As defined in this chapter, the term *psychedelic drugs* includes both classic hallucinogens [i.e., indolalkylamines and phenylalkylamines, such as lysergic acid diethylamide (LSD) and mescaline, respectively], “dissociative” drugs [i.e., arylcyclohexamines, such as phencyclidine (PCP) and ketamine], and substituted amphetamine analogues [i.e., phenylpropanolamines, such as 3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”)]. The use of psychedelic drugs dates from the dawn of recorded history and continues today. Indeed, in Western culture, their use appears to be on the rise. Despite the longstanding popularity of psychedelic drugs, controlled research evaluating their effects in humans has been surprisingly scant, and data from preclinical studies have been largely limited to the last several decades. This chapter reviews preclinical and clinical research involving indolalkylamines, arylcyclohexamines, and substituted amphetamines, for which LSD, PCP, and MDMA are used as the prototypes, respectively. Significant recent advances are highlighted, and promising areas toward which future research should be directed are identified.

**INDOLALKYLAMINES**

**Epidemiology**

Surveys in the United States and Western Europe reveal an increased use of indolalkylamine hallucinogens. For example, trend data in the United States, gathered from 15,000 high school seniors, showed a rise in prevalence of lifetime hallucinogen use from 6% to 13.7% between 1986 and 1999 (1,2). Similarly, in Great Britain, the use of LSD rose from 7% to 11% between 1989 and 1993. Among German drug abusers, the prevalence of LSD use was reported at 14.1%, and 7.2% of Danes reported the use of hallucinogenic mushrooms (3).

In the United States, a survey of 633 undergraduates found that 23.8% had experimented with hallucinogenic mushrooms, and 16.3% had had experience with LSD. Among LSD users, 6.6% reported problems associated with LSD (Abraham and Koob, unpublished data). Of this group, 46.9% reported symptoms of hallucinogen persisting perception disorder (HPPD), 37.5% described alcohol dependence, 25% major depression, 18.8% persisting delusions, 15.6% panic attacks, and 12.5% auditory hallucinations. LSD use is most likely to occur between the ages of 18 and 25. Use is more common in male Caucasians and Hispanics. Of note is that although the parents of LSD users tend to be of a higher socioeconomic status, the users themselves exhibit an inverse relationship between LSD use and educational achievement (4).

**Early Neurophysiologic Studies**

Work in the 1950s intimated that hallucinogens simultaneously activate and depress neural systems in mammals. In 1953, Gaddum (5) reported that LSD antagonizes the effects of serotonin (5-HT). In the visual system, LSD decreased by 80% the amplitude of the postsynaptic response in the lateral geniculate nucleus of the cat following stimulation of the optic nerve (6). Pentobarbital was found to sensitize the cells to LSD, and asphyxia transiently overcame the LSD effect. These observations were among the first to suggest that in the visual system, LSD is inhibitory, like γ-aminobutyric acid (GABA), and is antagonized by excitatory amino acids released during hypoxia.

Neurophysiologic studies in animals and humans indicate that hallucinogens produce arousal (7). Multiple EEG studies of LSD in rabbits, cats, and humans have documented an increasing shift of alpha frequencies to low voltage, fast rhythms, and alpha disappearance (8). In studies of evoked sensory potentials in cats, a low dose of LSD facilitated both auditory and visual primary responses, whereas high doses depressed auditory responses while con-
Behavioral Studies
A variety of behavioral models in animals have been employed to study psychedelics. The strength of such models over human studies is that ethical concerns are mitigated, experimental controls are more comprehensive, tissue is employed to study psychedelics. The strength of such models in animals is that they cannot provide a direct, reliable method to determine if or when an animal is hallucinating. Despite this limitation, drug discrimination paradigms have been useful in establishing comparative benchmarks between LSD, mesocline, and other hallucinogens, associating potency data with binding at specific receptor types, correlating animal potencies with human data, and describing structure–activity relationships (10). Sophisticated behavioral studies by Geyer et al. (11) suggest that LSD disrupts two fundamental mechanisms of filtering of sensory information, habituation and prepulse inhibition.

Neuropharmacology
The mechanism of action of the hallucinogens is one of the compelling questions in pharmacology, the answer to which promises insights into the mechanisms of perception, mood, and psychosis. Early studies of LSD in peripheral tissue implicated serotonergic receptors in the mechanism of hallucinogenic activity. Freedman (12) found that LSD decreases brain 5-HT turnover. This effect correlated with behavioral changes and the plasma half-life of LSD, was limited to hallucinogens, and was replicated in several species. Hirschhorn and Winter (13) showed that rats can discriminate LSD and mescaline from saline solution. Discrimination fell in the presence of serotonin antagonists, supporting a 5-HT-agonist mechanism for the action of hallucinogens.

In intracellular recordings from serotonergic dorsal raphe neurons of the rat brain in vivo, LSD directly inhibited firing, but other hallucinogens did not (14). In 1979, it was shown that the effects of LSD on cat behavior are dissociated from raphe responses and involve postsynaptic serotonin activity (15). The same year, Peroutka and Snyder (16) reported the discovery of multiple serotonin receptor types. A high density of 5-HT$_{1A}$ autoreceptors was found on raphe neurons, which explained the direct inhibition of this system by LSD (17). Based on the ability of receptor antagonists to block hallucinogen discrimination in animals, it was proposed that hallucinogens act as agonists at postsynaptic 5-HT$_2$ receptors (18). Hallucinogen potency in animals was found to correlate with affinity at the 5-HT$_2$ receptor (19).

Chemistry
Considerable work has been directed at structure–activity relationships of the ergoline hallucinogens (20,21). Substitution at the N(1) position of LSD abolishes activity, as does substitution at the C(2) position with a halogen. (R)-stereochemistries are essential at both C(5) and C(8) for activity. Reduction of the double bond at the 9,10 position abolishes hallucinogenic activity. Hydroxylation of C(13), which may occur in vivo, confers a high level of dopaminergic potency on ergolines (21). Most interesting is that ethylation of LSD at N(6) enhances potency, as determined in both animal and human studies. A monoalkyl amide, diastereomer of chlorobutyl LSD, is at least 50% more potent than LSD. In ligand binding at 5-HT$_2$, 5-HT$_{1A}$, D1, and D2 receptors, the (R)-2-butylamide substituent is likewise more potent. Cloning of the 5-HT$_2$ receptor permitted replacement of aspartate 120 in second transmembrane domain with asparagine. This resulted in a significant decrease in affinity for LSD and abolished phosphatidylinositol turnover. Additionally, aspartate 155 is required for agonist and antagonist binding (22). Second messenger systems in hallucinogen-responsive receptors represent another promising avenue to unraveling the mechanism of hallucinogens. 5-HT$_2$ receptors are coupled to at least three transduction systems: potassium channels, cationic $I_h$ channels, and phosphoinositide hydrolysis. The close correlation between hallucinogen affinities for the 5-HT$_2$ and 5-HT$_{1C}$ receptors raises the possibility that the latter may play an independent or complementary role in hallucinogenic activity. This is supported by the fact that LSD is an agonist at 5-HT$_{1C}$ receptors, as determined by phosphoinositide hydrolysis (23).

Recent Neurophysiologic Studies
More recent electrophysiologic studies of hallucinogens in animal models support the involvement of postsynaptic 5-HT$_2$ and 5-HT$_{1C}$ receptors in hallucinogenic activity. The locus ceruleus, considered a sensory novelty detector in the pons, projects widely throughout the brain. Hallucinogens indirectly decrease spontaneous activity in the locus ceruleus by activating GABA$_A$ inputs, and they enhance sensory responses of the locus ceruleus by activating excitatory inputs via N-methyl-D-aspartate (NMDA) receptors (24). 5-HT$_2A$-receptor antagonists block these effects. In rat piriform cortex, both 5-HT and hallucinogens at 5-HT$_2A$ receptors excite GABAergic interneurons, which then induce inhibitory postsynaptic potentials (25). In prefrontal cortex, the opposite occurs, where the drugs release glutamate and increase excitatory potentials (26). Both 5-HT$_2A$ and glutamatergic antagonists block this effect. Direct studies of neo-
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Recent Human Studies of Indolalkylamine Hallucinogens

The extraordinary mental effects of LSD described in 1943 by Hofmann prompted hope in the following two decades that a powerful therapeutic tool was at hand. The drug was used experimentally to treat neuroses, childhood schizophrenia, sociopathy, and alcoholism, and as a comfort to the terminally ill (28). Methodologies were inadequate by contemporary standards, and no treatment stands unambiguously as effective. In recent years, renewed interest in hallucinogen research has been sparked by the emergence of positron emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI) technologies. For example, PET studies by Vollenweider and colleagues (29) have shown that psilocybin, another hallucinogen, increases frontal glucose metabolism in healthy volunteers, which suggests that the behavioral effects of psilocybin involve the frontal cortex (Fig. 108.1). Similar imaging work has been done with the phenethylamine mescaline.

Human dose–response studies of hallucinogens since 1965 have been rare. Shulgin et al. (30) synthesized 179 phenethylamines and informally screened them in human volunteers for hallucinogenic potency. Strassman and Qualls (31), using DMT (N,N-dimethyltryptamine) in carefully screened and supervised subjects, were able to develop a hallucinogen rating scale and measure a number of dose-dependent neuroendocrine responses to the drug. Equally importantly, this work demonstrated that hallucinogen experimentation could be safe as well as informative.

Acute Adverse Psychiatric Effects of Hallucinogens

Clinically, the flow of thoughts, feelings, and perceptions that constitute a hallucinogenic experience can, on occasion, result in panic. Thus, a man who was using LSD while driving tried to crash the vehicle when he saw his companion turn into a giant lizard (32). The treatment for hallucinogen-induced panic is an oral benzodiazepine. The utter efficacy and rapidity of the response to this class of medications implicates GABA receptors as the neuromodulators of this hallucinogenic experience in humans.

Hallucinogen Persisting Perception Disorder

Hallucinogens sometimes appear to alter psychological functions years after drug use (32). Elkes et al. (33) originally noted recurrences of drug experiences, flashbacks, to occur episodically. Surveys among college students reveal that more than 40% of those using LSD report minor spontaneous visual experiences weeks to months after LSD use (32). Less common are patients who report persistent, continuous visual disturbances following LSD use. These peo-
ple are affected by a variety of disturbances, such as after-
imagery, geometric pseudohallucinations, halos around ob-
jects, and the trailing of visual images as they move through
the visual field (32).

Hallucinogen persisting perception disorder appears to
be a permanent, or slowly reversible, disorder of dis inhibi-
tion of visual processing, which suggests the defective sen-
sory gating described by Braff and Geyer (34). Evidence for
this comes from psychophysical experiments in which visual
signals in subjects with HPPD persisted significantly longer
than in LSD-naive controls (35). Quantitative electrophys-
ology (qEEG) in this population shows abnormalities in
visually evoked potentials as long as 26 years after last LSD
use, consistent with visual disinhibition (36). Thus, these
studies are consistent with others showing that the visual
system is especially sensitive to the effects of LSD. Second,
LSD hallucinations involve the cerebral cortex (37). Third,
inhibitory systems appear, at least in certain circumstances,
to be involved in LSD effects and probably LSD aftereffects.
Fourth, flashbacks may in certain cases become long-lived,
continuous, and probably permanent. And fifth, HPPD is
associated with cortical disinhibition.

Recently, it has been found that the GABA agonist mida-
zolam rapidly reduces experimentally induced afterimages
in persons with HPPD to approximate the responses from
controls without the disorder (Abraham, unpublished data).
Clinically, GABA agonists are known to reduce, but not
resolve, symptoms of HPPD symptoms. This modulation
of after-imagery suggests that the visual dysregulation of
HPPD may be related to a permanent loss of GABA-me-
diated inhibition. Risperidone, a 5-HT2 antagonist, has
been found to exacerbate HPPD in persons with the disor-
der (38). Nefazodone, also a 5-HT2 antagonist, is associated
with visual trailing phenomena. One suggestion regarding
the etiology of HPPD is that LSD in vulnerable persons
reduces the population of 5-HT inhibitory interneurons
imaging GABA efferents to glutamatergic neurons. Treatment
HPPD remains empiric and palliative. It may include
benzodiazepines, sertraline, naltrexone, and clonidine.
Nonaddictive agents are preferred in patients with histories
of addiction.

Psychosis

Studies of LSD administration to research subjects report
an incidence of subsequent psychosis in 0.08% to 4.6% of
the samples. Psychiatric patient status appears to be a risk
factor for the development of psychosis (39). Case histories
tend to support phenomenology of a schizoaffective presen-
tation with the added feature of visual disturbances. Positive
symptoms of schizophrenia tend to be present. Effective
treatments include neuroleptic, lithium, and electroconvul-
sive therapies.

ARYLCYCLOHEXAMINES

The arylcyclohexamine PCP ("angel dust," "peace pill")
can be considered the prototypical dissociative anesthetic.
Other drugs in this class include ketamine and dizocilpine
maleate (MK-801). PCP was first synthesized in the 1950s,
when it was marketed as a surgical anesthetic under the
trade name Sernyl. Initially widely used in surgical settings,
it was withdrawn in 1965 because of its association with a
variety of behavioral disturbances, including agitation, dys-
phoria, delirium, hallucinations, paranoia, rage, and vio-
ence (40). In approximately half of patients who received
PCP, a psychotic syndrome developed that sometimes per-
sisted for more than a week (41). Today, the psychotic syn-
drome produced by PCP or ketamine is considered a leading
drug model of schizophrenia (42).

Chemistry

Phencyclidine and other dissociative anesthetics consist of
a phenyl ring, a piperidine group, and a cyclohexyl ring.
The two conformations of drugs in this class are categorized
according to the cyclohexyl spine and subsequent location
of the phenyl ring. In particular, if the phenyl ring is located
in the axial plane, the drug is active, whereas location of
the phenyl group in the equatorial plane renders the drug
inactive. Ring number and substitutions can significantly
alter the potency of drugs in this class (43).

Epidemiology

Until recently, typical PCP users were white, blue collar
men with a high school (or partial high school) education
working in unskilled or semiskilled jobs (40). However,
dissociative anesthetics such as ketamine and PCP are in-
creasingly used in the growing "club" or "dance" culture,
and it appears that the popularity of these drugs has risen in
young adults. Data from the Monitoring the Future Study
indicate that lifetime prevalence rates of PCP use increased
from 2.4% to 2.7% in young men ages 18 to 29 from 1997
to 1998, whereas use among twelfth graders remained at
3.9% in 1997 and 1998 and fell to 3.4% in 1999 (2).

Neuropharmacology

The mechanism of action of dissociative anesthetics is both
unique and complex, involving a number of distinct neuro-
transmitter and neuromodulator systems. PCP behaves as
a cholinergic antagonist at both central and peripheral sites,
acting at both nicotinic and muscarinic receptors (44). PCP
is also a D2-receptor antagonist, and actions at this receptor
are believed to underlie many of the behavioral symptoms
that follow drug administration (40). In addition to D2
blockade, PCP increases the rate of dopamine release from
synaptic vesicles and prevents dopamine reuptake inactiva-
tion. Amphetamine-like activating effects of PCP are believed to involve not only dopamine uptake blockade but also actions of PCP in the frontal cortex and consequent neuromodulatory effects of the frontal cortex on the basal ganglia (45). Actions at σ and μ opiate receptors are thought to underlie the anesthetic effect of PCP, whereas actions at serotonin receptors may underlie its hallucinogenic effects (40). Notably, cross-tolerance occurs between PCP and the classic hallucinogens LSD, mescaline, and psilocybin (46), and PCP substitutes for LSD or mescaline in two-level drug discrimination studies in rats. PCP also binds to two specific serotonin receptors may underlie its hallucinogenic effects to underlie the anesthetic effect of PCP, whereas actions at adrenergic neuronal systems (59) and apoptotic changes observed in striatopallidal cells involving excess corticosteroids (58). Research is needed to determine whether PCP-induced neurotoxicity underlies the memory deficits seen in some PCP users.

**Behavioral Effects in Humans**

Phencyclidine produces a mixture of stimulant, depressant, anesthetic, and hallucinogenic effects, with the particular presentation dependent, in part, on dosage. In particular, low doses are associated with anticholinergic symptoms (red and dry skin, nystagmus, amnesia, conceptual disorganization); moderate doses are more likely to be associated with opiate receptor activity (anesthesia, dreamlike states); at high doses, dopaminergic symptoms predominate (hallucinations, paranoia). However, this rule of thumb should not be considered diagnostic. The mnemonic RED DANES was coined by Giannini and colleagues (48,49) to characterize eight acute symptoms of PCP intoxication that may be seen at any dose: rage, erythema, dilated pupils, delusions, amnesia, nystagmus in the horizontal plane, excitation, and skin dry. It is important to note that the toxic effects of PCP may persist for days because the half-life of PCP after overdose may be as long as 3 days (50).

In addition to acute toxicity, a number of researchers have reported persistent cognitive deficits in long-term PCP users, particularly in short-term memory function (51–54). Also, abrupt lapses into confusional states occurring weeks or months after PCP ingestion have been reported.

**Phencyclidine Neurotoxicity**

Olney and colleagues (55) were the first to report that single doses of PCP and related compounds (MK-801 and ketamine) lead to neurotoxic damage of neurons in layers III and IV of the posterior cingulate and retrosplenial cortex in rats. These cells display abnormal cytoplasmic vacuolization that is directly correlated with the potency of noncompetitive NMDA blockade. Initially, these were believed to be short-term changes, but higher doses of MK-801 were observed to cause necrotic changes persisting at least 48 hours after drug administration. Subsequently, other researchers reported a number of observations suggesting that PCP is neurotoxic. In particular, following PCP administration, vacuolization of neurons in hippocampal fields CA1 and CA3 and the subiculum has been demonstrated (56). PCP induces a microglial response and a 70-kilodalton heat shock protein in cerebellar Purkinje cells (57); most recently, it has been found that PCP induces apoptosis in striatopallidal cells in rats (58). The mechanisms for the actions of PCP at these various anatomic sites are likely to differ, with cortical injury involving activity of cholinergic, GABAergic, and adrenergic neuronal systems (59) and apoptotic changes observed in striatopallidal cells involving excess corticosteroids (58). Research is needed to determine whether PCP-induced neurotoxicity underlies the memory deficits seen in some PCP users.

**SUBSTITUTED AMPHETAMINES (MDMA, “ECSTASY”)**

**Chemistry**

3,4-Methylenedioxymethamphetamine bears structural similarity to both the psychomotor stimulant amphetamine and the hallucinogen mescaline. Of the two optical isomers of MDMA, the dextrorotatory isomer exhibits more potent central nervous system activity (60). In contrast, most potent hallucinogenic amphetamines are more potent in their levorotatory forms (61). The aromatic methylenedioxy substituent of MDMA is similar to the substance found in oils of the natural products safrole and myristicin, once proposed to be the intoxicants of sassafras and nutmeg (62).

**Epidemiology**

Data from the most recent Monitoring the Future Study indicate that MDMA use has continued to rise since 1989 (1,2). For example, annual use of MDMA among college students rose from 2.4% in 1997 to 3.9% in 1998, with lifetime figures reflecting similar increases, from 4.7% in 1997 to 6.8% in 1998 (1). Notably, figures from 1996 to 1999 indicate that approximately 3% of eighth graders and approximately 8% of twelfth graders have experimented with MDMA in their lifetime (2), which suggests that in the United States MDMA use begins at an early age.

**Patterns of Use**

At present, MDMA is used primarily for recreational purposes, although some still advocate the use of MDMA for psychotherapeutic purposes (63). During the last decade, the most frequently reported use of MDMA has been in the context of large, organized social events known as “raves,” often held in warehouses or dance clubs. Festively
dressed “ravers” use MDMA as their drug of choice and typically dance through the night to music accompanied by computer-generated videos and laser light shows. The amount of MDMA typically used during raves varies widely, with doses ranging from 75 to 1,250 mg over several hours.

**Acute Neurochemical Effects**

The most pronounced acute biochemical effect of MDMA is increased 5-HT neurotransmission, brought about by a calcium-independent release of 5-HT from nerve endings (64). MDMA-induced 5-HT release involves both vesicular and plasma membrane monoamine transporter (65). Actions at the serotonin transporter are also thought to lead to reuptake inactivation (66). MDMA also appears to release dopamine, but this effect is less pronounced than those on serotonin neurons (66). Unlike the actions of classic hallucinogens, the acute neurochemical actions of MDMA are primarily indirect rather than mediated directly at postsynaptic 5-HT receptors, for which MDMA has a low affinity (67).

The binding potential of MDMA at a number of postsynaptic receptor sites and reuptake sites has been evaluated (68,69). The affinity of racemic MDMA for receptors was initially found to be greatest for the serotonin transporter (SERT), followed in turn by the α2-adrenergic receptor, the 5-HT1A receptor, the histamine H1 receptor, and the muscarinic M1 receptor (70). In a subsequent study by Pierce and Peroutka (69), in which a more selective 5-HT2A-receptor agonist, 2,5-dimethoxy-4-<sup>77</sup>Br-amphetamine (DOB), was used, the binding potency of MDMA at 5-HT<sub>2A</sub> receptors was greater than that at α2-adrenergic receptors.

**Behavioral Effects in Animals**

The administration of MDMA in animals leads to typical signs of mild sympathomimetic stimulation; these include increased locomotor activity, heart rate, and body temperature in rats (71) and mydriasis, salivation, piloerection, and hyperthermia in dogs and monkeys (72,73). Locomotor studies suggest that MDMA can be distinguished from amphetamine, and in some behavioral paradigms, it appears to have a greater similarity to hallucinogens than to amphetamine (74).

In drug discrimination studies, MDMA substitutes for d-amphetamine in rats (75), pigeons (76), and monkeys (77). In contrast, despite structural similarities to mescaline, responses to MDMA differ from those to the hallucinogen DOB (61), but they are similar to those for the indolalkylamine α-methyltryptamine (78).

Animal studies investigating the abuse potential of MDMA are consistent with epidemiologic studies and abuse patterns previously described in humans. In particular, baboons self-administer MDMA (28). Rhesus monkeys trained to self-administer cocaine prefer MDMA to vehicle, and they sometimes administer MDMA at a higher rate than cocaine (79). In rats, MDMA lowers the electric threshold for self-stimulation in the medial forebrain bundle (80). Thus, in three different behavioral paradigms, MDMA appears to have significant potential for abuse.

**Human Studies with MDMA**

As would be predicted from studies in animals, MDMA exhibits both stimulant and hallucinogen-like activity. The stimulant effects of MDMA, typically noted shortly after drug ingestion, include increased heart rate, increased blood pressure, decreased appetite, increased alertness, and euphoria (81). Data regarding the effects of MDMA in humans come from both retrospective, uncontrolled studies and controlled, laboratory-based research. These studies are described below.

Greer and Tolbert (82) summarized experiences from 29 separate clinical therapy sessions during which MDMA was utilized as a psychotherapeutic adjunct. Patients received doses of MDMA ranging between 75 and 150 mg after a 6-hour fast (one subject, at his request, received a higher dose). A second dose of 50 or 75 mg was offered when the effects of the first dose began to subside. The 21 patients who were engaging in couples therapy reported increased closeness or enhanced communication with their partner, and all 29 patients reported positive attitudinal and emotional changes. Of the 29 patients, 22 reported “cognitive” benefits, such as “an expanded mental perspective, insight into problems, and issue resolution.” All patients reported adverse effects, including fatigue, jaw clenching, nausea, transient gait disturbance, and sympathomimetic symptoms.

In the first double-blinded, randomized study involving the prospective administration of MDMA to humans (83), subjects received MDMA orally at doses ranging from 0.25 to 1.0 mg/kg (17.5 to 70 mg in a 70-kg adult). These doses were associated with increased heart rate and blood pressure and positive psychological effects. In a second double-blinded, placebo-controlled study (84), the effects of MDMA (1.7 mg/kg; 119 mg in a 70-kg person) were evaluated in 13 MDMA-naïve healthy volunteers. MDMA was reported to enhance mood, a sense of well-being, and emotional sensitivity. Some subjects reported anxiety. Other symptoms reported included mild depersonalization and derealization, altered time perception, moderate thought disorder, poor coordination, heightened sensory awareness, and increased energy. A hypertensive reaction developed in one subject. Adverse subjective somatic effects of MDMA included jaw clenching, anorexia, impaired gait, and restless legs. After 24 hours, subjects’ complaints included poor energy and appetite, restlessness, insomnia, trismus, poor concentration, and brooding. In the most recent prospective, double-blinded study of MDMA administration in humans (85), the effects of 75 and 125 mg of MDMA were compared with those of 40 mg of amphetamine and placebo.
Both doses of MDMA led to significant increases in blood pressure (increases in systolic blood pressure averaging 40 mm Hg), heart rate (increases averaging 30 beats/min), and pupillary diameter in comparison with placebo. No hallucinations were reported following any drug. All active drugs led to increases in euphoria that were greatest following 125 mg of MDMA. MDMA was also reported to produce altered visual and auditory perception.

**Neuroendocrine Effects**

In rats, the systemic administration of MDMA leads to a pronounced elevation in levels of corticosterone and prolactin, accompanied by an elevation in temperature (86,87). These effects appear to be mediated by 5-HT receptors because they are attenuated or completely blocked by pretreatment with the 5-HT neurotoxin p-chlorophenylalanine (86). MDMA-induced increases in corticosterone levels and temperature are blocked by 5-HT2-receptor antagonists but not by 5-HT1A-receptor antagonists or nonspecific 5-HT-receptor antagonists. In contrast, MDMA-induced prolactin responses are not attenuated by either 5-HT1A-receptor or 5-HT2-receptor antagonists, which suggests that the two MDMA-induced neuroendocrine responses involve different 5-HT receptors.

Several studies have evaluated the neuroendocrine effects of MDMA in humans. MDMA doses of up to 75 mg are associated with increases in cortisol, and higher doses lead to increases in both cortisol and prolactin (83,85). Notably, evidence in both animals and humans is increasing that previous exposure to MDMA leads to alterations in neuroendocrine responses (87–92), possibly as a consequence of long-term effects on brain 5-HT neurons.

**Biodisposition in Animals**

The metabolic pathways of MDMA have been well characterized in several animal species. *In vivo* studies in rats have shown that MDMA is metabolized via N-demethylation, O-dealkylation, deamination, and conjugation (O-methylation, O-glucuronidation, and O-sulfation) (93). The (S)-(+) -MDMA isomer of MDMA appears to be metabolized more rapidly (94) and extensively (95) than the (R)-(−)-MDMA isomer, with half-life estimates being 73.8 and 100.7 minutes for (S)-(+) - and (R)-(−)-MDMA, respectively (94). Nonconjugated metabolites of MDMA are present in blood, brain, liver, feces, and urine for a 24-hour period following drug administration, with the exception of the O-dealkylated catechol metabolite, which is found only in brain tissue (93). This latter pathway, mediated via constitutive cytochrome P-450 isozymes, is a primary route of metabolism in rat brain microsomes.

**Biodisposition in Humans**

Three studies have evaluated the biodisposition of MDMA in humans (85,96,97). In the neuroendocrine study by Mas et al. (85), maximum concentrations of MDMA and elimination half-lives were evaluated for 75- and 125-mg doses of MDMA in healthy men. Maximum plasma concentrations were 130.9 and 236.4 ng/mL for the 75- and 125-mg doses respectively and reached peak at 1.8 and 2.4 hours following drug ingestion, respectively. Elimination half-life was 7.7 hours for the 75-mg dose of MDMA and 8.6 hours for the 125-mg dose. Plasma concentrations of (R)-(−)-MDMA exceed those of the (S)-(+) enantiomer (96). Most recently, de la Torre and colleagues (97) found that relatively small increases in MDMA doses are translated to disproportionate rises in MDMA plasma concentrations, even in persons with high levels of CYP2D6 activity (i.e., extensive metabolizers).

**Clinically Reported Adverse Effects**

Acute adverse medical effects of MDMA have been reviewed extensively elsewhere (98,99). These effects, which are undoubtedly related to the sympathomimetic and serotoninergic properties of MDMA, include nausea, vomiting, jaw clenching, bruxism, hypertension, palpitations, headaches, hyperreflexia, Difficulty walking, urinary urgency, diaphoresis, anorexia, muscle aches or tension, hot and cold flashes, nystagmus, blurred vision, insomnia, and dry mouth.

Aside from one report of an acute hypertensive crisis in a prospective study (84), serious acute medical complications of MDMA use have appeared in the literature as case reports or reports from poison centers and coroners. Among the serious problems that have been associated with MDMA use are cerebrovascular incidents (100) and arrhythmias (101), likely related to the potent sympathomimetic and vasoconstrictive effects of MDMA. Electrolyte imbalance or the syndrome of inappropriate secretion of antidiuretic hormone, sometimes associated with cerebral edema or seizures, has been reported by numerous authors (102,103).

Numerous reports of chronic medical sequelae of MDMA have also been published, and readers are referred elsewhere for a more comprehensive review of this topic (98,99). One serious adverse medical event associated with MDMA, multiple organ system failure, appears to be directly related to the use of MDMA in raves, where users become hot and dehydrated in crowded conditions. In this setting, MDMA is associated with a life-threatening syndrome involving dehydration, hyperthermia, seizures, rhabdomyolysis, disseminated intravascular coagulation, renal failure, and death (104–106). This is reminiscent of the phenomenon of aggregation toxicity in animals (107), in which the lethality of amphetamines is greatly potentiated by crowded housing conditions. Reports of hepatotoxicity, aplastic anemia, and toxic leukoencephalopathy in MDMA users may be related to contaminants in MDMA synthesis or represent idiosyncratic drug reactions (108–109).

Adverse neuropsychiatric effects have also been associated with MDMA. Acute psychiatric complications of MDMA include panic attacks (110), psychosis (111), delir-
Long-lasting and possibly permanent (123,124). Chronic neuropsychiatric syndromes reported in MDMA users include panic disorder (114), psychosis (115), aggressive outbursts (116), flashbacks (111), major depressive disorder (117), and cognitive disturbances (117).

**Serotonin Neurotoxicity**

Like its structural relative methylenedioxyamphetamine (118), MDMA is a well-documented serotonin neurotoxin in a variety of animal species (119–122). In nonhuman primates, MDMA-induced brain serotonin neurotoxicity is long-lasting and possibly permanent (123,124). The administration of MDMA in animals leads to the persistent loss of a variety of markers specific to brain serotonin neurons. These include brain 5-HT itself (121); 5-hydroxyindolacetic acid (5-HIAA), the major metabolite of serotonin (125); tryptophan hydroxylase, the rate-limiting enzyme in serotonin synthesis (126); and the SERT, a structural protein on the 5-HT nerve terminal (119). Anatomic evidence also indicates a persistent loss of brain serotonin axons and axon terminals. For example, following MDMA administration, quantitative autoradiographic studies with radioligands that bind to the SERT, and immunocytochemical studies in which antibodies are directed at either serotonin or the SERT, show pronounced, long-lasting reductions of the SERT and reduced density of serotonin axons with sparing of serotonin cell bodies (127). These selective serotonin deficits have been observed up to 7 years after drug discontinuation in nonhuman primates (123).

Efforts to determine whether selective serotonin neurotoxicity develops in human MDMA users, as in animals exposed to MDMA, have been limited by the paucity of available methods for assessing the status of central nervous system serotonin structure and function in living humans. At present, two methods for detecting MDMA-induced brain 5-HT neurotoxicity in living humans have been validated. These include measurement of spinal fluid 5-HIAA and PET neuroimaging of the SERT. Both of these methods have demonstrated capability for detecting MDMA-induced neurotoxic injury in nonhuman primates (128, 129). With these methods, two studies have shown decrements in human cerebrospinal fluid 5-HIAA that are similar to those seen in monkeys with known MDMA-induced 5-HT neurotoxic damage (92,130). Similarly, imaging studies with PET have revealed reductions in brain SERT binding in MDMA users that are similar to those seen in baboons with demonstrated MDMA-induced 5-HT damage (49). Further, reductions in the SERT could be correlated with the extent of previous MDMA use.

Studies attempting to identify the functional consequences of MDMA neurotoxicity in humans suggest that brain serotonin function is abnormal in human MDMA users. In particular, as previously described, abnormal neuroendocrine responses to the serotonin-releasing drugs fenfluramine and m-chlorophenylpiperazine (m-CPP) have been demonstrated in MDMA users. In the case of m-CPP, MDMA users also differ in their behavioral responses to drug. Several research groups have found cognitive impairments in MDMA users in comparison with controls, including decrements of visual and verbal memory, attention, and verbal reasoning (92,131–134). MDMA users have also been found to score higher on measures of impulsivity (88, 135,136, but not 130), consistent with work showing an inverse relationship between 5-HT markers and impulsivity (137).

**FUTURE RESEARCH DIRECTIONS**

Since Hofmann’s discovery of LSD in 1943, significant progress has been made toward understanding the mechanism of action of LSD and other drugs in its class (Fig. 108.2). Despite advances in understanding the mechanism of hallucinogenic action, many questions remain unanswered. During the next decade, it should be possible to refine further the 5-HT2A/1C hypothesis of psychedelic activity, to characterize better the neuroanatomy of the pharmacologic action of LSD, and to use modern neuroimaging techniques to compare and contrast the effects of LSD with those of idiopathic psychiatric illnesses in which hallucinations are a feature. Similarly, future studies of PCP may elucidate certain aspects of idiopathic psychotic illnesses. Clinical studies in PCP users, like those previously conducted in MDMA users, should be directed toward determining whether humans, like rodents, are susceptible to PCP neurotoxic injury and defining the functional consequences of such injury if it occurs.

MDMA research during the next decade should also yield significant advances. Preclinical studies aimed at determining the mechanism of MDMA-induced 5-HT neurotoxicity may not only increase our understanding of serotonin neuronal function but also provide insight into idiopathic neurodegenerative illnesses and neuronal responses to injury. Long-term studies in nonhuman primates and humans will be essential to learn whether recovery from MDMA-induced 5-HT neurotoxicity can occur (and if so, under what conditions), and will be useful in defining the functional consequences of MDMA-induced neurotoxicity. It may be possible, by using information derived from preclinical studies, to design treatments for persons in whom chronic MDMA-related neuropsychiatric illnesses develop. Increased efforts should be directed toward identifying those at greatest risk for the development of MDMA-related neuropsychiatric illnesses. Finally, cost-effective methods should be devised to detect MDMA-induced neurotoxicity, so as to identify those who may benefit from alternative, science-based treatment strategies.
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FIGURE 108.2. Schematic diagram of putative electrophysiological mechanism of action of hallucinogenic drugs. Depicted are serotoninergic hallucinogenic inputs at the raphe nuclei and locus ceruleus projecting to the vicinity of apical dendrites of layer V pyramidal cells in the neocortex. Hallucinogens, acting as partial agonists at 5-hydroxytryptamine subtype 2A (5-HT<sub>2A</sub>) receptors, induce the release of glutamate from excitatory nerve terminals. Also shown are inhibitory modulators of 5-HT<sub>2A</sub>-induced glutamate release: γ-aminobutyric acid (GABA), µ opiate, group II and III metabotropic glutamate, and possibly 5-HT<sub>1B</sub> receptors. NE, noradrenergic input; α<sub>1</sub>, α<sub>1</sub>-adrenergic receptor; mGluRII/III, group II and IIImetabotropic glutamate receptor; GABA, γ-aminobutyrate. (Modified from Aghajanian GK, Marek GJ. Serotonin and hallucinogens. Neuropsychopharmacology 1999;21:16S–23S, with permission.)

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