at either end of the bridge, although the waxing and waning of this phenomenon described by Koella et al. (48) points to some cyclic phenomena that must be occurring. In brief, there is evidence in humans that LSD induces a state in which aversive and competitive and conflictual stimuli are further disturbing, unpleasant, and indeed may contribute to post-LSD states where subjects are noted to avoid the noxious stimuli and strains of everyday life. Thus it would be important to study those behaviors that might be altered, even in the presence of what appears to be an organism tolerant to the psychotomimetic effects of LSD. Whether this would entail the use of evoked potential and information processing paradigms currently applied in the schizophrenias (15), or a study of adaptation to aversive stimuli, obvious research approaches are suggested. In our own observations in animals, it appears that, when tolerant, they are "willing to perform" rather than be distracted or absorbed by other stimuli during the acute phase of effects. When studying rat mounting

behavior in my laboratory, Gillette (37) noted a 40-min period of nonresponding which disappeared with tolerance, while the primary LSD effect of fewer "bucks for a bang" persisted. Rope climbing rats tolerant to LSD performed at the same speed but not with the same skilled movements. Thus the underlying sensitivities and deviations that may be uncovered during a tolerant state may help dissect components in both the LSD effects and mechanisms of tolerance.

Cross Tolerance

With appropriate dosage regimens, there is a cross tolerance of LSD and psychoactive congeners psilocybin, mescaline, and DMT. Although studies of tolerance development and loss with these substances have not been as systematically pursued as with LSD in humans, the phenomenon poses major questions as to which of the several different receptor systems, if any, under current study is uniquely relevant to that sequence of effects termed psychedelic. There is no cross tolerance to amphetamine. The series of methoxylated amphetamines developed by Shulgin have not been sufficiently described systematically in man for more than informed anecdote (57). The use of "mescaline units" to compare potencies (although not pattern of effect differences) appeared useful, but new human investigations are needed. There is no question that these substances, now used in currently select undergrounds, are relevant to this search and inquiry.

In general, in animal research, it is well to be cautious, whether bufotenin or 5-methoxylated tryptamines or other substances postulated to be useful "hallucinogenic" tools are used and to be aware of the status of knowledge of their effects in humans, let alone on a characteristic battery of effects in animals. In rat, for example, 5-methoxytryptamine (20 mg/kg) appeared to markedly increase 5-HT metabolism as judged by 5-HIAA, although interfering factors in measurement were not ruled out (29).

Obviously, it would be tempting to find those receptors or receptor-linked systems that provided some commonality (4,53), so that the effects of LSD and the spectrum of cross-tolerant drugs could be rationalized. The truly marked difference in biochemical effects (especially duration) and different aminergic mechanisms affected by these different but related psychotomimetics with respect to 5-HT and NE metabolism, and marked differences in duration of effects, have been emphasized elsewhere (33,34,63). How mescaline is and is not related to 5-HT calls for rigorous review and study. In summary, insofar as intensity of effects may be mediated by different characteristics of aminergic function, such factors should be sought in both man and animals in a more systematic way. The marked change in threshold dose for LSD after certain 5-HT depletions (of very small magnitude) is a key lead and paradigm for such studies.

Blockade, Attenuation, and Intensification

The question of blockade and modification or attenuation of the sequence of effects—of intensification or dampening of effects—requires precise and careful

definition. Unfortunately, with respect to BOL and blockade by chlorpromazine, the data in humans are not sufficiently precise to clarify issues for the animal researcher. While this is a topic for review in its own right, it is clear that BOL does not produce a typical psychedelic sequence in high dose, and the importance of distinguishing between subjectively fuzzy or hypnotic altered states and psychedelic effects is always important. It is evident that BOL does not produce the excitatory effects of LSD (in which plasma cortisol increases). It is most likely that a single dose does not block efficiently, and that BOL achieves clear-cut attenuating effects in man only when tolerance dosages are used preceding the LSD test. Why this would be so, on biologic grounds, is a puzzle.

Similarly, it is apparent that chlorpromazine does not prevent the LSD sequence of effects and, when given during the LSD experience, may mask perception of some of the changes but not the course of the march of events. Indeed, because of the effects of chlorpromazine per se, most clinicians treating "bad trips" have learned, if medications are to be used, to employ sedative antianxiety drugs, such as valium. Animal experiments tell us that remarkably small doses of chlorpromazine can be strikingly effective in blocking the effects of LSD on fixed ratio performance (30 μg/kg), and there was some early hint that less of a 5-HT elevation occurred with chlorpromazine pretreatment in rat brain (22).

In brief, LSD itself and pretreatment with psychoactive congeners are most effective in turning off or attenuating the LSD sequence of responses. Were human investigations possible today, systematic and rational design of pretreatment regimens could provide important tests of these issues and a variety of interesting hypotheses (e.g., possible effects of lithium, alpha-adrenergic agents, carbamazepine) designed to clarify mechanisms of action. Yohimbine, for example, while not psychedelic, produces a component seen to "oscillate" in LSD states (tension and anxiety).

Pretreatment with reserpine can enhance and prolong the LSD response in man (21). The paradigm used in our laboratories for both animals and man to study "drug-behavior interactions" was to conduct many tests after the acute effects of reserpine had diminished and most of the drug had been excreted (conceivably infinite amounts could be stored in membranes for the long period of reserpine effects). The effects observed 48 or 72 hr after reserpinization in humans were of a more intense LSD reaction with some degree of clouded consciousness and perhaps a prolongation of effects. On the other hand, when chronic MAO inhibition is established, the effects of LSD are diminished. The problem is to track in detail what components are diminished; but this order of information simply is not readily available. Therapists who have been using LSD clinically had also commented on this effect, but it is one that requires scrutiny so that useful detail is available to the animal researcher. Our own attempts to produce this in animals ran afoul of many complications in dosage regimens, but Lucki and Frazier (51) have indicated such an effect recently on the rat 5-HT "syndrome" and B. L. Jacobs (*personal communication*) in cats. Why it is that chronic MAO inhibition may be necessary (what is it that is

different in the chronically inhibited animal?) requires analysis; a panmonoaminergic subsensitivity of postsynaptic receptors might be investigated.

In attempts to deduce whether elevations of 5-HT would dampen LSD effects, agonistic effects of 5-hydroxytryptophan (5-HTP) have complicated animal studies. There are reports of mood changes and possibly some dampening effects on hallucinations in schizophrenic subjects with 5-HTP and, in one case, in a post-LSD psychosis (1). An agenda of human research as well as carefully conducted animal investigations is called for if we are to have precise definitions of blockade, attenuation, and intensification of effects. This is also relevant to the question of the magnitude of CNS changes necessary for the effects of a putative "psychotoxin" to be expressed. In animals, depletion of only 5 to 10% of 5-HT levels can lower the threshold dosage and intensify the effects of LSD (see refs. 32–34 for review). One is reminded of the small changes in 5-HT, produced by small doses of parachlorphenylalanine, that induce relapse of treated severe depressive disorders (39). The question of 5-HT antagonists blocking the hallucinogenic or psychotomimetic, rather than 5-HT-induced neuromuscular, effects or in drug detection paradigms requires focus. The search for a pure 5-HT antagonist recurrently promises a precise tool, and some progress is known. To apply these tools, at whatever receptor type they act, and to test for the range of biochemical, behavioral, physiologic, and electrophysiologic effects that have reliably characterized LSD and its interactions in animals (5) is necessary. In my view, the difficulties in demonstrating efficient blockade of LSD effects by 5-HT antagonists in such relevant paradigms are far more impressive than the successes. For specifically hallucinogenic and mental effects, such studies in man are lacking.

Dopamine Effects

Given the question of the interaction of LSD with CNS dopamine systems, there are tuberoinfundibular dopamine receptors for which LSD has high potency in man. Apart from this observation, with respect to biochemical, neurophysiologic, and behavioral responses to LSD, one does not see a dopamine agonist effect in animals without prior disruption or injury (such as axotomy or reserpine). In brain biochemical studies, it has been postulated that prior receptor occupancy may determine whether the usual antagonistic effects of LSD (e.g., signaling an increase of synthesis) occur. The only effect seen in humans that implicates dopamine was the occurrence of "antagonist" effects: oculogyric crises and extrapyramidal effects in some of the reserpine-pretreated women given LSD (21). In brief, we have no evidence of clear-cut dopamine-mediated mental effects of LSD, and the concept of prior occupancy might offer a research paradigm for human and behavioral studies.

Two "Psychotomimetic" Phases of LSD Effects

Human investigations point to dimensions for which psychobiologic study is relevant. I have noted the two phases of LSD effects relevant to understanding

the different "psychotomimetic" aspects of the LSD experience. Psychedelic experience in early phases of clinical psychosis (10), where meaningfulness and portentousness are prime characteristics of the experience (the sense of truth is enhanced, but not the necessity to test the truth of the senses), can occur in a variety of states where sensations and perceptions have heightened intensity and meaning. In studies of critical flicker fusion in pigeons (7), analysis of the effect of low dose LSD (20 μg/kg) in improving accuracy evoked the explanation of "enhanced sensory impact" of the flicker. This heightened awareness (differing from simple threshold effects) can be studied with sophisticated study designs.

Characterizing the psychobiology of the second phase in animals, of what in the human is clearly a paranoid state, also invites special research designs. The heightened vigilance and inefficient scanning (61) noted in humans to explain paranoid "mislocations" or misattributions (26) perhaps could provide a start. The EEG signs in animals of a shift in attentiveness and valuation of positive reinforcement (16,69,70), coupled with enhanced sensitivity to stimuli and noxious input, have also been noted (32). It should be remarked, however, that aspects of the first phase of the LSD experience—the heightened awareness, mislocation of cues, and the "visualness" or "sensoriness" of the experience—can be seen in a number of disorders. I have described this in watching the development of amphetamine psychosis, where, prior to interpretations and stabilizing delusions (which "explain" and "contain" what is odd), illusionary and heightened perceptual effects are quite common prodromes, and so too in the very early phases of delirium tremens. If amphetamine psychosis and the second phase of LSD are similar in man, differentiating these in animal study, and accounting for tolerance with one and not the other, provides an interesting challenge.

Perceptual Constancies and Distortions

This cannot be an occasion for scrutiny of the phenomenology of perceptual and hallucinatory changes induced by LSD. These have been reviewed in part by Siegel and Jarvik (60), and recent publications (2) focus on various aspects of the visual experience that may persist in chronic users. The characteristic persistence of reports of geometric frames against which perceptual illusions occur has long been noted, and a pioneer in such investigations, Heinrich Klüver (47), emphasized that aspects of the very mechanisms that process perception seem themselves to be brought into relief. As CNS visual systems are now elegantly characterized, further studies in animals seem possible. Klüver (47) noted the "anchoring" cortical systems to which information of the outside world arrives and the variability of subcortical systems; he speculated on hallucinogen-induced changes in the balances of these.

One could summarize many effects of LSD as affecting those stabilizing perceptual anticipations and adaptations, and those constancies and habits that normally smooth over the disparate details of our perceptions and actions. Thus

after one brief exposure, some individuals note persistent aftereffects. I reported (26) one of the first scientists working with LSD who was bothered for months after his single LSD experience by the flashing of the telephone poles at the periphery of his vision as he commuted daily, attempting to read his morning *London Times*. Normally, one can suppress the irrelevant in order to focus. There, in brief, is an apparent sensitization in which some aspects of the altered state can recur. Some individuals experience micropsias during the LSD state and do so in occasional flashbacks afterwards. The flashbacks do not appear to be like a television replay but do represent aspects of the experience that seem to persist and be reevoked, sometimes with external stress, sometimes without apparent explanation. How can a lifetime of perceptual habit be changed in a single, 6-hr experience? In those vulnerable to undesired long-term effects, the breakdown of constancies, whether these are viewed as perceptual or in terms of psychologic defenses (or in terms of regulation of the access of primitive thought and memories to consciousness), seems critical. This is clearly an important area for psychobiologic study.

One interesting aspect for study deriving from human investigation is the "double registration," the persistence of a mental image of what has just been seen, superimposed on an ongoing experience. For example, while I was measuring pupil size and asking individuals to look at a red X on the wall, one subject said to me: "You are Jesus Christ on the Cross." When queried as to why this florid expression of ambivalence toward a well-motivated researcher (with an odd middle name), he reflected that, in fact, he simply was able to see the X at the same time he was looking at me. This kind of overlapping—a failure to suppress a prior percept—was tested by Appel, Peterson, and myself in an uncompleted experiment in monkeys, where the animals were trained to respond differently to a circle and a square, and differently to the circle in a square. Under LSD, they frequently responded to the separated stimuli as if they were overlapping.

An interesting account of such perceptual changes, noted by a lifelong sufferer from Gilles de la Tourette's syndrome (8), suggests also that sensitization and subjective representation of sensorimotor processes (events occurring just prior to overt response) are dimensions requiring psychobiologic study in the "tic" syndrome. With Aghajanian's demonstration of facilitatory (but not direct) effects of both LSD and mescaline (iontophoretic or intravenous) on input to motor nuclei (53) [and, when given intravenously, on input to the locus ceruleus (4)], the feedback, if any, to sensory representations of this altered state of the motoneuron (or to "setting" sensory gates which seem strikingly "opened") would be of interest. One can wonder, when afferent flow to motor nuclei has enhanced effect, if there are also changes at the "upstairs" sources of input to these nuclei that might be subjectively registered. Thus Bliss (8) describes "mounting tensions" felt (or projected) on the skin and in muscle groups; for the compelling reduction of these tensions, action was needed. Prior to the tic, intense shifting phantom sensations, poorly confined as to modality (synes-

thesias?), were noted, along with the failure to confine a prior perceptual input to its normal temporal boundaries.

In this sense of altered sensorimotor processing, the pavlovian conditioning experiments with LSD and remarkable response to a very low dose of LSD in "sensory processing" is important to pursue with respect to neural processes entailed (39,43). In brief, LSD can be having effects on various different information processing aspects of stimulus and response, which may eventually provide a clue to some of these strange effects during the LSD experience, as well as aftereffects. Whatever the underlying mechanisms, they also could be relevant to the range of clinically encountered post-LSD phenomena.

POST-LSD EFFECTS

In terms of clinical disorders seen in a small subset of long-term users of LSD, studies are appearing with increasing frequency (11,12,14,66). Some (65) implicate a higher risk for "LSD psychosis," with strong family histories of major psychosis or psychopathology. Clinicians know that in these schizophrenia-like disorders with a history of drug use, there can be a ready precipitation of a period of acute symptoms triggered by continued drug use. Whether or not low cerebrospinal fluid (CSF) 5-HIAA proves to be a marker for vulnerability or is drug induced (11,14), it has been noted in these patients long after drug use is discontinued; acute changes in CSF are not yet studied, nor are total body measures of tryptophan metabolism available during the acute state in humans. The problem in these LSD-associated mental illnesses with a chronic course is that we do not know if LSD is a specific stressor in genetically vulnerable people, or whether in the very experience of LSD episodes there is a specific sensitization or learning or persisting biologic change that creates or reinforces vulnerability to subsequent psychotic states. Schizophrenic subjects are not more sensitive than others to the drug, nor did the group of postdelirium tremens subjects (picked for a history of three or more episodes) show a hallucinatory diathesis. Thus there is no ready explanation for these drug-associated disorders. The broad question is how LSD produces a short- or long-lasting change in the ability to regulate the switch between internal and external adaptations and between realistic and dereistic thinking and experiencing, which ranges from mild perceptual oddities to schizophreniform chronic psychoses.

Bowers and I (10,12) had characterized the LSD state as a multipotential state, out of which different outcomes, with respect to the particular trip, depended on prior expectancy and adaptations taking place within the drug state. The outcome could be seen as mystic, religious, a curiosity, a significant event, or a constant disturbance. I have indicated (26) that some of the LSD flashbacks were reminiscent of the traumatic war neuroses in which an unexpected experience (such as being buried alive by a shell burst) is repeatedly experienced as an intrusive and frightening memory, as if one were retrospectively trying to master an uncontrollable event. There is a psychobiology developing in which

the elicitation of behaviors to cope during a period of stress seems to lead to less noxious aftereffects; as such experimental paradigms advance, animal studies with LSD could be designed. While sensitization and habituation have been evoked in numerous LSD studies in man [and in studies of either the stimulation or ablation of the raphe nuclei (32)], one suspects that these complicated and probably different processes, along with facilitation, will be useful in understanding, at the neuronal level, these disorders of perception and sensitization to noxious inputs.

OVERALL TACTICS OR APPROACHES

Attempting to conceptualize these various disinhibitions, rearrangements, and enhancements of mental operations, I have argued (26,33) that LSD as a tool may be limited for a variety of reasons. One cannot have an LSD trip without the drug in sufficient quantity to affect an array of systems postsynaptic to the raphe, and probably other critically identified receptors. In other words, it is important to utilize LSD for what it can best explain and for the leads to basic processes it can provide. I have pointed to the heuristic utility of appreciating the small order of magnitude of biochemical change (5–10%) which could miscue and disrupt central signaling systems. If binding or carrier proteins or macromolecules within the nerve ending can be altered by LSD and the disposition of 5-HT thereby affected (32,41), at the least fundamental knowledge of basic processes from the regulation of 5-HT ion channels to a more refined grasp of processes regulating binding and release might ensue from such research, whatever its relevance to hallucinogenic events.

None of these leads can directly explain the psychedelic or hallucinogenic response; although it is clear that, among other neural systems, optic pathways are affected by LSD, various imbalances in other systems and in affect and cognition are involved. Furthermore, it is prudent to define each psychotomimetic drug in its own right. It is possible that LSD may have peculiar biophysical and biochemical effects not shared by psychoactive congeners, and we should not be surprised that slight molecular changes in any medicinal will produce not only a somewhat different range of effects but act through different mechanisms. Thus if there are different paths to the effects by which the compounds under question are commonly related, both commonalities and differences should be a key purpose guiding research in this area. Do the receptors linked to drug discrimination studies have any linkage to electrophysiologic or biochemical or other aspects of the LSD response? What processes account for cross tolerance of these different molecules with similar effects?

At the least, we should more systematically classify those drugs that produce a psychedelic sequence in man and show cross tolerance with LSD with respect to the different receptor systems that apparently rank order these drugs in terms of their potency. Such rank order effects have been noted on molluscan ganglia (35) in the clam heart on excitation of cardiac muscle; in liver fluke on glycolysis

and an adenylate cyclase system (52); directly on the cyclase in cockroach thoracic ganglia (57); on FR schedules of reinforcement (5); by Aghajanian on the most LSD sensitive of CNS tissues, the raphe perikarya; and on differences between raphe perikaryal and postsynaptic effects. These and other systems classify potency of LSD and related drugs fairly well; other systems do not. Without commenting on the question of what order of magnitude of effect in receptor binding studies (such as the S1 and S2 receptors) should be required, it would be helpful if some attempt at deducing physiologic ranges of the concentration of the involved amines and drugs were reported in *in vitro* studies. Low affinity binding sites have also been suggested as relevant (32). Similarly, the loose ascription of low and high dose across different species (without regard to half-life) or effector system need not continue to confuse discourse. ,

It would be useful to employ a standard array of drugs, of "R" and "S" isomers at equivalent dosages determined on reliable human and animal behavioral, physiologic, and receptor assays. Similarly, in utilizing agonists and especially serotonin antagonists, the pharmacology and physiologic effects of different agents should be mapped out to avoid false deductions of functional significance. The literature is replete with observations that require scrutiny or refutation [such as a putative hallucinogenic effect of the serotonin agonist, quipazine (70)]. Where synthesis or release is directly studied (45), this simplifies understanding of the aminergic effects of the different compounds; but where they are indirectly deduced, as generally is the case, confusion remains [such as that cited in a recent review (34) with respect to DOM and catechol turnover]. The above sampling is random, but the problem nevertheless is real.

Finally, the failure to utilize both threshold and maximal doses to determine correlations with a sequence and duration of effects, such as in electrophysiologic studies of postsynaptic events (32), may leave us in ignorance of similarities and differences among the psychotomimetics. I have also wondered whether the low potency of LSD (as compared to psychoactive congeners) in affecting NE release and synthesis (despite LSD enhancing input to the locus ceruleus) is at all related to the remarkable behavioral and biologic potency of the drug. The studies of Horita, fractionating excitatory and other effects of LSD in the rabbit and showing that after depletion, repletion with L-DOPA restores excitatory effects of LSD, still presents an unfinished story and one that, if pursued with other precursors and systems, might help in putting together the puzzling picture. Similarly, systematic study of the role of mescaline and phenylethylamines with respect to 5-HT receptors or 5-HT-mediated effects could clarify matters. Obviously, looking at the range of striking differences in regard to NE metabolism and duration of effects of drugs such as mescaline and psilocybin on NE (63) or on hydroxytryptamine (29), when compared to LSD, the question of their commonalities somewhere along the sequence of drug-induced CNS events remains a central challenge. Possible effects of psilocybin on reuptake and MAO (29) also require focus.

Electrophysiologic and behavioral observations in LSD-treated animals may give some hint as to the switch in attentiveness in the presence of a moderately high state of arousal, which is characteristic of LSD in man. One would expect further clarification of the physiologic role of the raphe with respect to REM sleep because, in nature, this is one state in which a natural shift to primary process thinking and plastic and sensory thought and perceptual processes (with a compelling sense of conviction) can occur.

The nervous system is constantly surprising because of the regulations that can occur in the absence of one or another key nucleus or amine (46). In general, however, it has been my impression that we seek eventually to reconstruct a picture of how the brain functions when its elements are present. Thus disruptions of one or another system have led us to appreciate the "unannounced" role of amines in modulating and buffering various sensory inputs and regulation of vital functions (23). In human investigations, one strategy has been to study those measurable aspects of arousal and evoked potentials found in schizophrenia, and to apply such measures to the animal or LSD-treated human (17); or we clinically look for a clue to altered receptors in brain in study of peripheral receptors. While we cannot tell from where we will derive essential new information, it should be possible to systematically compare the range of psychedelic compounds within the human, to use our knowledge of modern receptorology with respect to 5-HT and the catechols, to focus on key sensorimotor links or limbic and cortical "imbalances" in regulating sensorimotor functions, and to perceive, thereby, what is necessary and sufficient for the sequence of effects.

Whether techniques, such as PET, in animals or humans will advance our knowledge, the obvious gain will be in our ability to pose tougher questions. It is a difficult and elusive area in which to sort and seek the key mechanisms; what is astonishing is that, with each passing period of review, new and clarifying knowledge has ensued. This bridge watcher, while urging that we do intellectually and conceptually what we can to gain leverage on the problem, obviously believes that, with the current rate and direction of experiments, the bridge is well worth pacing.

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