

# Hallucinogenic Drugs

Katherine R Bonson, *National Institute of Mental Health, Bethesda, Maryland, USA*

Hallucinogens are a class of drugs that produce complex psychological and physical effects and constitute one of the oldest classes of drugs used by humanity. Investigation of their neurochemical and behavioural effects may indicate therapeutic applications. Their recreational use also warrants continued investigation of their actions and effects.

## Introduction

Hallucinogens are one of the oldest classes of drugs used by humanity. Although they have been used by people in ritual settings for thousands of years, they remain contemporary drugs that have their own distinct sub-culture and usage today. According to the 1996 National Household Survey on Drug Abuse, hallucinogens are the second most frequently used illicit drug in the United States after marijuana, with 10% of the adult population (about 2.1 million people) having tried them at least once. This means that more Americans have used hallucinogens than have used cocaine, heroin or other illegal drugs. These statistics are similar to those found in other countries. Thus, research on the effects, pharmacology and history of hallucinogens, while neglected in large part since the 1960s, remains a pertinent area of investigation.

## Widespread Use of Hallucinogenic Drugs Throughout Human History

Ancient cultures, almost exclusively in the New World, identified hallucinogen-containing plants and incorporated their unusual effects into religious and mystical rituals. Mescaline is one of the oldest known, with archaeological evidence of use dating back some 3000 years. It is found in high concentrations in the peyote cactus and is ingested by chewing the 'buttons' of this cactus.

Although Spanish colonialists attempted to eradicate ceremonial use of peyote, the practice spread beyond Mexico in the late nineteenth century to native American tribes of Central and North America. At that point, writers of European descent were introduced to peyote, including the poet William Butler Yeats, who was impressed with the 'intense pleasure' that it produced. In the following century, Aldous Huxley described his experience with mescaline in *The Doors of Perception*. The Huichol tribe in Mexico is perhaps the most famous for its modern-day use of peyote, involving long journeys to gather the plants for religious purposes. In the United States, it is illegal to possess or grow peyote for recreational use. Members of

## Introductory article

### Article Contents

- Introduction
- Widespread Use of Hallucinogenic Drugs Throughout Human History
- Different Classes of Hallucinogenic Drugs
- Conditions of Use that Influence the Behavioural Effects of Hallucinogens
- Pharmacology of Hallucinogens
- Negative Aspects of Hallucinogen Use
- Hallucinogen-like Effects from Nonhallucinogenic Drugs
- Conclusion

the Native American Church, however, do have the legal right to use peyote in religious ceremonies, following many years of court battles.

Psilocybin-containing mushrooms furnish another hallucinogen and have been used in the indigenous cultures of Central America since ancient times, with ceremonial mushroom-shaped stones dating to 1000 BC. Psychedelic mushrooms first appear in recorded history when European explorers came into contact with Central American tribes in the sixteenth century. In their writings there is the description of participants at the coronation of Montezuma II consuming 'inebriating mushrooms' and having heavenly visions. These fungi were known by the name 'Teonanacatl', which translates to 'divine mushroom'.

More recently, in 1955 R. Gordon Wasson (then vice president of J.P. Morgan bank) and his wife popularized knowledge of this native psilocybin culture after they experienced the mushrooms themselves through contact with the curandera (healing woman) Maria Sabina in Mexico. Scientific interest followed, leading to the infamous 'Good Friday' experiment in which divinity students in Boston were given either 30 mg of psilocybin or a small amount of vitamin B combined with amphetamine in a double-blind study held in a chapel. Not surprisingly, only those students who received the active hallucinogen reported religious or mystical experiences.

Native use of hallucinogens does not always originate with the use of a single plant. One notable example is ayahuasca (also known as yage), an admixture of two plants, *Psychotria viridius* (which contains the hallucinogen DMT) and *Banisteriopsis caapi* (which contains harmaline, a monoamine oxidase (MAO) inhibitor) that are boiled together into a foul-tasting brew. The harmaline is a necessary component because DMT is not active orally unless the naturally occurring enzyme MAO in the gut that metabolizes DMT can be blocked from acting. Use of ayahuasca was first recorded in the 1850s by European explorers in Brazil and Peru. Participants in Amazonian rituals ingest ayahuasca in a structured religious ceremony

in which the ensuing hallucinations are interpreted as visions from god. This practice inspired modern accounts of ayahuasca use, including *The Yage Letters*, by William Burroughs and Allen Ginsburg. Today, an ayahuasca-based religion is widely practised in Brazil.

One important structural variant of DMT is 5-methoxy-DMT (5MeO-DMT). This compound is found in the bark of trees in the *Virola* genus, which is ground up by tribes in South America who use it as a snuff. The powder is forcefully blown into the nostrils of a tribe member through long, narrow tubes made from bones. Intense hallucinations result, typically followed by a stupor.

No account of the history of hallucinogen use would be complete without mention of the prototypic modern hallucinogen, lysergic acid diethylamide (LSD; the S stands for *Sauer*, the German word for acid). LSD was synthesized in 1938 by Albert Hofmann at the Sandoz Laboratories in Switzerland when he developed a series of compounds to strengthen uterine contractions during labour. While working with these chemicals in 1943, Hofmann noticed peculiar sensations. He decided to go home, where he fell into a state of 'extreme activity of the imagination'. Several days later, intrigued by his strange responses, he deliberately ingested what he thought was a minute amount of the drug (250 µg) and subsequently experienced a wild bicycle ride while attempting to go home. We now know that 250 µg is a substantial dose of LSD. He later wrote of his experience, 'There surged upon me an uninterrupted stream of fantastic images of extraordinary plasticity and vividness and accompanied by an intense, kaleidoscope-like play of colors.'

LSD was not the first hallucinogen to be produced synthetically (the first was mescaline in the 1880s), but it was the one to make the biggest impact on modern society. Long before hippies embraced LSD in the 1960s, there was an active underground use of LSD by intellectual suburbanites in the 1950s who were interested in its effects on the mind and on creativity. Access to LSD at that time was legal and it often came from psychiatrists who were investigating its behavioural effects in humans. LSD remains the most easily accessible street hallucinogen and it is often sold as other, more exotic psychedelics.

Finally, MDMA ('Ecstasy') has become a drug of choice at 'raves', all-night dance parties featuring electronic music and colourful light shows. MDMA was synthesized in the early part of the twentieth century, but only gained popularity in the 1980s for its ability to induce emotional openness and its stimulant-like properties.

## Different Classes of Hallucinogenic Drugs

The classic hallucinogens are generally divided on the basis of chemical structure into two families: tryptamines

(indolealkylamines) and phenethylamines. Tryptamines contain an indole ring, which is a six-membered ring attached to a five-membered ring containing nitrogen. Phenethylamines are compounds containing a phenyl ring attached to an ethyl group ending in a nitrogenous amine group.

## Tryptamines

### LSD

LSD is a tryptamine, but it has a much more complicated chemical structure than most tryptamine hallucinogens and is better classified as an ergoline. The chemical base for synthesis of LSD comes from a black fungus (*Claviceps purpurea*) that grows on rye, known as ergot. LSD is one of the most potent drugs known and its effects can be felt after an oral dose of only 25–50 µg (0.025–0.050 mg). The dose of LSD found on the street typically ranges from 50 to 100 µg.

The half-life of LSD (the amount of time it takes for one-half of the dose of the drug to be metabolized in the body) is approximately 3 h. Since it takes about 3–4 half-lives before most drugs cease to have noticeable effects, the duration of action of LSD will range from 9 to 12 h in most people.

### Psilocybin mushrooms

Psilocybin is a tryptamine hallucinogen with a phosphoryloxy substitution at the 4-position of the indole nucleus (4-phosphoryloxy-*N,N*-dimethyltryptamine). Hydrolysis of psilocybin in the body strips off the phosphoric acid and leaves psilocin, which is about 1.4 times as potent as a hallucinogen as the parent compound. When the ratio of the biological potency of these two drugs is compared, it is the same as the ratio as that of the molecular masses of the drugs.

Psilocybin is present in certain mushrooms genera, including *Psilocybe*, *Stropharia* and *Panaeolus*. Mushrooms comprise about 90% water, but there is on average approximately 2–3 mg of psilocybin per gram of dry weight mushroom. The potency of psilocybin is about 1/100 of that of LSD, making the typical dose of psilocybin between 5 and 15 mg. Since the half-life of the active metabolite psilocin is approximately 1.5 h, the psilocybin experience will generally last approximately 4–6 h.

Psilocybin mushrooms are available on the street either fresh or dried. Common lore holds that fresh hallucinogenic mushrooms will turn blue when crushed; while this is true for some species, it is not a reliable identifying characteristic and cannot be used for determining whether a mushroom is safe to consume.

### DMT and related compounds

Dimethyltryptamine (DMT) is another psychedelic tryptamine. It is present chemically in a variety of plants

(including *Psychotria viridis*), as well as in minute quantities in the human body. This led to the speculation that perhaps DMT could induce psychosis endogenously, but this has never been shown to be true. DMT is biologically active in pharmacological doses and a seemingly endless series of substitutions on the basic DMT structure are also hallucinogenic.

As mentioned above, DMTs are not active by ingestion without inhibition of the enzyme MAO in the gut. Use of DMT is therefore typically by smoking the chemical in powder form or through injection. A dose of 50–100 mg is sufficient for hallucinogenic effects when DMT is smoked, but as little as 4 mg is needed when it is used intravenously. Both methods are extremely rapid in delivering DMT to the brain (smoking is actually faster because of a more direct blood route) and the effects subside within 60 min.

## Phenethylamines

### Mescaline

Chemically, mescaline is 3,4,5-trimethoxybenzeneethanamine, or 3,4,5-trimethoxyphenethylamine. The most familiar source of mescaline is the peyote cactus, *Lophophora williamsii* but it is also found in significant quantities in the San Pedro cactus, *Trichocereus pachanoi*. An average human dose is approximately 400 mg, making it 10 000 times less potent than LSD. Mescaline is a long-lasting hallucinogen, persisting for 12–15 hours. A notable side effect of mescaline is an early and intense nausea, often accompanied by vomiting. This response is so typical that it has been incorporated into the ritual use of the drug as a symbolic cleansing phase.

### DOM and related compounds

In the mid-1960s, structure–activity relationship investigations led to the synthesis of a new phenethylamine hallucinogen, DOM (2,5-dimethoxy-4-methylamphetamine). (It should be noted here that the name amphetamine is simply chemical shorthand for its structure:  $\alpha$ -methylphenethylamine.) An effective dose of DOM ranges from 3 to 10 mg orally. An extensive family of DOM derivatives have been synthesized, including DOB (substituting bromine at the 4-position) and DOET (substituting an ethyl group at the 4-position). These drugs have a long onset time (up to 2 h) and their effects can persist for 15–20 h. The unusually long duration is related to the chemical structure. The presence of an  $\alpha$ -methyl group on the phenethylamine physically prevents easy enzymatic degradation of the drug, extending the time the drug acts in the body.

In contrast, a related series of phenethylamine hallucinogens without the  $\alpha$ -methyl group are short-acting (2–6 h) because the metabolizing enzyme has easy access for biological degradation. Recently, one of these, 2-CB (2,5-dimethoxy-4-bromophenethylamine), a derivative of

DOB, has become a popular street drug, especially among college students.

### MDMA

In addition to the traditional phenethylamine psychedelics, MDMA (3,4-methylenedioxymethamphetamine) and MDA (3,4-methylenedioxyamphetamine) form a class of phenethylamines known as the hallucinogenic amphetamines. This term is something of a misnomer, since MDMA is characterized as having the ability to increase emotional warmth and stimulate the desire for movement rather than to produce hallucinations. However, users do note that some of the physical and psychological effects of MDMA do bear a similarity to those of true hallucinogens. A typical dose of MDMA, which lasts 2–4 h, is 125 mg. It is not uncommon for users to ‘boost’ with another dose of the drug when the effects of the initial dose begin to subside.

## Conditions of Use that Influence the Behavioural Effects of Hallucinogens

Hallucinogenic compounds are usually ingested orally, while some DMT-based hallucinogens are not active orally by themselves and are typically smoked. When taken by mouth, the effects of hallucinogens usually begin within 30–60 min. The duration of these effects is determined by the chemical structure of the drug and can range from a few hours to more than a day. Acute tolerance develops rapidly, so that ingesting the same dose of the same hallucinogen a short period after the first dose will not reproduce the same level of response. Tolerance to a single dose of most hallucinogens persists for several days and limits the abuse potential of these drugs.

More than most other classes of drugs, the response a person has to hallucinogens depends as much on psychological factors as on pharmacological factors such as chemical structure or dose. The common term for someone experiencing the effects of a hallucinogen is that of ‘tripping’. The initial effects are somatic and include sympathomimetic signs like increased heart rate and respiration, dilated pupils, and the sensation of butterflies in the stomach. Within an hour after the onset of physical responses, many (but not all) individuals begin to experience visual hallucinations. The ethnobotanist Richard Schultes of Harvard University, for example, spent decades identifying Amazonian hallucinogens but claimed that he never hallucinated when ingesting the plants with local tribespeople.

When visual hallucinations do occur, they can take the form of moving patterns and shapes, often in colourful interplays. Walls may seem to breathe and the appearance of everyday objects can take on amusing or upsetting qualities. In contrast to the effects of marijuana, which are often described as being ‘dream-like’, hallucinogens may

impart a 'super-real' quality to existence. Senses may seem to merge, leading to the experience of synaesthesia, where smells may be 'heard' or colours may be 'tasted'. Auditory hallucinations are also possible, despite clinical lore suggesting that such effects can only occur with schizophrenia.

During and after the peak of the hallucinatory phase, pronounced psychological changes of an intensely personal or mystical nature can begin to occur. Indeed, it is these unique effects that characterize hallucinogens as a class, perhaps more so than hallucinations themselves. These responses can include changes in meaning or insight, alterations in the ability to concentrate, development of selective attention, misperceptions of time, and a sense of losing control that can lead to a depersonalization or an 'anxious passivity'.

As the dose of any hallucinogen is increased, there will initially be a quantitative increase in the effects of the experience. Above a certain dose range for each individual psychedelic, the hallucinogenic response may progressively take on a qualitatively different character. At such higher doses, an individual's connection to the real world may begin to erode significantly, such that ego boundaries may disintegrate, one's thoughts may seem to merge profoundly with the universe, and hallucinations may be so profuse that it is difficult to see one's surroundings.

It is extremely uncommon for any other class of drugs to produce effects that are so profound that a single exposure will lead an individual to claim that her or his 'life has been changed' – whether positively or negatively. As a means of encapsulating such psychological changes in an understandable manner, many religious tendencies have been founded in response to the psychedelic experience. Shamanistic rituals involving peyote or psilocybin mushrooms have been conducted since prehistory, with adherents ingesting these plants to produce visions of gods or ancestors with knowledge of the future.

In modern times, recreational users of hallucinogens often view their consumption of these drugs as enhancing personal or spiritual growth. It is this belief that led to early suggestions that hallucinogens had great potential as aids in psychotherapeutic contexts. Despite the fact that decades of encouraging therapeutic work with these compounds often went unpublished, there has been renewed interest in and approval of research studies into the usefulness of hallucinogens for such purposes, both in the United States and elsewhere. Applications under investigation include administration of LSD to treat drug abuse or administration of MDMA to ease psychological distress in terminal cancer patients.

As the acute effects of hallucinogens subside, after several hours, users can experience a variety of emotions ranging from feeling at peace to feeling unsettled and suspicious. Most 'bad trips' typically happen after the peak of drug effects. This is because once frank hallucinations have stopped, some people can begin to think that they no

longer are under the influence of a drug. Yet if unusual psychological responses continue, such people may be unprepared and may feel anxious. It is worth noting that emergency-room visits are rare in hallucinogen users because direct physical distress is unlikely.

One concept that has aided in the process of calming someone during a bad drug experience is that of 'set and setting'. This phrase suggests that the response a person will have to hallucinogens is based on the 'set' of the mind (e.g. contented or agitated) and the setting in which the person consumes the drug (e.g. comfortable living room with friends or alone in an unfamiliar situation). The incidence of negative reactions is obviously reduced under conditions where people can be made to feel at ease with both the mindset and the circumstances in which they take hallucinogens.

In contrast to other psychedelics, MDMA does not typically induce hallucinations. Rather, MDMA has effects that remind users of both the sensory-enhancing qualities of hallucinogens and the energizing properties of amphetamines. More profoundly, MDMA often creates an emotional state of deep trust and lowered defences. Therapists applied this quality of this class of drugs, also known as 'empathogens' or 'entactogens', as a means of accessing difficult psychological problems in their patients or in couples counselling.

## Interactions with other drugs

Given that hallucinogens of all classes have virtually no physiologically toxic effects in typical doses, users have often been somewhat cavalier in combining hallucinogens with other drugs to alter the quality of the 'high' produced. While adverse reactions are unusual, there are some interactions that should be mentioned.

The most important of these is that acute or chronic administration of an MAO inhibitor can have life-threatening effects when combined with MDMA (or any other amphetamine). The idea behind using an MAO inhibitor with a psychedelic is usually based on an awareness of the pharmacology of ayahuasca, where an MAO inhibitor can activate a tryptamine hallucinogen with relative safety. The combination of an MAO inhibitor and MDMA is not safe, and there are numerous reports in the medical literature of a dangerous increase in blood pressure known as a hypertensive crisis when these drugs are taken together. Individuals should be severely cautioned against exposing themselves to this sort of risk.

Other antidepressants can have profound psychological effects on the human hallucinogenic response that do not seem to involve adverse physiological effects. Specifically, prolonged use (3 weeks or longer) of serotonin-reuptake inhibitors (such as fluoxetine (Prozac)) or MAO inhibitors (such as phenelzine (Nardil)) will significantly reduce or eliminate the hallucinogenic response to the classic

hallucinogens. In contrast, prolonged use of lithium or tricyclic antidepressants (such as desipramine (Norpramine)) will produce an exacerbation of the hallucinogenic response, often to a very unpleasant degree.

However, acute (single-dose) administration of antidepressants does not appear to have the same effect. Acute administration of serotonin-reuptake inhibitors or MAO inhibitors, for example, seems to potentiate the response to LSD. This difference in effect, based on duration of antidepressant administration, seems to be related to adaptive changes in serotonin levels and neurotransmission.

## Pharmacology of Hallucinogens

The pharmacology of the classic tryptamine and phenethylamine hallucinogens has been studied by scientists since the beginning of the twentieth century, but it is only since the 1970s that we have had a clearer picture of the distinct mechanisms of action of these chemicals on the brain. The initial focus of these efforts was the neurochemical serotonin (also known as 5-HT, 5-hydroxytryptamine). This is because serotonin itself is a tryptamine and contains an indole ring, as do all tryptamine hallucinogens. Research has subsequently shown that serotonergic receptors are the primary binding sites of both tryptaminergic and phenethylamine hallucinogens.

Although phenethylamine hallucinogens chemically resemble the neurotransmitter noradrenaline, many years of investigation have demonstrated that this neurochemical system is not directly responsible for their effects. However, noradrenergic systems do become hyperresponsive to sensory stimulation after any hallucinogen has been administered. This suggests that noradrenaline may contribute to hallucinogen-induced alterations in the processing of sensory information by the brain. Similarly, dopaminergic systems may play a role in the characteristic responses to some hallucinogens, both directly through activation of dopamine receptors and indirectly through modulation by serotonergic systems, but they are not responsible for the psychedelic effects of these drugs per se.

The serotonergic systems of the brain are so complex that there are currently 14 known serotonin receptor subtypes. Of these, only a few appear to play a significant role in the hallucinogenic response. The most critical receptor is thought to be the 5-HT<sub>2A</sub> site. This is based on the fact that there is a high correlation between binding of both tryptamine and phenethylamine hallucinogens at the 5-HT<sub>2A</sub> receptor and their ability to produce hallucinatory effects in humans. Tryptamine hallucinogens also have high binding affinity at 5-HT<sub>1A</sub> receptors, which may be important for certain aspects of their hallucinatory response that distinguish them from phenethylamine hallucinogens. Additionally, hallucinogens have high binding affinity to the 5-HT<sub>2C</sub> receptor, as well as to two

more recently identified receptor subtypes, 5-HT<sub>6</sub> and 5-HT<sub>7</sub>, that have not been fully characterized.

Investigations of the pharmacological mechanism of action of hallucinogens have typically been in animals. In addition to biochemical studies of receptors, observational investigations of behaviours following the administration of hallucinogens have also been conducted. One of the most frequently used techniques is that of drug discrimination. In this operant conditioning method, an animal is trained to press a bar on one side of a test cage when it is given a hallucinogen, and a bar on the other side of the test cage when it is given saline. The discrimination between the internal sensations (known as interoceptive cues) evoked by a drug or by saline can be learned reliably after repeated training sessions. It is then possible to test whether the animal will press the hallucinogen-associated bar when it is injected with a challenge compound that may have hallucinogenic effects. If it does, the challenge drug is said to demonstrate stimulus generalization with the training drug, presumably because the animal has received similar interoceptive stimulation.

For instance, it has been shown that when a rat is trained to discriminate LSD, it will later identify the hallucinogens mescaline or psilocybin as being more like LSD than like saline in this test. Generalizations such as this hold true between all hallucinogens in a variety of training and testing conditions in both rats and in humans. In fact, there is a near-perfect correlation between the ED<sub>50</sub> (the median effective dose) of hallucinogens in drug discrimination in rats and their hallucinogenic potency in humans. Additionally, there is a near-perfect correlation between behavioural potency and the affinity of a hallucinogen to bind at the 5-HT<sub>2A</sub> receptor. Drug discrimination has also been used to show that pretreatment of a rat with 5-HT<sub>2</sub> antagonists will block the ability of the rat to identify the interoceptive cue of a hallucinogen, causing the rat to press the saline bar. Impressively, a recent clinical study has shown that 5-HT<sub>2</sub> antagonists can prevent humans from feeling any of the effects of a behaviourally-active dose of psilocybin. Taken together, these data form the basis of the theory that the 5-HT<sub>2A</sub> receptor is critical in the hallucinogenic response.

Hallucinogens also evoke distinct behaviours in animals. These behaviours have been used to suggest selective activation of serotonin receptors. Both tryptamine and phenethylamine hallucinogens will cause a rat to shake its head or its full body (a behaviour known as 'wet dog shakes') if given in sufficient doses. Experiments with serotonin antagonists have shown that these behaviours are directly related to activation of the 5-HT<sub>2A</sub> receptor. In contrast, most tryptamine hallucinogens (but only a few phenethylamine hallucinogens) produce the 'serotonin syndrome', a behavioural complex involving flat body posture, movement of the front paws in a 'piano playing' motion, splayed rear legs and a tail standing straight up ('Straub tail'). Again, through serotonin antagonist

studies, it has been shown that this syndrome is related to stimulation of 5-HT<sub>1A</sub> receptors. If a novel hallucinogen is thought to have a particular receptor binding profile, watching for these two types of behaviours after administration of the drug can be indicative of where the drug might be acting in the brain.

Another behavioural test that has been shown to be sensitive to hallucinogens is the Behaviour Pattern Monitor (BPM). The BPM is a large test chamber that can localize rat movement using photobeams. When rats are given LSD or other hallucinogens and placed in the BPM, there is a decrease in their natural tendency to explore an unfamiliar test chamber. This is interpreted as an increase in neophobia. Hallucinogens also increase the tendency of rats to avoid the open space in the centre of the BPM, interpreted as an increase in the response to aversive or threatening stimuli. Both of these effects are blocked when rats are pretreated with 5-HT<sub>2</sub> antagonists. The behavioural patterns produced by hallucinogens are distinct from those produced by other drugs.

All of the behavioural methods detailed above have been used to demonstrate that tolerance develops rapidly to repeated doses of hallucinogens. Thus, the initial administration of a hallucinogen will produce the expected behaviour, but giving the same drug again at the same dose a day later will produce less of that behaviour. Continued administration will further reduce and then eliminate the behaviour. Cross-tolerance has also been demonstrated in these tests, such that once an animal is tolerant to one hallucinogen, it will also be tolerant to other hallucinogens at comparable doses of efficacy. It has been shown that behavioural tolerance is the result of a decrease in (downregulation of) serotonin receptors following continual drug stimulation. These data support the idea that there is a common neurochemical mechanism of action responsible for the behaviours at the receptor level.

Mechanistically, MDMA is different from other hallucinogens in that its effects do not seem to rely on direct activation at serotonergic receptors (although there is rather poor affinity for 5-HT<sub>2A</sub> and 5-HT<sub>1B</sub> receptors). Instead, MDMA acts dualistically as a serotonin-reuptake inhibitor (like the antidepressant fluoxetine (Prozac)) and as a serotonin releaser (like fenfluramine (Pondimin), the weight-reduction drug). It also has the ability to inhibit MAO. All of these actions cause the increase of serotonin in the synapse, thereby increasing serotonergic neurotransmission. This can result in the well-known effect of hyperthermia. In rats, the increase in core body temperature due to MDMA can be exacerbated by enclosed spaces and a lack of hydration – exactly the conditions found at ‘raves’. It is debatable, however, whether the human deaths attributed to MDMA use in clubs are the direct result of drug ingestion or rather can be attributed to club conditions or mixing of classes of drugs.

Interestingly enough, animals will self-administer nearly every drug that is used recreationally or is abused in humans, but this is not the case with hallucinogens. It is unclear why this is so, and it suggests that the explanation for human hallucinogen use may involve more than simple reinforcement theories or associated neural tracts.

## Negative Aspects of Hallucinogen Use

It should be stated first that hallucinogens are like any other psychoactive drug in that they can produce unpleasant or disturbing psychological effects that may be difficult for a user to overcome while under the influence of the drug. Intoxication with any drug can similarly cause irrational and highly risky behaviour. Although the stereotyped ‘bad trip’ that can result from hallucinogen use is certainly an undesirable and unique condition, it is seen much less frequently among users of psychedelics than are the drunken rages seen in alcohol users or the manic craving for drugs seen in cocaine users.

Many myths that have no factual basis have been promoted over the years regarding hallucinogens. There is no known lasting physical or neural damage from hallucinogen use, nor is there any evidence of physical dependence, a withdrawal syndrome or addiction to these drugs. One would have to consume massive amounts of a hallucinogen to overdose and die. The threat of damage to sex chromosomes is nonexistent. Hallucinogens do not remain in or destroy the cerebrospinal fluid, and physical side effects like stomach cramps are probably not from a poor-quality drug but are instead related to the intrinsic properties of hallucinogens acting on the mesenteric serotonergic system.

One of the most famous negative attributes related to hallucinogen use is that of ‘flashbacks’, as well as the more recent ‘posthallucinogen perceptual disorder’. These states clearly exist in some individuals who have taken hallucinogens, but the frequency of these reactions in the population of users is known to be extremely rare. There is no evidence that these responses are based on chemical insult to the brain and it is probable that these after-effects are psychological phenomena not unlike the persistence of memories about events with significant emotional valence (such as becoming engaged or going to war). Additionally, hallucinogens should not be confused with THC (tetrahydrocannabinol; the psychoactive component of marijuana) in that they are not fat-soluble and therefore are not able to be harboured in or released from adipose tissue long after use. There is no evidence that THC can induce flashbacks.

Another negative concern is that MDMA is a neurotoxin. Part of this association may be from a confusion of MDMA with the ‘designer drug’ 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (a derivative of the

opioid meperidine), which did indeed cause dopaminergic degeneration and subsequent Parkinson-like immobility. In contrast, MDMA can induce a persistent reduction of serotonergic nerve terminals when given in rodent studies. Whether this effect constitutes neurotoxicity is controversial. Careful analysis reveals that the doses used in such rats studies are comparable to 3–4 times the doses typically consumed by humans. Since it is not uncommon for users to take much larger quantities of MDMA when ‘boosting’, it is possible that alterations in serotonin systems may occur with very frequent, high-dose use of the drug. Recent clinical studies have suggested that MDMA users have deficits in performance on a selected number of cognitive tasks (such as certain tests of memory). It is difficult to know whether these data represent behavioural toxicity since the reported effects are present only in individuals who have taken extremely high doses of MDMA for extended periods, there is a lack of baseline measurement prior to MDMA use, and the contributions of other illicit drugs also consumed are not taken into account.

## Hallucinogen-like Effects from Nonhallucinogenic Drugs

Other classes of drugs may also induce effects that are similar in some fashion to those of hallucinogens. Although these other drugs have certain effects that resemble hallucinogens, they elicit their own distinct physical and psychological responses based on their unique pharmacology. Drugs with certain effects that may resemble those of hallucinogens include:

- Cannabinoids such as marijuana
- Dissociative anaesthetics like PCP (phencyclidine), ketamine, or the cough suppressant dextromethorphan, which act as NMDA (*N*-methyl-D-aspartate) channel blockers
- Deliriant such as the anticholinergics scopolamine or atropine
- Kappa and/or sigma opioid receptor agonists such as pentazocine
- Inhalants such as nitrous oxide that act nonspecifically at opioid receptors
- Muscimol, a GABA agonist found in the mushroom *Amanita muscaria*

In addition, hallucinations can be induced without drugs, under conditions such as high fever, discontinuation

of chronic drug use, extreme physical or psychological stimulation, oxygen deprivation and psychotic states. What is fascinating is that the nervous system has so many different mechanisms to produce a hallucinatory response accompanied by unusual mental states.

## Conclusion

Hallucinogens are a class of drugs that produce a complex set of psychological and physical effects that have been experienced by humans throughout the ages. Many of these hallucinogens occur naturally in plants, while others have been synthesized in laboratories, based on two primary chemical structures, tryptamines and phenethylamines. Only in the latter part of the twentieth century have scientists been able to identify the precise sites within the serotonergic systems of the brain that are responsible for the unique responses of hallucinogens. Given that these drugs are widely used recreationally and may have therapeutic applications, continued investigation into the neurochemical and behavioural responses they produce will continue.

## Further Reading

- Aghajanian GK and Marek GJ (1999) Serotonin and hallucinogens. *Neuropsychopharmacology* **21**(2)(suppl.): S16–S23.
- Halpern JH, Pope HG Jr (1999) Do hallucinogens cause residual neuropsychological toxicity? *Drug and Alcohol Dependence* **53**(3): 247–256.
- Heffter Research Institute (2000) Research at the frontiers of the mind. [www.heffter.org]
- Metzner R (1998) Hallucinogenic drugs and plants in psychotherapy and shamanism. *Journal of Psychoactive Drugs* **30**(4): 333–341.
- Nichols DE (1997) Role of serotonergic neurons and 5-HT receptors in the action of hallucinogens. In: Baumgarten HG and Göthert M (eds) *Handbook of Experimental Pharmacology, Serotonergic Neurons and 5-HT Receptors in the CNS*, pp. 563–585. Heidelberg, Germany: Springer-Verlag.
- Shulgin A and Shulgin A (1991) *PIHKAL (Phenethylamines I Have Known and Loved)*. Berkeley, CA: Transform Press.
- Shulgin A and Shulgin A (1991) *TIHKAL (Tryptamines I Have Known and Loved)*. Berkeley, CA: Transform Press.
- Vollenweider FX (1998) Advances and pathophysiological models of hallucinogenic drug actions in humans. *Pharmacopsychiatry* **31**(2)(suppl.): S92–S103.
- Winter JC, Fiorella DJ, Timineri DM *et al.* (1999) Serotonergic receptor subtypes and hallucinogen-induced stimulus control. *Pharmacology, Biochemistry and Behaviour* **64**(2): 283–293.