CHAPTER

61

Neuropharmacology of Lysergic Acid Diethylamide (LSD) and Other Hallucinogens

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OUTLINE

The hallucinogens are a class of agents capable of producing a complex syndrome of mental and perceptual alterations. The unique subjective experiences induced by these compounds are typically far removed from normal waking states and are difficult to describe using conventional language. This class of substances produces such a wide range of effects that it has been difficult to name them, although numerous terms have been proposed: psychedelics, psychotomimetics, psychodysleptics, illusinogenics, delusinogenics, dysleptics, misperceptionogens, psychoticants, psychotoxins, schizogens, entheogens, oneirogens, mysticomimetics, phantasticants, psychotaraxics, and phanerothymes. Unfortunately, these names are either overly specific (referring to one particular effect) or are nonneutral terms reflecting their perceived utility. Although the term *hallucinogen* is a misnomer – these drugs rarely provoke actual hallucinations and do not usually impair reality testing – it is the term most consistently used in the scientific literature; therefore, *hallucinogen* is the designation that will be used in this chapter. These substances are sometimes referred to as *serotonergic hallucinogens* or *classical hallucinogens* to distinguish them from other pharmacological classes that produce some degree of hallucinogen-like effects.

THE HISTORY OF HALLUCINOGENS

Humans discovered thousands of years ago that the ingestion of certain plants can induce marked alterations of consciousness and perception. Hallucinogens derived from botanical sources have been used by numerous cultures throughout the world, often for mystical, ritualistic, or divinatory purposes, but also to induce inebriation and to cure illnesses. Notable examples include the mescaline-containing peyote cactus (*Lophophora williamsii*; see Fig. 61.1), *teonanácatl* mushrooms

FIGURE 61.1 Illustration of the hallucinogenic peyote cactus (*Lophophora williamsii*) from *Curtis's Botanical Magazine* (1847).

(the fruiting bodies of members of the genus *Psilocybe*, which contains psilocybin), and *ayahuasca*, an infusion or decoction prepared from *Banisteriposis caapi* and admixture plants. Despite the important role that these substances have played in human history, hallucinogens generally escaped from the attention of academic researchers until the end of the nineteenth century. The modern era of scientific investigation of hallucinogens began in 1897, when Arthur Heffter isolated the alkaloid mescaline from peyote. Over the next few decades a few investigators, most notably Kurt Beringer in Germany and Heinrich Klüver in the United States, systematically investigated the effects of mescaline in humans. Despite these pioneering efforts, hallucinogens remained mere scientific curiosities until the discovery of (+)-lysergic acid diethylamide (LSD). LSD was first synthesized by Albert Hoffman, a Swiss chemist working for Sandoz, in 1938. Five years later, in 1943, Hoffman accidentally discovered that LSD is an extremely potent hallucinogenic agent, capable of producing effects at doses as low as 20–30 μg. The results of the first human study with LSD were reported in 1947 by Hoffman's colleague Walter Stoll, who observed that the drug produced effects that were very similar to the symptoms of schizophrenia. The finding that minute doses of LSD could produce such striking mental changes led to a flurry of studies with the drug, and rekindled scientific interest into mescaline and other hallucinogens. Some of this work was driven by the possibility that hallucinogens could be used as a model of psychosis, whereas other investigators theorized that hallucinogens might possess therapeutic efficacy against psychiatric disorders, chronic pain, or substance abuse.

The discovery of the hallucinogenic effects of LSD coincided with the isolation of serotonin (5-hydroxytryptamine, 5-HT). 5-HT was initially isolated as a vasoconstrictive agent in serum, but was later found to be present in the central nervous system of mammals. LSD and 5-HT contain an indole nucleus, indicating a link between 5-HT and the action of LSD. In 1953, Gaddum demonstrated that LSD can block the contractile effect of 5-HT on smooth muscle. Based on that finding and on the presence of 5-HT in the brain, Wolley and Shaw proposed that 5-HT plays a role in mental disorders. This proposal is noteworthy as it represents one of first times a neurochemical was specifically linked to brain function. Given the important role that LSD played in this proposal, it could be argued that the discovery of LSD helped usher in the modern era of neuropharmacology and biological psychiatry.

During the 1950s and 1960s, hundreds of clinical studies were conducted with LSD and a variety of other hallucinogens. Although some of these studies produced positive results, by modern research standards much of this work was methodologically flawed, lacking appropriate control groups, randomization, or blinding. Moreover, some of the experimentation was potentially unethical, involving subjects who were incapable of giving informed consent. Military and intelligence agencies also investigated these agents to determine whether they could be used as incapacitating agents or to facilitate interrogation. In parallel with these events, lay interest into hallucinogenic substances increased, and by the late 1960s these compounds had become popular recreational drugs. In response to the widespread nonmedical use of hallucinogens, legislation was enacted throughout the world to restrict their use. Despite these regulations, illicit use of hallucinogens has continued at rather constant levels for the past four decades, although the incidence of hallucinogen use has generally been lower than is found with stimulants, depressants, or cannabinoids.

EFFECTS OF HALLUCINOGENS

Humans

Hallucinogens produce marked alterations of consciousness. Because of the highly subjective nature of hallucinogen effects, verbal self-reports have traditionally been used to assess their effects. Despite their different chemical structures, hallucinogens such as LSD, psilocybin, and mescaline produce remarkably similar subjective effects in humans. Conversely, subjects can readily distinguish the effects of hallucinogens from those of other drug classes, including cannabinoids, anticholinergics, stimulants, opioids, and *N*-Methyl-D-aspartic acid (NMDA) antagonists such as phencyclidine (PCP) and ketamine. The effects of hallucinogens are extremely variable, but in general they produce alterations of mood, affect, cognition, and perception. The most common perceptual effects occur in the visual modality, including hypersensitivity, distortions, illusions, and elementary hallucinations, but alterations of tactile, auditory, gustatory, and olfactory perception can also occur. Other common effects include changes in the sense of time and space, synesthesia, derealization (feelings of unreality), depersonalization (changes in body image), loosening of ego boundaries, and impaired concentration. Hallucinogens can provoke experiences that are very similar to spontaneous mystical states, with some subjects in recent clinical trials with psilocybin rating the drug-induced spiritual experience as among the most meaningful events of their lives. There may also be vegetative effects such as nausea, malaise, headache, mydriasis, sweating, and increases in blood pressure and heart rate. The effects of hallucinogens depend on the personality and mood of the individual taking them and the environment in which they are taken, and depending on the circumstances the nature of experience can range from pleasurable to highly aversive. Hallucinogenic drugs can induce severe panic reactions, more commonly known as *bad trips*, and prolonged psychotic or depressive reactions have occurred in individuals with preexisting psychopathology. Under proper conditions, however, adverse reactions to hallucinogens are extremely rare. Hallucinogen effects can sometimes spontaneously reoccur after the acute reaction has subsided, sometimes months or even years later, a phenomenon known as *flashbacks.*

To improve the accuracy and reliability of the assessment of hallucinogen effects, several rating scales have been utilized. One of the most thorough and extensively used is the Altered States of Consciousness Questionnaire (APZ), developed by Dittrich to provide an etiology-independent assessment of altered states of consciousness. According to the studies that have assessed hallucinogen effects using either the original APZ scale or later variants such as the 5D-ASC, hallucinogen effects occur in five core dimensions: (1) *Oceanic Boundlessness (OB)*, positive experiences of derealization and depersonalization; (2) *Anxious Ego Dissolution (AED)*, experiences of thought disorder, delusion, and loss of control that are usually perceived as being negative; (3) *Visionary Restructuralization (VR)*, including elementary hallucinations, visual imagery, altered meaning of percepts, and facilitation of recollection and imagination; (4) *Auditory Alterations (AA)*; and (5) *Reduction of Vigilance (RV)*, which includes drowsiness and cognitive alterations. Hallucinogens dose-dependently increase scores in these five dimensions, although higher doses are generally required to alter AED and AA scores. Studies using the APZ have shown that the subjective effects of hallucinogens can be distinguished from those of other pharmacological agents, such as ketamine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"), confirming that fundamental differences exist between their effects and presumably their pharmacological mechanisms. The Hallucinogen Rating Scale (HRS), developed to assess the effects of *N*,*N*-dimethyltryptamine (DMT), can also be used to characterize the effects of other hallucinogens, but has not been as widely used as the APZ.

There is some overlap between the effects of hallucinogens and the symptoms of schizophrenia, but exactly how much similarity exists is controversial. As early as 1913, Knauer and Maloney recommended that psychiatrists should self-administer mescaline to gain insight

into the experiences of their patients, but Berringer was the first to propose that mescaline could be used as an experimental model of psychosis. Studies conducted during the 1950s and 1960s confirmed that LSD, mescaline, and psilocybin can provoke states in normal individuals that resemble the earliest symptoms of schizophrenia. There is a close parallel between acute psychotic decompensation and the loss of control over thinking induced by hallucinogens. There are, however, substantial differences between schizophrenic symptomatology and the effects of LSD-like drugs. Most notably, hallucinogens typically produce visual but not auditory hallucinations, whereas the opposite is true of schizophrenia. It is also rare for hallucinogens to induce social withdrawal and catatonia but these symptoms are often found in schizophrenia patients. Given those differences, it has been proposed that the effects of PCP and ketamine are more appropriate models of schizophrenia because they produce a broad range of schizophrenia-like effects in normal subjects. More recent investigations have demonstrated that the effects of DMT primarily resemble the positive symptoms of schizophrenia, whereas ketamine produces effects that resemble the negative symptoms and cognitive deficits seen in schizophrenia. Other studies have confirmed that psychotic patients show elevated APZ scores compared with healthy controls. Based on these findings, it appears that the state induced by hallucinogens models a specific subset of schizophrenia symptoms.

Animals

Given the constraints on human studies, animal behavioral models have been the principal method used to study the pharmacology of hallucinogens over the last three decades. Due to the complexity of hallucinogen effects, as well as their highly subjective nature, it has been difficult to develop tests of hallucinogenic activity in animals. Animal models of hallucinogen effects can be divided into two classes, those that assess behaviors that are analogous to the effects of hallucinogens in humans, and models based on behaviors that have no human counterpart. Despite the limitations associated with these models, they have proven invaluable in the study of the pharmacological and neurochemical effects of hallucinogens. Importantly, recent human studies with hallucinogens have corroborated the findings of earlier animal studies, supporting their cross-species translational validity. Hallucinogens have been shown to produce the following effects in rodents: (1) potentiation of the neophobia and agoraphobia normally exhibited in response to an open-field; (2) impairment of habituation; (3) reduction of prepulse inhibition, an operational measure of sensorimotor gating, indicating diminution of pre-attentional filtering mechanisms; (4) induction of abnormal motor behaviors such as head twitches, wet-dog shakes, and ear scratching; (5) increases in impulsive behavior; and (6) alteration of temporal perception. Rodents and other laboratory animals can also be trained to discriminate the interoceptive stimulus effects of hallucinogens from almost all other drugs. The drug-discrimination paradigm has demonstrated considerable utility in structure–activity studies and in the identification of some of the neurochemical actions of hallucinogens. Because this paradigm requires extended training and repeated administrations of the hallucinogens, however, it is more suited to the study of the chronic effects of hallucinogens than the study of the acute effects that are more likely related to the subjective effects reported by humans.

MECHANISM OF ACTION

As was noted earlier, LSD, psilocybin, and mescaline produce virtually identical subjective experiences in humans. Repeated ingestion of hallucinogens can induce marked tolerance, and LSD, psilocybin, and mescaline have also been shown to produce cross-tolerance. These factors indicate that the serotonergic hallucinogens act through a common mechanism. There is substantial evidence that the characteristic effects of hallucinogens are mediated primarily by 5-HT_{2A} receptor activation. First, all serotonergic hallucinogens act as 5-HT_{2A} receptor agonists, and some hallucinogens are highly selective for 5-HT_{2A} and 5-HT_{2C} receptors. Second, most of the effects of hallucinogens in animals and humans are blocked by 5-HT_{2A} antagonists, whereas antagonists selective for other 5-HT receptors (including 5-HT_{2C}) are generally ineffective at blocking hallucinogen effects. For example, Franz Vollenweider and colleagues have shown that the subjective and behavioral effects of psilocybin in human volunteers are blocked by the selective 5-HT_2 antagonist ketanserin and the D_2/5-HT_{2A} antagonist risperidone, but are relatively unaffected by the dopamine (DA) D_2 antagonist haloperidol. Similarly, deletion of the gene encoding the 5-HT_{2A} receptor eliminates many of the behavioral effects of hallucinogens in mice. Third, there is a significant correlation between the potency of hallucinogens in animals and humans and their affinity for the 5-HT_{2A} receptor, but not for non-5-HT_2 sites. Fourth, chronic administration of hallucinogens to rodents induces 5-HT_{2A} receptor desensitization, whereas other receptor subtypes are unaffected. Given the aforementioned evidence, there is a general consensus that the 5-HT_{2A} receptor is responsible for mediating the characteristic effects of hallucinogens.

Although the 5-HT_{2A} receptor is the primary site through which hallucinogens act, interactions of

hallucinogens with other 5-HT receptor subtypes, including 5-HT_{1A}, may contribute to or modulate their effects. Certain indoleamine hallucinogens, including LSD and 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT), bind to the 5-HT_{1A} receptor with relatively high affinity, and there is evidence that a subset of their behavioral effects in rodents is mediated by 5-HT_{1A} activation. Furthermore, the mixed 5-$HT_{1A/1B}$/β-adrenergic antagonist pindolol has been shown to intensify the subjective effects of the hallucinogen DMT, indicating that 5-HT_{1A} activation by DMT normally acts to attenuate its 5-HT_{2A}-mediated effects. LSD is also a potent agonist at several DA receptors, and this action may play a role of some of the effects of LSD as well as contribute to the uniquely high potency of the drug. Indeed, it has been shown that the discriminative stimulus effects of LSD in rats are time-dependent, with a first phase mediated by 5-HT_{2A} receptors and a second phase involving DA D_4 receptors.

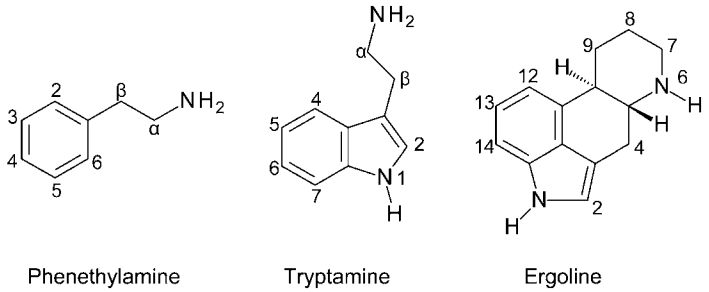
CHEMICAL CLASSES OF HALLUCINOGENS

There are two main classes of serotonergic hallucinogens: phenylalkylamines and indoleamines. The phenylalkylamines contain a phenethylamine group (see Fig. 61.2) and are similar in structure to the endogenous neurotransmitters DA and norepinephrine. Indoleamines, by contrast, contain an indole nucleus and have a structure similar to that of 5-HT. The indoleamines can be subdivided into the chemically simpler tryptamines and the ergolines, which contain a more complex, tetracyclic ergoline structure. Only a few of the hallucinogens listed in this section have been formally evaluated in clinical trials, but anecdotal human data have been reported by Alexander Shulgin and others.

Phenylalkylamines

A variety of substituted phenylalkylamines have hallucinogenic effects. Most of these compounds act as selective 5-HT_2 agonists, although they are relatively nonselective for 5-HT_{2A} versus 5-HT_{2C} receptors. Mescaline (3,4,5-trimethoxyphenethylamine) is the prototypical compound in this class, but has relatively low potency, requiring several hundred milligrams to produce effects lasting up to 12 h. Structure–activity relationship (SAR) studies have demonstrated that certain structural modifications can markedly increase the potency of mescaline (see Fig. 61.3). One of the first structural modifications was the introduction of a methyl group into the α-position to afford the phenylisopropylamine ("amphetamine") 3,4,5-trimethoxyamphetamine (3,4,5-TMA), which is approximately twice as potent as mescaline. The increase in potency is likely due to a combination of factors, including facilitated CNS penetration and resistance to metabolic deamination of the side chain. Studies also examined the effects of rearranging and/or removing one or more of the methoxy groups in TMA. TMA-2 (2,4,5-TMA), formed by shifting the *meta*-methoxy group in TMA to the *ortho*-position, was found to be the most potent TMA isomer. TMA-2 is orally active in the range of 10–20 mg, and the increase in potency is accompanied by a corresponding increase in 5-HT_{2A} affinity. Of the mono- and di-methoxylated amphetamine derivatives, only 2,5-dimethoxyamphetamine (2,5-DMA) retains potent hallucinogenic activity. The findings with 2,5-DMA and TMA-2, both of which have methoxy groups in the 2- and 5-positions, indicated that this substitution pattern is optimal for activity.

Based on the fact that addition of a 4-methoxy group to 2,5-DMA (to afford TMA-2) increases its potency, a large series of 2,5-DMA derivatives with different 4-position substituents were examined, a few of which are illustrated in Fig. 61.4. One of the first derivatives synthesized had a methyl group in the 4-position; this compound (2,5-dimethoxy-4-methylamphetamine, DOM) was found to be extremely potent, producing effects at doses of 3–10 mg and having ~10-fold higher 5-HT_{2A} affinity than TMA-2. DOM has appeared on the illicit market as "STP," named after a popular motor oil additive, but recreational use has generally been limited due to its long duration of action (>24 h after high doses). Potency can be increased even further by



Phenethylamine Tryptamine Ergoline

FIGURE 61.2 Three chemical classes of hallucinogens.

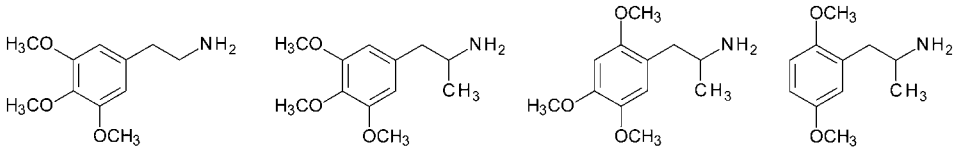
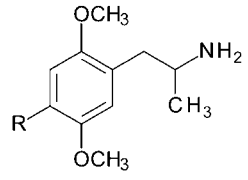


FIGURE 61.3 Structural modifications increase the potency of mescaline.

lengthening the 4-methyl group in DOM by one (2,5-dimethoxy-4-ethylamphetamine, DOET) or two (2,5-dimethoxy-4-proylamphetamine, DOPR) methylene units, but longer or bulkier alkyl groups are generally not tolerated. The most potent members of this series have a halogen atom in the 4-position, such as iodine (2,5-dimethoxy-4-iodoamphetamine, DOI) or bromine (2,5-dimethoxy-4-bromoamphetamine, DOB). DOB is almost as potent as LSD, producing effects at doses of 1–3 mg, and acting for 18–30 h. It has been proposed that 2,5-DMA derivatives with hydrophobic or electronegative moieties in the 4-position exhibit high 5-HT_{2A} affinity because those atoms/groups interact with a specific lipophilic pocket within the receptor binding site. This idea is consistent with the fact that that 2,5-DMA derivatives with polar 4-position substituents have very low 5-HT_{2A} affinity and are inactive as hallucinogens. Molecular modeling studies indicate that the 2,5-substitution pattern is optimal for binding because the two methoxy groups are positioned to form hydrogen bonds with specific serine residues in the binding pocket. It appears that 3,4,5-trisubstituted compounds such as mescaline bind to the 5-HT_{2A} receptor in a different orientation than the 2,4,5-trisubstituted compounds.

Phenylisopropylamines possessing a 3,4-methylenedioxy group, such as MDMA and MDA (3,4-methylenedioxyamphetamine; Fig. 61.5) are psychoactive and have become popular recreational drugs. These compounds, however, differ from classical hallucinogens with regard to their pharmacology and subjective effects. In contrast



R =	Name
-Br	DOB
-I	DOI
$-CH_3$	DOM
$-CH_2CH_3$	DOET
$-CH_2CH_2CH_3$	DOPR

FIGURE 61.4 Potent derivatives of 2,5-dimethoxyamphetamine (2,5-DMA).

to the hallucinogens, MDMA acts primarily by increasing the carrier-mediated release of 5-HT and, to a lesser extent, DA and norepinephrine. Although MDMA does produce some minor hallucinogen-like perceptual alterations, its primary effects include stimulation, euphoria, and feelings of empathy and closeness to others. There are also differences in the SAR of MDMA and the hallucinogenic amphetamines. First, the *R*-(−)-enantiomers of the hallucinogenic amphetamines are more potent than the *S*-(+) isomers, whereas the opposite is true for MDMA. Second, while *N*-methylation of the hallucinogenic amphetamines dramatically reduces activity, *N*-methyl-MDA (i.e. MDMA) retains activity. Third, replacing the α-methyl group in the hallucinogenic amphetamines with an α-ethyl group abolishes the activity; by contrast, the α-ethyl analog of MDMA (methylbenzodioxybutanamine, MBDB) is only slightly less potent than MDMA. Based on these pharmacological and chemical differences, it is now recognized that MDMA belongs to a distinct drug class, and will not be discussed in this chapter.

The α-desmethyl (i.e. phenethylamine) homologs of the 2,4,5-trisubstituted amphetamines are also active (Fig. 61.6). They have been referred to as the "2C" family of compounds because the ethylamine side chain contains two carbon atoms, as opposed to the three carbons in the amphetamines. Typically, the phenethylamines are less potent than their amphetamine counterparts, a difference that may be explained by the fact that the phenethylamines have lower 5-HT_{2A} efficacy than their α-methyl counterparts and are more susceptible to side chain deamination. One example is α-desmethyl-DOB (2C-B, "Nexus"), which is approximately 10-fold less potent than DOB. Other compounds in this group include α-desmethyl-DOM (2C-D), α-desmethyl-DOI (2C-I,) and α-desmethyl-DOET (2C-E). Phenethylamines with *S*-alkylthio substituents in the 4-position are also active. A notorious example is 2,5-dimethoxy-4-propylthiophenethylamine (2C-T-7, "Blue Mystic"). In

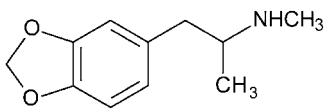
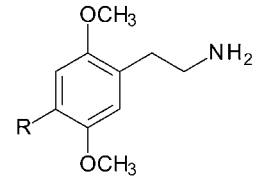


FIGURE 61.5 3,4-methylenedioxymethamphetamine (MDMA).



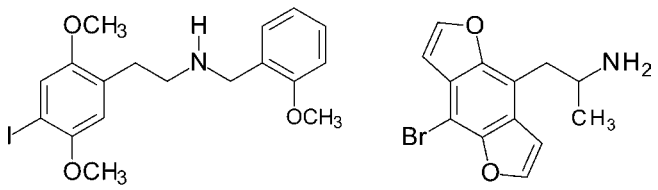
R =	Name
-Br	2C-B
-I	2C-I
$-CH_3$	2C-D
$-CH_2CH_3$	2C-E
$-SCH_2CH_2CH_3$	2C-T-7

FIGURE 61.6 Phenethylamines related to 2C-B.

addition to activating the 5-HT_{2A} receptor, 2C-T-7 inhibits the enzyme monoamine oxidase (MAO), and severe adverse reactions have occurred when 2C-T-7 is abused in combination with sympathomimetic substances.

Although phenylalkylamines with *N*-alkyl substituents typically have low potency or are completely inactive, recent studies have demonstrated that *N*-substitution with a benzyl or another small arylmethyl group dramatically increases the 5-HT_{2A} receptor affinity of phenethylamines. For example, addition of an *N*-(2-methoxy)benzyl group to 2C-I increases 5-HT_{2A} receptor affinity by almost an order of magnitude. Interestingly, however, substitution with an *N*-benzyl moiety does not increase the affinity of phenylisopropylamines. It appears that there is a specific interaction between the *N*-benzyl aromatic ring and a phenylalanine residue in the 5-HT_{2A} receptor binding site, resulting in increased binding energy. 25I-NBOMe (Fig. 61.7) and other *N*-benzyl-substituted phenethylamines have been marked over the Internet, but at the present time human potency data are not available.

It was recently recognized that one or both of the alkoxy groups of the phenylalkylamine hallucinogens can be incorporated in furanyl, dihydrofuranyl, and/or pyranyl rings without diminishing activity. In fact, when both of the methoxy groups of DOB are incorporated into furanyl rings, there is a significant increase in potency and 5-HT_{2A} affinity. This compound, known as bromo-dragonfly (Fig. 61.7), has appeared on the illicit market in Europe and has been associated with several overdose deaths. These findings suggest that the orientations of the oxygen lone pairs in this substance are optimal for interacting with the 5-HT_{2A} receptor.



25I-NBOMe Bromo-dragonfly

FIGURE 61.7 Phenylalkylamines that activate the 5-HT2A receptor with extremely high potency.

Tryptamines

Like the phenylalkylamines, the tryptamine hallucinogens act as 5-HT_2 receptor agonists, but they are much less selective, binding to a variety of 5-HT receptor subtypes with moderate to high affinity. Some of these compounds are also substrates for the 5-HT transporter (SERT) and agonists at σ_1 receptors, but it is not yet clear whether these actions play a role in their behavioral effects. DMT, the prototypical agent in this class, is widely distributed in the plant kingdom but also occurs endogenously in mammals, including humans. The structure of DMT is illustrated in Fig. 61.8. When taken alone, DMT is not orally active due to first-pass metabolism by MAO; therefore, in Western societies DMT is usually smoked or administered parenterally, with doses of 50–75 mg producing extremely intense but short-lived effects. Interestingly, DMT is orally active if combined with an MAO inhibitor, and this phenomenon is responsible for the activity of *ayahuasca*, which is prepared from DMT-containing plants in combination with a plant containing MAO inhibitors such as harmine and harmaline. Although *ayahuasca* has traditionally been used in South America, the use of this preparation has recently spread to Europe and North America.

Lengthening one or both of the amine nitrogen alkyl substituents in DMT results in homologs that are orally active. Notable examples include *N,N*-diethyltryptamine (DET), *N,N*-dipropyltryptamine (DPT), and *N*-methyl-*N*-isopropyltryptamine (MIPT). *N,N*-diisiopropyltryptamine (DIPT) is also orally active, but this compound is somewhat unusual in that its primary effect is auditory distortion. The potencies of the *N,N*-dialkyltryptamines are increased by the presence of a 4-hydroxy or a 5-methoxy group on the aromatic indole benzene ring. For example, psilocin (4-hydroxy-DMT) and its phosphate ester psilocybin, the active principles of the *teonanácatl* mushrooms, are active at doses of 10–20 mg. Likewise, 5-MeO-DMT, the primary component of a variety of South American snuffs prepared from species such as *Anadenanthera peregrina* and *Virola theiodora*, is active at doses as low as 3–5 mg when smoked or administered parenterally. 5-Methoxy-MIPT (5-MeO-MIPT) and 5-methoxy-DIPT (5-MeO-DIPT, "Foxy Methoxy") have been used recreationally in Europe and North America, and both are more potent than their unsubstituted parent compounds.

A second group of tryptamine hallucinogens contain an α-alkyl substituent. This group includes

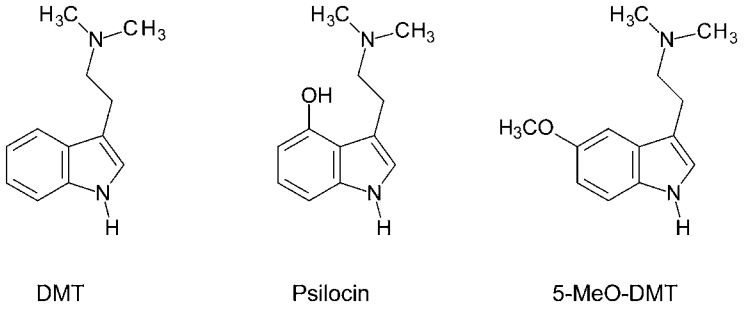


FIGURE 61.8 Tryptamine hallucinogens.

α-methyltryptamine (AMT, Indopan), which was used as an antidepressant in the former Soviet Union. A related compound, α-ethyltryptamine (AET, Monase), was used as an antidepressant in the USA, but was withdrawn from the market after several patients developed agranulocytosis. In addition to activating 5-HT receptors, these compounds inhibit MAO and increase monoamine release, and hence have stimulant and MDMA-like effects in addition to effects characteristic of classical hallucinogens.

Ergolines

A third class of hallucinogens have a tetracyclic ergoline structure. These compounds are derivatives of lysergic acid amide (lysergamide) and act as nonselective agonists at 5-HT, DA, and norepinephrine receptors. Several lysergamides occur naturally in the seeds of plants of the Convolvulacaea family, such as *Ipomoea violacea* and *Turbina cormbosa*, which have been used ritualistically in Mexico. Ergot (*Claviceps purourea*), a parasitic fungus that infects rye, contains ergotamine and other peptide derivatives of lysergic acid; although non-hallucinogenic, these ergopeptides are used as precursors in the synthesis of hallucinogenic lysergamides. The semisynthetic lysergamide LSD (*N*,*N*-diethyllysergamide; Fig. 61.9) is one of the most potent hallucinogens, with typical doses ranging from 60–200 μg. LSD contains two chiral centers and its action is highly stereospecific, with 5*R*,8*R* being the only active configuration. The diethyl amide group in LSD is optimal for activity, and potency drops by an order of magnitude if other alkyl groups or heterocyclic rings are substituted. It has been reported, however, that derivatives of LSD in which the *N*(6) methyl group is replaced by other alkyl groups are active, with the 6-ethyl compound (*N*(6)-ethyl-nor-LSD, ETH-LAD) being slightly more potent than LSD. There is a complete loss of activity if LSD is brominated or iodinated in the 2-position, and these substances (2-bromo-LSD and 2-iodo-LSD, respectively) act as 5-HT_{2A} antagonists. Consistent with its antagonist activity, pretreatment with 2-bromo-LSD completely blocks the effects of subsequent LSD administration.

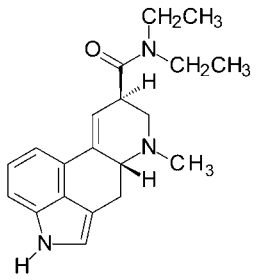


FIGURE 61.9 Structure of (+)-lysergic acid diethylamide (LSD).

HALLUCINOGEN EFFECTS ON NEURONAL ACTIVITY

Raphe Nuclei

The largest groups of serotonergic neurons are found in the midbrain in the dorsal and median raphe nuclei (DRN and MRN, respectively), and are the source of serotonergic projections that terminate throughout the brain. George Aghajanian and colleagues first reported in 1968 that low intravenous doses of LSD completely inhibit the firing of serotonergic DRN and MRN neurons, and it was subsequently shown that many indolealkylamine hallucinogens have similar effects. The inhibition of 5-HT neurons by hallucinogens is mediated by activation of 5-HT_{1A} receptors that are expressed as autoreceptors. Based on these findings, it was proposed that LSD and other agents may induce hallucinogenic effects due to their ability to decrease 5-HT outflow, which could potentially disinhibit brain regions that are normally tonically inhibited by 5-HT. Further investigation, however, revealed that effects on raphe activity are unlikely to play a role in hallucinogenesis. The primary evidence for this dissociation is threefold: (1) phenylalkylamine hallucinogens such as mescaline and DOM lack 5-HT_{1A} agonist activity and do not reliably inhibit the firing of serotonergic raphe neurons, (2) many non-hallucinogenic drugs inhibit the firing of DRN and MRN neurons, and (3) 5-HT_{2A} antagonists

block many of the behavioral and subjective effects of hallucinogens but do not attenuate the inhibition of 5-HT neurons.

Locus Coeruleus (LC)

Most central noradrenergic projections originate from the locus coeruleus (LC), a nucleus located in the pons. LC neurons are hyperresponsive to arousing or novel stimuli, and fire in response to reward and punishment. In rats, administration of hallucinogens such as mescaline and LSD increased the sensory-evoked firing of LC neurons while reducing their spontaneous activity, indicating that hallucinogens increase in the signal-to-noise ratio of the noradrenergic LC output to the neocortex. These effects appear to be mediated by 5-HT_{2A} receptors in LC afferent regions, and hallucinogens have no effect on LC activity when applied directly to this region. It has been theorized that the ability of hallucinogens to increase the apparent novelty and intensity of sensory and affective responses may be a consequence of their effects on LC activity.

Cortex

Several converging lines of evidence indicate that the cortex is an important site of action of the hallucinogens. The cortex contains two types of neurons: excitatory neurons that release glutamate (Glu), most of which are pyramidal neurons, and inhibitory interneurons that release gamma-aminobutyric acid (GABA). 5-HT_{2A} receptors are densely expressed in the cortex, especially in the anterior regions. A variety of brain imaging techniques, including Positron emission tomography (PET), SPECT, and fMRI, have shown that psilocybin, mescaline, DMT, and ayahuasca have profound effects on network activity in regions of the prefrontal, temporal, parietal, and occipital cortices known to be involved with self-awareness, emotional processing, visual and spatial perception, memory, and multisensory integration. An [^{18}F]fluorodeoxyglucose PET study found a correlation between the effects of psilocybin on the APZ scale and increases in metabolic activity in the prefrontal cortex (PFC) and anterior cingulate cortex (ACC), indicating that those regions play a specific role in mediating the subjective effects of psilocybin. A subsequent PET study with the 5-HT_{2A}-selective radiotracer [^{18}F]altanserin revealed that psilocybin-induced increases in 5D-ASC scores are correlated with the level of 5-HT_{2A} occupation in medial PFC (mPFC) and ACC. There is also evidence that the mPFC and ACC play an important role in mediating the behavioral effects of hallucinogens in rodents. Administration of hallucinogens to rodents increases the expression of the immediate early gene *c-fos*, a marker of neuronal excitation, in mPFC and ACC. One group has reported that infusion of LSD directly into ACC produces complete substitution in rats trained to discriminate LSD; they also found that injection of the selective 5-HT_{2A} antagonist M100907 into ACC blocks the stimulus effects of systemic LSD. Similarly, the head twitch response (HTR), a 5-HT_{2A} receptor-dependent behavior that occurs in rats and mice after administration of hallucinogens, can be induced in rats by infusion of DOI directly into the mPFC. It was also recently shown that intra-mPFC infusions of DOI produce deficits in response inhibition in rats.

Hallucinogens produce a variety of effects on the activity of neocortical neurons, especially in mPFC layer V. Although most pyramidal neurons in cortical layers II–V and a smaller percentage of interneurons express 5-HT_{2A} receptors, expression of the receptor is especially dense along the proximal apical dendrites of layer V pyramidal neurons. Electrophysiological recordings from cortical pyramidal neurons have shown that activation of 5-HT_{2A} receptors by DOB and DOI increases cellular excitability by inducing membrane depolarization and attenuating the slow after-hyperpolarization current, which is mediated by calcium-activated potassium channels. Based on these findings, it appears that 5-HT_{2A} receptors regulate how pyramidal neurons respond to excitatory input. Hallucinogens and other 5-HT_{2A} agonists also markedly increase spontaneous glutamatergic excitatory input to mPFC layer V pyramidal neurons. Studies were initially unable to locate any glutamatergic neurons that were spontaneously excited by 5-HT_{2A} activation, and therefore this effect was thought to be mediated by the action of a retrograde transmitter on thalamocortical afferents. Recent work, however, indicates that a subpopulation of pyramidal neurons in deep layer V increase their firing in response to 5-HT_{2A} receptor activation, resulting in an increase in recurrent glutamatergic network activity. It appears that the facilitation of glutamatergic activity by hallucinogens plays an important role in mediating their effects. Compounds that suppress the ability of hallucinogens to increase recurrent glutamatergic network activity in mPFC, such as agonists of metabotropic $Glu_{2/3}$ ($mGlu_{2/3}$) receptors, block the behavioral effects of hallucinogens and effects on *c-fos*. Evidence has emerged that $mGlu_2$ and 5-HT_{2A} receptors may form functional complexes in cortex, and the ability of $mGlu_{2/3}$ receptors to modulate hallucinogen effects may be linked to the existence of these complexes. There is also evidence that hallucinogens can excite GABAergic interneurons, possibly as an indirect consequence of recurrent Glu activity, leading to increased inhibitory input to pyramidal neurons.

Hallucinogens disrupt PFC network activity, and after administration of hallucinogens, individual pyramidal neurons are less likely to fire in synchrony with other pyramidal neurons, and low-frequency network activity is attenuated. Since the efficiency of cortical information processing is dependent on cortical synchrony, these effects could markedly alter how the PFC functions. Furthermore, the increase in recurrent cortical network activity induced by hallucinogens could compete with responses induced by sensory input, potentially altering sensory processing. Since pyramidal neurons in PFC layer V are the source of projections to other cortical and subcortical structures, hallucinogen effects on PFC activity and processing could profoundly affect how the PFC regulates activity in those projection sites. For example, systemic administration of DOI to rats increases the output of mPFC neurons projecting to DRN and the VTA in the midbrain, which give rise to serotonergic and dopaminergic projections, respectively. It has been proposed that one of the major effects of hallucinogens may be to alter the function of cortico-striato-thalamic pathways (CSTC loops) that regulate the gating of cortical information processing. Altered activity in these circuits, due to the direct and indirect effects of hallucinogens on their cortical and subcortical components, could produce gating deficits that would result in sensory overload, hallucinations, and disruptions of normal cognitive processes. Indeed, one of the known effects of hallucinogens in humans and rodents is disruption of measures of sensorimotor gating such as prepulse inhibition. The hypothesis that hallucinogens act by disrupting CSTC feedback loops has received some support from imaging studies showing that psilocybin alters activity in cortical and subcortical components of the "limbic" CSTC loop.

POSSIBLE THERAPEUTIC EFFECTS OF HALLUCINOGENS

Due to cultural and political pressure, clinical research with hallucinogens ceased in the 1970s. In recent years, however, there has been a resumption of research to investigate the potential clinical applications and neuropharmacology of hallucinogens. The first of these studies, using intravenous DMT, was conducted by Richard Strassman at the University of New Mexico in the early 1990s; this investigation confirmed that DMT can be safely administered to volunteers in a hospital setting. Subsequent studies conducted by several groups in the United States and Europe have examined the subjective effects, neuropharmacology, and neurophysiology of DMT, psilocybin, mescaline, ayahuasca, and LSD. Recent investigations have demonstrated that psilocybin can produce positive effects on mood and behavior, and several clinical trials are underway to assess whether these effects may help to reduce stress and anxiety in cancer patients. A preliminary clinical trial has assessed whether psilocybin can reduce symptoms of obsessive–compulsive disorder (OCD), and there was some evidence of efficacy. Additionally, anecdotal findings indicate that hallucinogens may be highly effective treatments for cluster headaches, and a pilot study in six patients has shown that cluster headaches can be alleviated by administration of 2-bromo-LSD. Another context where hallucinogens have been investigated is as potential adjuncts to psychotherapy, with hallucinogens serving to facilitate the relationship between therapists and patients, reduce defensiveness, and alter behavior patterns. To date, however, the results of these studies are unpublished. Although clinical investigation of hallucinogens is still at the exploratory stage and it is unclear whether these substances will ever become approved medications, it is clear that further work is warranted.

SUMMARY

Hallucinogens have profound effects on mental function and have been used by humans for millenia. Actions at 5-HT receptors, particularly the 5-HT_{2A} subtype, are responsible for these effects. Although studying hallucinogen phenomenology is difficult in humans and animals because of the complexity and range of potential effects, all hallucinogens produce states similar to those induced by prototypical compounds mescaline, psilocybin, and LSD, and act as 5-HT_{2A} agonists. Although still preliminary, work has begun to unravel some of the neurobiological mechanisms through which hallucinogens alter consciousness, with studies showing changes in the activity of specific brain regions as well as effects at the network level. Hallucinogens provoke mental effects such as mystical states, synesthesia, and schizophrenia-like symptoms that are rarely observed in normal individuals, potentially facilitating the laboratory investigation of these phenomena as well as providing insight into the pathology underlying certain psychiatric disorders. There is also evidence that hallucinogens may have therapeutic efficacy in patients with existential anxiety, OCD, and cluster headaches. Human attitudes toward hallucinogens have historically been complex, and while these drugs have sometimes been worshipped as deities, in more recent years they have been demonized. Given their potential value as therapeutics, it is possible that in the future they may also be viewed as healing substances.

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SEE ALSO

Serotonin and Behavioral Stimulant Effects of Addictive Drugs, Neuropharmacology of Ecstasy (MDMA) and Other Designer Drugs, Ecstasy (MDMA) and other designer drugs: Neuroimaging

List of Abbreviations

AED	anxious ego dissolution
AA	auditory alterations
ACC	anterior cingulate cortex
CSTC	cortico-striato-thalamic pathways
DMT	*N*,*N*-dimethyltryptamine
DA	dopamine
2,5-DMA	2,5-dimethoxyamphetamine
DOM	2,5-dimethoxy-4-methylamphetamine
DOET	2,5-dimethoxy-4-ethylamphetamine
DOB	2,5-dimethoxy-4-bromoamphetamine
DOI	2,5-dimethoxy-4-iodoamphetamine
DIPT	*N*,*N*-diisiopropyltryptamine
DRN	dorsal raphe nuclei
GABA	gamma-aminobutyric acid
5-HT	5-hydroxytryptamine
LC	locus coeruleus
LSD	lysergic acid diethylamide
MDMA	3,4-methylenedioxymethamphetamine
5-MeO-DMT	5-methoxy-*N*,*N*-dimethyltryptamine
MIPT	*N*-methyl-*N*-isopropyltryptamine
mPFC	medial PFC
mGlu$_{2/3}$	metabotropic Glu$_{2/3}$
MRN	median raphe nuclei
OCD	obsessive–compulsive disorder
PET	Positron emission tomography
PFC	prefrontal cortex
SAR	structure-activity relationship
TMA	trimethoxyamphetamine

Glossary

Classical hallucinogen a drug that activates the 5-HT$_{2A}$ receptor and produces subjective and behavioral effects similar to LSD, mescaline, and psilocybin.

Depersonalization a state of altered self-awareness, for example, distortions of body image or body sensation, loss of ego boundaries, feelings of nonexistence, or the perception that all or part of the body is some other animate or inanimate object.

Derealization a perceptual disturbance in which the external environment, including objects, people, or events, is experienced as being unreal or dream-like.

Monoamine oxidase (MAO) enzymes that catalyze the oxidative deamination of monoamines, including the neurotransmitters serotonin, DA, and norepinephrine. Certain MAO inhibitors are used clinically as antidepressants.

Phencyclidine (PCP) a noncompetitive NMDA receptor antagonist that was developed as a surgical anesthetic but was found to produce side effects such as hallucinations, agitation, disorientation, and cognitive disturbances. Phencyclidine, also known as 1-(1-phenylcyclohexyl)piperidine, has been abused recreationally for its dissociative effects.

Psychedelic a term proposed by psychiatrist Humphry Osmond to describe the effects of hallucinogenic drugs, meaning "mind manifesting."

Serotonin a monoamine neurotransmitter found in the brain of vertebrate animals. Serotonin is also known as 5-hydroxytryptamine or 5-HT.

Synesthesia a perceptual phenomenon where sensory stimulation in one modality is perceived in a different modality; for example, auditory stimuli may be perceived visually.

Further Reading

Aghajanian, G.K., 2009. Modelling "psychosis" in vitro by inducing disordered neuronal network activity in cortical brain slices. Psychopharmacology 206, 575–585.

Geyer, M.A., Vollenweider, F.X., 2008. Serotonin research: contributions to understanding psychoses. Trends in Pharmacological Sciences 29, 445–453.

Halberstadt, A.L., Geyer, M.A., 2011. Multiple receptors mediate the behavioral effects of indoleamine hallucinogens. Neuropharmacology 61, 364–381.

Martinez-Price, D.L., Krebs-Thomson, K., Geyer, M.A., 2002. Behavioral psychopharmacology of MDMA and MDMA-like drugs: a review of human and animal studies. Addiction Research and Theory 10, 43–67.

Nichols, D.E., 2004. Hallucinogens. Pharmacology and Therapeutics 101, 131–181.

Schultes, R.E., Hofmann, A., 1980. The Botany and Chemistry of Hallucinogens. Charles C. Thomas, Springfield.

Shulgin, A.T., Shulgin, A., 1991. PiHKAL: A Chemical Love Story. Transform Press, Berkeley.

Shulgin, A.T., Shulgin, A., 1997. TiHKAL: The Continuation. Transform Press, Berkeley.

Studerus, E., Kometer, M., Hasler, F., Vollenweider, F.X., 2011. Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies. Journal of Psychopharmacology 25, 1434–1452.

Vollenweider, F.X., Geyer, M.A., 2001. A systems model of altered consciousness: integrating natural and drug-induced psychoses. Brain Research Bulletin 56, 495–507.