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Hallucinogens, Phantasticants, and Club Drugs

The drugs discussed in this chapter do not have a lot in common. At one time in the past, they all might have been referred to as *hallucinogens*. It may be true that many of these drugs can cause hallucinations at high enough doses, but some of these drugs are not often taken in such high doses that hallucinations result—other effects seem to be important to the user.

Many of these drugs have a profound emotional effect. They make the user feel in touch either with others around them or with their inner selves, feel closer to God or the universe, or just feel ecstatic, enhancing the enjoyment of music and dancing and being with other people. For this reason a variety of other names have been suggested that describe some of the other effects. These include *phantasticants, psychedelics* (mind manifesters), *entactogens* (touching within), and *empathogenics* (empathy creators). The latter three were proposed in an attempt to describe an effect of these drugs that causes the user to achieve insights into him- or herself and achieve a closer empathy with others. They have been proposed by those who feel that these drugs are useful tools in psychotherapy (Metzner, 1993). Because the mental state created by some of these drugs is superficially similar to psychosis (and almost identical in others), the name *psychotomimetics* (psychosis mimics) is also sometimes used. More recently, some of these drugs have become associated with the club scene and are used to enhance the pleasure of music, dancing, and being with others. When used this way they are simply referred to as *club drugs*.

Note that cannabis could have been included in this chapter because it has many effects in common with these drugs, but in this book it has been given a chapter of its own. This separate treatment does not reflect any special property of cannabis. Cannabis was given a chapter of its own because of its widespread use and the abundance of information on it.

LSD AND THE MONOAMINE-LIKE DRUGS

The molecular structure of many drugs with hallucinogenic and phantasticant properties bears a resemblance to the monoamine neurotransmitters: serotonin, dopamine, and norepinephrine. *LSD* (lysergic acid diethylamide) and many other drugs

are similar to serotonin, which is an indoleamine. Mescaline has a structure similar to the catecholamines dopamine and norepinephrine. Even though they differ somewhat in structure, there is a considerable overlap between the effects of these *indoleamine-like* and *catecholamine-like* drugs, so they can be discussed together. In the next section we will discuss ecstasy, which is a cross between mescaline and amphetamine and has properties of both.

All the indoleamine-like drugs have effects that are similar to LSD and differ from LSD mainly in potency and duration of action. These include *psilocybin*, the ingredient in magic mushrooms; *lysergic acid amide*, found in morning glory seeds; *DMT*, found in the bark of a tree in the jungles of South and Central America; *bufotenine*, found in plants and in the venom on the backs of toads; and *harmine* and *harmaline*, which are found in a tropical vine that grows in South America and is used by the native peoples in the area to make an intoxicating drink (W. McKim, 2003).

Mescaline is a catecholamine-like drug. It, too, has many effects in common with LSD but is about 1/2,000th as potent. It is the active ingredient in a cactus known as the *peyote* (*Lephophora williamsii*), which is native to the deserts of Mexico and the southwestern United States. The peyote is a small, spineless cactus that barely sticks out of the ground and has a thick, tuberous root. It has been used for centuries in Mexico and was a sacred plant of the Aztecs.

Since LSD is the most widely used and studied member of the monoamine-like drugs, it will be discussed in detail as a representative of this class. In fact, it also shares some effects with ecstasy and some other drugs in this chapter.

History of LSD

LSD is a synthetic drug; however, a number of similar chemicals occur naturally in the *ergot fungus* that infects grains, especially rye. During the Middle Ages in Europe, there were outbreaks of what is now called *ergotism*, a reaction caused by eating the fungus-infected grain. There were two kinds of effects caused by different fungi. One kind severely constricted blood flow to the limbs and made them feel excessively warm. Eventually, this condition would lead to gangrene, and the limb would just fall off. In 1039, a religious order was formed in France to treat people afflicted with this kind of ergotism. The patron saint of this order was St. Anthony, and the disease became known as *St. Anthony's fire* because of the sensation of heat. The other type of ergotism was characterized by convulsions, delirium, and hallucinations. That these afflictions were caused by the fungus was not discovered until more than 700 years later, in 1777. In fact, St. Anthony's fire was caused by derivatives of lysergic acid in the ergot fungus.

The story of LSD begins in the twentieth century. One of the effects of the lysergic acid derivatives in ergot was contractions of the uterus, a fact that was known to midwives who used it to aid in childbirth. This prompted Albert Hoffman of the Sandoz Laboratories in Basel, Switzerland, to experiment with the derivatives of lysergic acid in the hope of finding a new medicine. He had no inkling that he was dealing with a hallucinogen. In 1938, he synthesized a series of lysergic acid compounds but found none of them particularly interesting and went on to other things. Five years later, in 1943, Hoffman made a new batch of the twenty-fifth derivative (which he called LSD-25) and tried some new experiments, but he began to feel very peculiar and had to go home. He suspected that the reason for his strange sensations was that he had accidentally taken some of the LSD-25. To test this theory, a few days later he deliberately ingested 0.25 mg (250 micrograms), which he thought was an extremely small dose. His plan was to start with a dose that was so small that it would have no effect and slowly work up, but he did not know the extreme potency of LSD. A quarter of a milligram is a rather large dose, several times what is required to cause a powerful hallucinatory effect. Hoffman experienced the first LSD trip.

Sandoz did not know what to do with LSD, so the drug was distributed for testing to laboratories in Europe and the United States. It was thought that it might be useful in the treatment of mental

disorders and alcoholism or at least as a means of studying psychotic behavior. Some researchers, like Humphry Osmond at the University of Saskatchewan, believed that LSD offered the power to provide great personal insights and possessed considerable psychotherapeutic potential. LSD was used in experiments in mental hospitals and laboratories until the mid-1960s, when it broke out of the laboratory and into the street.

Timothy Leary, a research professor in the Department of Social and Human Relations at Harvard University, was always considered by his colleagues to be a bit unconventional and radical in his views. The psychedelic revolution began for Leary in 1960. While he was in Mexico, he ate some mushrooms containing psilocybin, which caused him to have a "full-blown conversion experience." When he returned to Harvard, he and his colleague, Richard Alpert, distributed psilocybin to as many people as they could get to take it. In 1961, they tried LSD, started a new religion, and adopted LSD as a sacrament. In 1963, Leary and Alpert were dismissed from Harvard, a move that generated considerable publicity for them and the drug. They coined the phrase that was to become the philosophy of the hippie movement of the 1960s: "Turn on, tune in, drop out."

LSD had its heyday during the 1960s and early 1970s, the years of the hippie movement, which reached its peak at the Woodstock Music Festival in 1969. LSD has not vanished since then, but the pattern of its use is now somewhat different. In the 1960s, LSD was used as a true psychedelic: High doses were consumed in order to achieve vivid hallucinations and personal or cosmic insights. Using these high doses was not always a pleasurable experience. Gordon Wasson, who explored the religious use of many hallucinogenic plants, was asked once why he did not take hallucinogens all the time. He replied, "Ecstasy is hard work." It has been suggested that drug users in more recent years are not as interested in insight as they are in pleasure (Baumeister & Placidi, 1983).

LSD is now taken in smaller doses. The effect is a euphoric high similar to that of marijuana, and powerful mind-altering states are neither desired nor achieved. LSD is now used more as a phantasticant or entactogen than as a hallucinogen.

Dosage and Sources

LSD is sold on the street as *hits*. In the 1970s, a hit contained about 100 micrograms of LSD with a range of 0 to 300 micrograms (S. H. James & Bhatt, 1972) and does not appear to have changed much over time. There has always been great variation in the dosage available in a hit.

Hits of LSD have traditionally been absorbed in blotting paper, which may be plain or are printed with various cartoons or mosaic patterns. More recent variations include the *gel tab*, LSD in gelatin that is set in molds of various shapes or flat squares called *window panes*. LSD is also now available in candies or tiny pills called *microdots*. There is usually a larger dose of LSD in gelatin than in blotting paper because the gelatin protects the drug from deterioration caused by light and exposure to air.

Pharmacokinetics

LSD is usually taken orally and is effective by this route. Effects usually begin between 30 and 90 minutes after ingestion. Only 1 percent of the drug ever reaches the brain. The half-life of LSD is about 110 minutes in humans. It is extensively metabolized in the liver, and the metabolites are secreted into the digestive system in the bile and excreted in the feces. Mescaline is also readily absorbed from the digestive system and has a similar half-life (Brown, 1972).

Effects on the Body

There are few physical side effects of LSD, the most consistent being a dilation of the pupils. Mescaline often causes a period of nausea during the early stages of its effect.

Neurophysiology

Even though LSD has been around for a long time and has been studied extensively, its effects on the nervous system are still not clear. While it

is a serotonin receptor blocker in the peripheral nervous system, in the central nervous system (CNS) it appears to be a selective agonist at some serotonin receptors, particularly the 5-HT_{2A} receptor. This is also true for other indoleamine-like hallucinogens and the catecholamine-like hallucinogens. This effect on 5-HT_{2A} receptors is one of the few effects all these drugs have in common and seems to be responsible for the subjective effects of both classes of drugs (Marek & Aghajanian, 1999).

There are two regions of the brain that appear to be involved: the locus coeruleus (LC) and the cortex. The LC is located in the lower brain and receives input from many sensory sources throughout the body, and it sends axons to almost every area of the brain including the cortex, where it releases NE (see Chapter 4). It is involved in fear and emotional responses and appears to function as a novelty detector. Stimulation of 5-HT_{2A} receptors by both indoleamine- and catecholamine-like hallucinogens has two indirect effects on the LC. First, they suppress output of the LC, although they do so via different mechanisms. In addition—and perhaps more important—they also enhance the response of the LC to novelty. This might explain some of the effects hallucinogenic drugs of this type have on perception. As we see later, after taking mescaline, for example, people often report that it is like seeing things for the first time.

In the cortex, these drugs change the response of large glutaminergic neurons to synaptic input by prolonging excitatory postsynaptic potentials. This effect is mediated through their effect on serotonin synapses. This effect is most prominent in the medial prefrontal cortex, where there is a large concentration of 5-HT_{2A} receptors. This area of the cortex is important in information processing and perception and may be involved in hallucinations.

Subjective Effects

Hallucinogenic Effect. How does a scientist go about studying hallucinations? Hallucinations are, by definition, in the realm of subjective experience, and one of the first principles of scientific inquiry is that all scientific data must be public and observable to anyone. It is, however, possible to study the verbal reports of people who are experiencing or have experienced hallucinations, but then arises the problem of how to organize such a mass of words into something meaningful. Heinrich Kluver (1966), who started his work in the 1920s, combined reports of subjects in his own experiments on mescaline and those of other researchers and noticed that there were consistencies. Mostly, these people described vivid visual images, and the researchers were aware that the images were not real. If they closed their eyes, they would see these images against a black background; if they opened their eyes, the images would be projected on whatever they were looking at. Kluver noticed that the images were frequently geometric patterns, and he identified four types of patterns that resembled (a) a grating or lattice; (b) a cobweb; (c) a tunnel, funnel, or cone; and (d) a spiral. Kluver remarked that images of these types also appear in fever deliriums, insulin hypoglycemia, and states that occur just before drifting off to sleep (*hypnogogic states*). Unfortunately, what Kluver described was only the first of two stages of imagery; the second stage, described by others, is more complex and involves meaningful images of people, animals, and places. Even during this phase, there are some common elements among individuals. For example, 60 to 70 percent of all subjects report seeing small animal or human figures that are friendly and caricature-like, and 72 percent of all subjects report religious imagery.

Despite the great interest surrounding these observations, no comprehensive, systematic, or scientific work on them was attempted until the 1970s. The problem was tackled with surprising ingenuity and success by Ronald K. Siegel (R. K. Siegel & Jarvik, 1975) of the University of California at Los Angeles (UCLA). Siegel adopted a variation of the technique of trained introspection, which had been used by the early German schools of psychology. Siegel trained his observers to use a code to describe their experiences. They were able to code images, colors, and movement

by using a series of letters and numbers that they could express as fast as the images appeared. When they demonstrated that they were well trained, Siegel gave them a series of blind tests in which they were given placebos or any of a number of drugs in random order and left in a darkened room to report their experiences. Neither the subjects nor the researchers scoring the imagery codes knew what drug had been given.

Whereas the subjects given placebos saw a predominance of random forms, those getting the hallucinogenic drugs saw far more lattice and tunnel forms, confirming the observations of Kluver. During control sessions, subjects saw primarily black and violet forms, but in hallucinogenic sessions, they saw more colors, ranging into the yellow, orange, and red end of the spectrum. Finally, in all conditions, aimless and pulsating movement was reported, but in hallucinogenic sessions there was an increase in "explosive" movement.

After demonstrating that all of these drugs appeared to create similar types of images, Siegel was also able to show that at higher doses, people sometimes go through a phase where they see themselves being swept up into their own hallucination. This is followed by a stage where the images lose their geometric quality and become meaningful pictures of real objects. These images can change rapidly, as fast as 10 times a second, but the changes are not without a pattern. Each image appears to be related to the one before it. Figure 16-1 illustrates this point. Siegel also noted that the images during this stage were related to the subject's surroundings; for example, sounds such as footsteps induced an image of someone walking. Another interesting finding was that the colors appeared to shift from the blue end of the spectrum to the red end as the effect of the drug increased in intensity.

Because all these drugs have such similar effects, Siegel wondered whether the similarities might be due to cultural factors since all his subjects came from a similar culture (UCLA). To answer this question, he visited a remote tribe of Huichol Indians in the Sierra Madre range of Mexico. These Indians make brightly colored pictures of their peyote visions from colored yarn. Siegel found that the experiences represented by

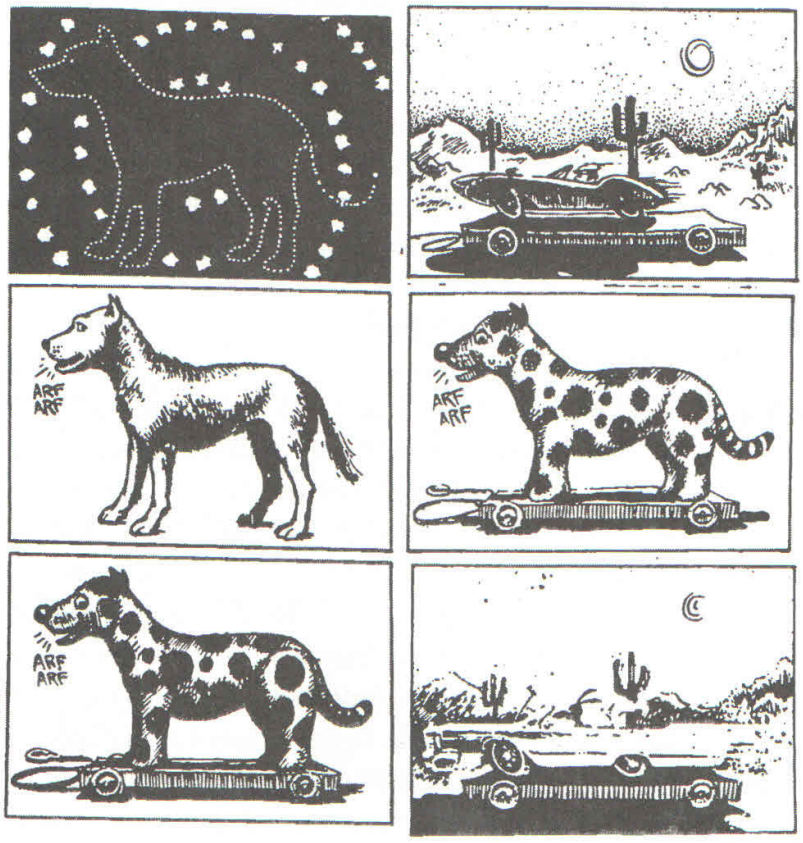

Figure 16-1 This series of drawings (read from top to bottom, column by column) illustrates the systematic changes in complex meaningful imagery reported after taking mescaline. Note that each scene contains an element of the previous one. Pen and ink drawings by David Sheridan. (From R. K. Siegel & Jarvik, 1975.)

the Huichols in their yarn pictures were identical to those reported by the subjects in his laboratory.

Siegel postulated that the nature and structure of hallucinations must be determined by the nature and structure of the visual system and the brain, not by the drug, because (a) these hallucinatory experiences are similar among vastly different drugs; (b) the experiences resemble the effects produced by other nondrug hallucinations, such as those from fever, hypoglycemia, and migraine headaches; and (c) the experiences are similar between cultures. In other words, the hallucinations are a result of nonspecific interference in brain functioning; the drug intensifies what might be considered normal background noise in the perceptual systems, and this noise is then organized, by the normal processes of perception and cognition, into images and patterns (R. K. Siegel, 1977; R. K. Siegel & Jarvik, 1975).

Siegel's study addressed only the visual property of the hallucinogenic experience, but LSD can cause entactogenic and empathogenic effects as well. These experiences often have a profound effect on emotions, insights, and feelings, which are not as easily studied and can be conveyed only by less scientific modes of expression, as we shall see.

Phantasticant and Perceptual Effects. These drugs can cause users to feel that the experiences they are having are of great emotional significance. Often these experiences can be religious in nature. It is for this reason that drugs like LSD have been widely used in traditional religions. The religious nature of the hallucinogenic experience is described here by R. Gordon Wasson (1972) in this account of his participation in a Mazatec Indian psilocybe mushroom rite:

> It permits you to see more clearly than our perishing mortal eyes can see, vistas beyond the horizons of this life, to travel backwards and forwards in time, to enter other planes of existence, even (as the Indians say) to know God. It is hardly surprising that your emotions are profoundly affected and you feel that an indissoluble bond unites you and the others who have shared in this sacred agape. All that you see during this night has a pristine quality; the landscape, the edifices, the carvings, the animals—they look as though they had come straight from the Maker's workshop. (p. 197)

Another commonly reported experience is the greatly enhanced pleasure derived from viewing art and, especially, listening to music:

> Ordinarily I am not particularly susceptible to music. This time, lying on the cot, I became acutely aware of the Montoya record playing. This was more than music: the entire room was saturated with sounds that were also feeling—sweet, delicious, sensual—that seemed to be coming from somewhere deep down inside me. I became mingled with the music, gliding along with the chords. Everything I saw and felt was somehow inextricably interrelated. This was pure synesthesia, and I was part of the synthesis. I suddenly "knew" what it was to be simultaneously a guitar, the sounds, the ear that received them, and the organism that responded, in what was the most profoundly consuming aesthetic experience I have ever had. (J. Richardson in Aanonsen & Osmond, 1970, p. 53)

Club drugs appear to have a similar effect when it comes to the music played at raves and in clubs. It has a loud, strong, repetitive beat and creates the urge to dance, which is enhanced by this effect of drugs like LSD and ecstasy.

Entactogenic and Empathogenic Effects. Another commonly reported effect is that the hallucinogens seem to provide insight into one's past and one's own mind, revealing repressed thoughts and unrecognized feelings. Such insights are similar to those that psychoanalysis attempts to achieve through psychotherapy. It was this effect that inspired Humphry Osmond to suggest that hallucinogens might be useful tools in psychotherapy and prompted the use of the term *entactogenic* (touching within) to describe this effect. Here is a description of the experiences of psychologist Bernard Aaronson, who took LSD as part of an experiment:

> We sat on the bench under the trees and talked about the loneliness of being, and talked about how people are forever needing things they expect you to provide. For what seemed a long time, I cried as I have not cried

since I was a baby, for all the people in the world who need things and whose needs cannot be met. I cried too for all the people around me that I botched in the giving or to whom I cannot give because I am depleted. . . . I expressed great hostility toward both my parents and with H.'s help analyzed my feelings as they derived from my relationship with each of them. I analyzed my relationship with my next older brother, and examined the meaning in my life of my relationship with that friend whom I love the most. (Aaronson & Osmond, 1970, pp. 47–48)

A more complete account of the subjective experiences of hallucinogens is beyond the scope of this book. A good selection of accounts of drug experiences may be found in Grinspoon and Bakalar (1979b).

Perception

As we have seen, people who use LSD frequently report that their perceptions are much keener and that their sight and hearing have become more acute. There have been a few studies of the effects of LSD on visual sensory thresholds, but their results are not consistent. In general, however, impairments of sensory functions attributable to LSD are reported more often than improvements (Hollister, 1978).

It is clear that LSD increases the enjoyment of music, but it has not yet been established whether there are any changes in auditory thresholds. The perception of the passage of time is distorted in most individuals; however, the direction of distortion is not consistent. In most cases, time is perceived as slowing down (10 seconds seem more like 20), but in some experiments the reverse has been reported (Hollister, 1978).

Behavior and Performance

One of the difficulties with measuring human performance under the influence of hallucinogens is maintaining the motivation of the subject to cooperate. Like marijuana, hallucinogens frequently cause subjects to become inattentive to the task and so caught up in internal experiences that they lose their motivation to perform, as well as they are able, tasks that they may feel are irrelevant at the time. It has been suggested that Carlos Castaneda (1973), an anthropology student who wrote extensively about his experiences after taking several different types of hallucinogens, could not have had the experiences he describes because he claims to have been able to continue to take notes while under the influence of the drugs (R. K. Siegel, 1981).

The available data show mostly that LSD impairs reaction time. Oddly enough, performance on a pursuit rotor task may be improved by LSD (Rosenbaum, Cohen, Luby, Gottlieb, & Yellen, 1959).

Functioning on intellectual tasks is also impaired. Like THC, LSD causes a deficit in short-term, or working, memory. Other impairments are seen in problem-solving and cognitive functions such as mental addition and subtraction, color naming, concentration, and recognition (Hollister, 1978, p. 397).

Claims have been made that LSD-like hallucinogens improve creativity, but again, as with THC, these are difficult to substantiate experimentally. There is little doubt that LSD changes the sort of work done by artists, but it is debatable whether these changes are improvements.

Discriminative Stimulus Properties

Nonhumans readily learn to discriminate LSD from saline. The stimulus cue of LSD is not blocked by cholinergic blockers such as atropine, opiate antagonists such as naloxone, or dopamine blockers such as chlorpromazine. Although there is some variability between drugs and laboratories, it appears that the stimulus properties of LSD can be blocked by central-acting serotonin agonists but not by peripheral serotonin agonists; these findings confirm that serotonin receptors in the CNS are involved in the subjective effects of LSD. Serotonin is further implicated in studies in which rats were trained to perform a response when given electrical stimulation of the

Raphé nuclei, a serotonin-containing system implicated in sleep (see Chapter 4). Later this response was performed by rats given LSD, indicating that the Raphé stimulation was regarded as being similar to LSD. In addition, LSD injected directly into the Raphé system produces the same stimulus effects as when given intraperitoneally: All these data support the notion that the subjective effects of LSD depend on serotonin receptors in the Raphé system (Hirschorn, Hayes, & Rosecrans, 1975).

Tolerance

In humans, tolerance to the effects of LSD and psilocybin and related drugs develops rapidly. If LSD is taken repeatedly, its effects disappear within 2 or 3 days; no amount of drug will be effective. This tolerance dissipates quickly, and sensitivity returns within a week. This is one reason why these drugs are seldom taken continually. The ability of LSD to disrupt the operant behavior of nonhumans also shows rapid tolerance. There is cross-tolerance between LSD and psilocybin and mescaline but no cross-tolerance between LSD and d-amphetamine or THC (Brown, 1972, p. 50).

Withdrawal

No withdrawal symptoms to LSD or any similar drugs have been found. This may be because they are seldom taken continuously for any period of time.

Self-Administration

Nonhumans. It is widely accepted that LSD and similar monoamine-like hallucinogens are not self-administered by nonhumans. In fact, they appear to have aversive effects. It has been demonstrated that laboratory animals will work to avoid being given LSD. In one experiment, rhesus monkeys learned to press a lever to turn off a stimulus that normally preceded an infusion of LSD and, thus, prevented the infusion (Hoffmeister & Wuttke, 1975). Nevertheless, a study done in 2004 did show transient self-administration of DMT, mescaline, and psilocybin in some monkeys with a history of self-administering MDMA (discussed later in this chapter; Fantegrossi, Woods, & Winger, 2004). This suggests that the occasional use of these drugs may be reinforcing in some individuals. This may explain why, outside the laboratory, there are reports that nonhumans will, from time to time, consume plants that contain LSD-like drugs. There are also reports that dogs in Hawaii enjoy eating mushrooms that contain psilocybin and that mongooses prefer to eat the species of toad that contains bufotenine (R. K. Siegel & Jarvik, 1975).

Humans. The self-administration of hallucinogens like LSD in human cultures is almost universal and very ancient, but its use is different from the use of most other drugs. First, they are never continuously consumed. They are indulged in sporadically and on special occasions. The use of hallucinogens in most cultures is usually associated with religious ceremonies. Frequently, the drugs are taken only by priests and shamans for the purpose of divination, talking to the dead, or seeking direction from a deity. Even in modern Western culture, hallucinogens are usually taken episodically. At the height of LSD's popularity in the 1960s, some people used it as often as possible and organized their lives around its use, but the rapid development of tolerance prevented a continuous trip. These "acid heads" were likely a phenomenon of the hippie lifestyle. Unlike other heavily used drugs such as alcohol, LSD use, for most people, does not increase over time. Initially, there may be a period during which a user will take the drug more frequently, but after a few years, most hallucinogen users mature out; people seem to get tired of the experience, and hallucinogen use decreases or stops altogether.

LSD use among teenagers in the United States remained fairly high throughout the 1990s but has been steadily declining. In 1996, 8.8 percent of grade 12 students reported using LSD within the past 30 days. In 2004 this number had dropped

to 2.2 percent (Johnston, O'Malley, Bachman, & Schulenberg, 2005).

Harmful Effects

The media have given great attention to the behaviors that may be provoked by the acute effects of such drugs. For example, stories appear occasionally about young LSD users who jump out of windows because they believe that they can fly. There are also reports of murders being committed under the influence of the drug. Events such as these undoubtedly occur, but they are extremely rare and probably occur with no greater frequency under the influence of LSD than under the influence of alcohol or any other drug.

Much more common but of less concern is the *acute psychotic reaction* or *freak-out*, which occurs when the user is having a bad trip, an unpleasant experience. Freak-outs happen when the experience is unpleasant and the user forgets that the experience is caused by a drug. The user fears going permanently insane, and the reaction is panic. Panic reactions are not normally seen in experienced users, are frequently a result of an unusually high dose (or a mixture) of drugs, and do not constitute a serious medical emergency. Panicky trippers can usually be talked down: Put in close contact with someone who talks to them constantly, reassuring them that their state is drug induced and will get better. If their attention can be concentrated on this fact, the effects of the drug can be decreased and the panic dispelled. For example, after one young man was talked down from a freak-out, he reported that the drug was causing every object in his entire world to melt and change shape. He concentrated on the person talking to him; that person was the only object that remained constant.

One disturbing effect of many hallucinogens is that some of their effects may be experienced briefly at various times long after the drug has worn off. These episodes are called *flashbacks*. In a similar effect, called *trailing phenomena*, objects seem to move in a jerky, discontinuous fashion as though being illuminated by stroboscopic light. No one understands flashbacks or trailing phenomena. They may occur unpredictably for years after only a single use of LSD. They normally last only a few seconds or minutes and are frequently associated with the use of other drugs such as ecstasy or marijuana or with times of emotional stress. One theory of flashbacks is that they are manifestations of a temporal lobe seizure, but there is little evidence to support this view (Hollister, 1978).

Psilocybin, LSD, and mescaline are not very toxic. There are no recorded cases of anyone dying from an overdose of any of these drugs.

ECSTASY AND SYNTHETIC MESCALINE-LIKE DRUGS

The structure of the mescaline molecule has been altered to form a family of drugs that is a combination of catecholamine-like hallucinogens and amphetamine. These drugs are all synthetic, and many such drugs have been discovered. Much of this research was done in the hope of finding a drug with a medically useful property. So far, the only use for these new substances has been in the drug subculture. Perhaps the best known of these is ecstasy.

The term *ecstasy* usually refers to *MDMA* (3,4-methylenedioxymethamphetamine) but may also refer to a mixture of *MDMA* and *MDEA* (N-ethyl-3,4-methylenedioxyamphetamine) and *MDA* (3,4-methylenedioxyamphetamine), drugs with similar potencies and effects (H. Kalant, 2001). It was originally synthesized by the Merck drug company and was patented in 1914. It was never developed or used for any purpose until the late 1960s, when it first appeared on the drug scene (R. K. Siegel, 1986). It also has been known as *X, Adam, MDM, M&M, e, xtc*, and *beanies*.

During the 1960s, many other synthetics were invented and manufactured in clandestine labs in an attempt to circumvent the law, which identified only specific chemicals as illegal. At that time, slight changes in the molecule could make a

drug legal until such time as there was specific legislation against it. Such drugs have become known as *designer drugs*, and they appeared on the street with a bewildering variety of names such as DMA, DOM, DOET, and so on. For the most part, these substances are more potent and considerably more toxic than mescaline, and they cause more unpleasant side effects, such as headaches and nausea. Unlike commercially developed drugs, many designer drugs were not screened for adverse effects, and some had extremely toxic effects and caused a number of deaths. Most of these designer drugs based on mescaline have virtually disappeared, but some, like ecstasy, are still around and are used more widely than ever.

Prior to July 1985, when it was reclassified by the governments of the United States, the United Kingdom, and Canada, some psychiatrists gave MDMA to their patients because it seemed to enhance intimacy and communication between the patient and the therapist (the terms *entactogen* and *empathogen* were invented with ecstasy in mind) (Adler, Abramson, Katz, & Hager, 1985; Verebey, Alrazi, & Jaffe, 1988). When it was reclassified in 1985, its use, even for psychotherapeutic purposes, was banned because it was discovered that the drug had neurotoxic effects; it was shown that a dose of about four times the normal effective dose causes a depletion of serotonin in the brain of rats 1 week after a single administration, a finding now confirmed in humans (Baggott, Jerome, & Stuart, 2001).

Ecstasy is sold in white or colored tablets that may or may not be marked with a symbol. Each pill may contain up to 100 mg or more of MDMA and may also contain varying amounts of MDEA, MDA, PMA (paramethyoxyamphetamine), and MBDB (3,4-methhlenedioxy-phenyl-N-methylbutanamine). A review of the purity of ecstasy tablets showed that in the late 1990s, as many as 20 percent of tablets did not contain MDMA at all; many contained only drugs like caffeine, ephedrine, or ketamine. However, these purity problems have not persisted into the 2000s, and non-MDMA tablets are now infrequent (Parrott, 2004).

Pharmacokinetics

Ecstasy can be taken orally and reaches a peak blood level in about 2 hours. The majority of the drug is either excreted unchanged or metabolized to MDA. It has a half-life of about 8 hours, thus taking about 40 hours for 95 percent of the drug to be eliminated. For this reason, many of its effects persist for several days after use.

Ecstasy is most often used by teens and young adults attending dance clubs and all-night dances or raves, although its use is associated with an increasing number of other activities such as sex. It produces a marked increase in wakefulness, endurance, and energy, and it creates in the user euphoria, an increased sense of well-being, sharpened sensory perception, greater sociability and extroversion, and a heightened sense of closeness to other people. As with LSD, these effects are subject to rapid acute tolerance, which generally means that ecstasy is unlikely to be used continuously. As with LSD, this tolerance dissipates within a few days.

Neurophysiology

Ecstasy and similar synthetics increase transmission at synapses that use serotonin, norepinephrine, and, to a lesser extent, dopamine. It works primarily by causing the release of the neurotransmitter and blocking transmitter reuptake.

Behavior and Performance

A dose of 75 to 100 mg induces a state similar to that caused by marijuana or low doses of phencyclidine (PCP), with no hallucinations, and an enhanced awareness of emotions and sensations—effects similar to the entactogenic effects described earlier in the section on LSD (Lamb & Griffiths, 1987; R. K. Siegel, 1986).

Effects of ecstasy include increased muscular tension, which causes jaw clenching and tooth grinding (*bruxism*) and a restless movement of the legs. Body temperature goes up in a warm environment, and there may be a stiffness in the back and legs for a few days. There often is a loss

of appetite, headache, nausea, blurred vision, and insomnia (Kalant, 2001). For a few days after use, people often report a difficulty in concentration, fatigue, and depression similar to the crash or comedown after use of amphetamine and cocaine (see Chapter 11).

Discriminative Stimulus Properties

Although not as much is known about mescaline and the synthetic mescaline-like drugs, it appears that increased serotonin activity is important in their stimulus effects. Rats trained to discriminate saline from MDMA will generalize the response to a serotonin (5-HT_{1A}) agonist. It has also been shown that MDMA will enhance the stimulus effects of LSD. This might be the basis of *candy flipping*, the practice of taking ecstasy and LSD together (Glennon & Young, 2000). MDMA stimulus properties do not generalize to cocaine or mescaline.

Tolerance

Similar to LSD, psilocybin, and mescaline, tolerance to the effects of ecstasy develops rapidly in humans.

Self-Administration

Nonhumans. It has been shown that, unlike LSD, MDMA is readily self-administered by primates (Lamb & Griffiths, 1987). Research with rhesus monkeys has shown that the reinforcing effects of MDMA follow an inverted U-shaped function with lower doses and higher doses not being effective reinforcers (Fantegrossi, Ullrich, Rice, Woods, & Winger, 2002). In this experiment, the reinforcing effects could be blocked by a drug that selectively blocked 5-HT_{2A} receptors, but this drug would not block the reinforcing effects of cocaine and methamphetamine, suggesting that the reinforcing effects of MDMA are mediated by a different mechanism from the one used by the psychomotor stimulants. This is odd considering that other drugs that increase serotonin activity at these receptors, such as LSD and the selective serotonin reuptake inhibitors (SSRI's), are not self-administered.

Human Epidemiology. The use of ecstasy steadily increased among young people in the United States and Europe throughout the 1990s until 2000. In the United States, ecstasy use increased in high school students, and the number of mentions of ecstasy in emergency room admissions about doubled between 1994 and 1999 (NIDA, 2001). A similar trend was seen in the United Kingdom and Canada (Morgan, 2000). But ecstasy use has undergone a drastic decline since peaking in 2000, when 3.6 percent of grade 12 students in the United States reported using the drug in the previous 30 days. In 2004, that figure dropped to 1.2 percent. This decline was accompanied with a general increase in perceived risk of using the drug. (Johnston et al., 2005).

Withdrawal

Ecstasy is known to have hangover effects but, like LSD, is never taken repeatedly, so withdrawal effects are not seen.

Harmful Effects of Ecstasy

Earlier reports of dopamine neurotoxicity have been shown to be in error (see Box 16.1), but there is good evidence that after chronic use, there is depletion in serotonin in the brain that is in proportion to the extent and intensity of use and that appears to be irreversible. There is considerable evidence from studies of chronic users that this depletion in serotonin shows up as problems in many of the areas of behavior known to be associated with serotonin in the brain. Chronic users show sleep disorders, depression, persistent anxiety, impulsiveness and hostility, and selective impairment of memory and attention (Wareing, Fisk, & Murphy, 2000). The cognitive deficits seem to dissipate about 6 months after use is stopped, but the anxiety and hostility may remain for years. It is likely that the recovery is due to an up-regulation of serotonin receptors or some other regulatory adjustment to compensate for the decreased serotonin in the brain (Morgan, 2000).

BOX 16-1 Making Mistakes in Science

In September 2003, a study was published by George Ricuarte and his colleagues at Johns Hopkins Medical School showing that doses of ecstasy in the range of human usage also caused severe dopamine neurotoxicity in two species of nonhuman primates (Ricaurte, Yuan, Hatzidimitriou, Cord, & McCann, 2002). The reason this particular study is remarkable is that it was later retracted by the authors. After publication they were unable to replicate the findings and discovered that there had been a mix-up in the labeling of a bottle; the drug that was used was not ecstasy but methamphetamine (Ricaurte, Yuan, Hatzidimitriou, Cord, & McCann, 2003). This retraction caused quite a stir in many circles since the study had been given wide publicity by antidrug organizations. Many have been left with the impression that all the cautionary studies with ecstasy are not to be trusted and that ecstasy is, in fact, safe to use. On the contrary, this retraction illustrates the way that science works and the importance of replication. We cannot expect every published result to be free from all errors, but the ultimate test is whether a research finding can be reliably reproduced. If it cannot be replicated, this often leads to an investigation that identifies the errors, and, as in the case of this experiment, the results are retracted. More often than not, erroneous findings are eventually ignored if they cannot be replicated. In any case, none of this affects the finding that ecstasy causes serotonin depletion in humans and nonhumans.

One of the more troubling and dangerous effects of ecstasy is the loss of heat regulation in the body, causing an increase in body temperature. This may not be serious in many circumstances, but at a rave where the user is dancing vigorously in a warm environment, it can cause symptoms similar to heatstroke, muscle tissue damage, kidney failure, and liver damage. In addition, if one is dancing vigorously, this also causes profuse sweating, and the body can become dehydrated and lose large amounts of salt. Dancers often attempt to compensate by drinking large amounts of water that, without replacement salt, can dilute the blood and create an electrolyte imbalance. This in turn can cause organs, including the brain, to swell, resulting in epilepsy-like seizures.

Lethal Effects

The therapeutic index of ecstasy is about 15 (Gable, 2004); however, there is a great range of doses that have been known to cause death, some within the range of recreational drug use. Death may result from a number of different mechanisms. In one study of 87 ecstasy-related deaths, eight were related to the heart or circulatory system, four were caused by liver damage, nine were caused by swelling of the brain resulting from blood dilution, 30 were caused by overheating, 14 were caused by suicide or accident, and in 22 cases the cause could not be determined (Kalant, 2001).

A complicating factor is that there is nothing in the way of quality control in the clandestine labs that manufacture ecstasy, and the pills may also contain amphetamine, ephedrine, and other substances like PMA. PMA was developed in a clandestine lab in Canada in the early 1970s and was distributed in the illicit drug market in the United States and Canada. This drug is extremely potent, second only to LSD, but it is also very toxic and has a therapeutic index of 2.5, making it very dangerous to use (Schmidt, 1987). A number of deaths were attributed to PMA before warnings could be spread about it.

In addition, in many ecstasy-related fatalities, other drugs have also been consumed, often alcohol or amphetamine or other club drugs like GHB.

DISSOCIATIVE ANESTHETICS: PHENCYCLIDINE AND KETAMINE

Phencyclidine, also known as PCP, is a synthetic drug that was developed by the Parke-Davis Company as an analgesic and anesthetic in 1963 and marketed as Sernyl. For this purpose, it proved very effective and safe because it did not depress the heart, blood pressure, or respiration. It caused a trance-like state rather than a loss of consciousness. It has been classified as a *dissociative anesthetic* because it seemed to separate people from sensory experience. In 1965, it was withdrawn from the market because patients reported that while they were recovering from the drug, they experienced a delirium, disorientation, and agitation referred to as *emergence delirium*. It was then marketed as Sernylan, and its use was restricted to nonhumans. It started to be sold on the street in 1965 under the names *crystal*, *angel dust*, *hob*, and *horse tanks*, but it did not become popular during the 1960s.

Ketamine was first synthesized in 1962 and marketed as Ketalar in 1969 as a safer replacement for PCP. It is a more potent anesthetic, has a shorter duration of action than PCP, and has milder emergence effects. Ketamine continues to be used as an anesthetic for children and as a veterinary anesthetic under the name Ketaset and Vetalar. It has the street names of *K*, *Special K*, or *kitkat*. It is now widely used as a club drug at dance clubs and all-night dance parties or raves. It also has the reputation of being used as a date rape drug.

Ketamine sold on the street is probably diverted from legitimate veterinary use. It comes in liquid form and is colorless and tasteless. It may be swallowed or injected. Often the liquid is heated and turned to a white powder that is snorted.

Pharmacokinetics and Dose

PCP and ketamine are weak, lipid-soluble bases and are effective orally. They are readily absorbed through most moist tissues and so can be absorbed through the nasal membranes when snorted.

A normal dose of PCP is 5 to10 mg. The effects of PCP are felt rapidly, within a minute after inhalation and intravenous injection and from 20 to 40 minutes after oral administration. The duration of the peak effect varies from 10 to 90 minutes, and the effects may last from 4 to 8 hours. Drug levels fall rapidly at first as the drug is absorbed into body fat, but then low levels may persist in the body for several weeks as the drug is released from body fat (Gorelick & Balster, 2000).

Ketamine can be snorted, injected, or taken orally. Oral administration is slowly absorbed and subject to first-pass metabolism, so the drug is often administered intranasally. Ketamine is rapidly absorbed, and effects last from 35 to 40 minutes. A normal dose of ketamine is called a *bump* and contains about 75 to 125 mg. A typical oral dose of ketamine is 175 mg, and a typical intranasal dose is 50 mg (Gable, 2004).

Neurophysiology

The dissociative anesthetics alter the functioning of norepinephrine, dopamine, acetylcholine, and serotonin, but it is believed that the principal effect responsible for their reinforcing properties is that they block NMDA receptors for glutamate and aspartate, which are excitatory transmitters in many parts of the brain, including the cortex (K. M. Johnson, 1987). PCP and ketamine have a receptor site located in the ion channel normally activated by an NMDA receptor. When occupied by PCP or ketamine, this receptor blocks the ion channel and makes these transmitters ineffective in the same manner as the alcohol molecule (Dinwiddie & Farber, 1995; Gorelick & Balster, 2000; see also Chapter 6).

These drugs appear to act as reinforcers by directly decreasing the output of the neurons of the nucleus accumbens that are normally inhibited by dopamine (Wise, 1998), although they do so without directly altering dopamine activity (Carlezon & Wise, 1996) in a manner similar to the barbiturates and benzodiazepines (see Chapter 7).

There may be an endogenous substance that acts at the PCP/ketamine receptor, but its existence remains uncertain.

Behavior and Performance

The available data mostly show that PCP impairs reaction time and disrupts performance on a pursuit rotor task (Rosenbaum et al., 1959).

The dissociative anesthetics are known to cause amnesia for events that occur while under the influence of the drug. Although no studies of the effects of PCP on memory in humans have been conducted, PCP does seem to be more disruptive of memory in nonhumans than LSD, THC, opiates, and other psychoactive drugs (Balster, 1987). It is known that integrity of NMDA receptors are vital in the formation of long-term memories, and so it is not surprising that drugs like PCP and ketamine that block NMDA receptors are powerful amnesic drugs. In addition, it has been demonstrated that ketamine induces a type of thought disorder very similar to that seen in schizophrenic patients (Adler et al., 1999).

PCP and ketamine are not hallucinogenic in the sense that LSD is. Taken at usual doses, the dissociative anesthetics cause relaxation, warmth, a tingling feeling, and a sense of numbness. There are euphoric feelings, distortions in body image, and a feeling of floating in space. When these effects wear off, they are sometimes followed by a mild depression that may last from 24 hours to a week. At higher doses, the user may become stuporous or even comatose. Psychotic behavior occurs frequently and may include anything from manic excitation to catatonia, in which the user assumes one position and does not move for a prolonged period of time. There may be sudden mood changes accompanied by laughing and crying; disoriented, confused, and delusional thought; drooling; and repetitive (stereotyped) actions. This psychotic state may slowly disappear as the drug level declines, but sometimes the psychosis requires hospitalization and lasts for weeks.

Stimulus Properties

Dissociative anesthetics appear to have unique stimulus properties. Animals trained to discriminate PCP and ketamine do not generalize this response to any other class of drugs, including stimulants, depressants, and hallucinogens, and no drug has been shown to antagonize their stimulus properties. They generalize only to other drugs known to block NMDA receptors, such as dextromethorphan (see later in this chapter), indicating that this effect is likely the basis for their stimulus properties.

Tolerance

Traditionally, PCP is used sporadically, like LSD, but continuous use became common in the 1970s and 1980s. When the drug is used every day, tolerance develops, and there is some evidence of dependence and withdrawal symptoms (Grinspoon & Bakalar, 1979b). Users frequently need only a few puffs of a PCP-laced cigarette to get high when they first try the drug, but within 2 to 6 weeks, they may be smoking two joints at a time to accomplish the same effect. Tolerance also seems to develop to the analgesic effects in burn patients. Tolerance has also been demonstrated in nonhumans and appears to take place at physiological and behavioral levels rather than in pharmacokinetics (Balster, 1987; Gorelick & Balster, 2000). Rapid tolerance also develops to the reinforcing effects and discriminative stimulus properties of ketamine in rats (Rocha et al., 1996).

Withdrawal

Research with nonhumans has shown that there may be some withdrawal after continual use of PCP. The symptoms include vocalizations, grinding of the teeth, diarrhea, difficulty staying awake, anxiety, confusion, and tremors. No systematic studies of PCP withdrawal in humans have been done (Gorelick & Balster, 2000).

Self-Administration

Nonhumans. PCP is self-administered by monkeys, dogs, baboons, and rats either by intravenous infusion or orally (Balster, 1987; Carroll, 1993; Griffiths, Bigelow, & Henningfield, 1980). PCP injected directly into a part of the nucleus

accumbens and the frontal cortex has been shown to be reinforcing, an effect that is not diminished by a dopamine antagonist, showing that this effect is independent of dopamine transmission (Carlzon & Wise, 1996). It has also been demonstrated that ketamine is self-administered intravenously by both rats and monkeys (Moreton, Meisch, Stark, & Thompson, 1977) and that tolerance develops fairly rapidly to ketamine's reinforcing effects in the rat (Rocha et al., 1996).

Human Epidemiology. Patterns of PCP use are similar to LSD. Most use is experimental or occasional, but, unlike LSD, some occasional users become heavy chronic users. Unfortunately, even though tolerance does develop to the reinforcing effects of dissociative anesthetics, the tolerance is not complete enough to discourage continuous use as is the case with LSD (Linder, Lerner, & Burns, 1981).

Not until the decline of LSD in the 1970s did PCP use start to increase. Before PCP became popular in its own right, it was more widely used than most people suspected because it was often mixed with other drugs or sold as something else, like THC, mescaline, or psilocybin. Even today it is sold as "embalming fluid" and sometimes turns up in pills reputed to be ecstasy. While its use has declined, it is still popular in some metropolitan areas and among certain groups who continue to take it by itself or mixed with marijuana or cocaine (Gorelick & Balster, 2000). Since the mid-1990s, even these small numbers have declined. In 2004, less than half of 1 percent of high school students in the United States reported using PCP within the past 30 days (Johnston et al., 2005).

Ketamine was little used until it entered the club scene in the 1980s and its popularity expanded. Its use, however, appears to have leveled off. Ketamine use among high school students in the United States has shown little change since 2000 with about 2 percent of grade 12 students reporting use within the past 12 months (Johnston et al., 2005).

Harmful Effects

PCP and kertamine have the reputation of causing people to be violent and to commit violent, uncontrolled acts toward other people. A recent, careful examination of the literature on the drug has not found any systematic evidence that these drugs specifically cause violent or criminal behavior. It is true that the psychotic state induced by large doses of dissociative anesthetics causes disorientation, agitation, and hyperactivity, and these effects are difficult to manage and have the potential for injury to the individual and others nearby. However, PCP and ketamine do not seem to turn normal, innocent people into dangerous and violent criminals (Brecher, Wang, Wong, & Morgan, 1988; Gorelick & Balster, 2000). Research and experience with laboratory animals even suggest that PCP has a taming effect on normally aggressive animals (Balster, 1987).

Long-lasting psychotic behavior has been reported after PCP use, even in individuals without any psychotic tendencies. This PCP psychosis may last several months in some individuals.

Acute behavioral effects of PCP and ketamine can sometimes be responsible for injury and death. For example, users have drowned in pools or hot tubs while trying to swim to increase a sensation of floating. In addition, because the drugs are anesthetics, rather severe injuries have been tolerated or self-inflicted without pain or any effort at avoidance. Although the exact frequency of this sort of event has not been documented, it is probably more likely to happen with PCP than with LSD and the other serotonin-like and norepinephrine-like hallucinogens.

Genetic Damage and Reproduction. It does not appear that PCP or ketamine are teratogenic, but PCP has been shown to slow the growth of the fetus, precipitate labor, and cause fetal distress. Children born to mothers who use PCP often show muscle stiffness, tremor, irritability, and impaired attention and behavior control that may last for several years, although it is difficult to be sure that these effects are due specifically to PCP

because of other maternal drug use (Gorelick & Balster, 2000).

Lethal Effects

A lethal dose of the ketamine is 25 times the effective dose for intranasal administration (Gable, 2004). Although toxic effects may vary, high doses cause coma, convulsions, and respiratory arrest. Brain hemorrhage and kidney failure have also been reported. The lethal effects of PCP and ketamine are potentiated by the presence of depressant drugs such as alcohol or barbiturates in the body.

DEXTROMETHORPHAN

Dextromethorphan is a synthetic, opiate-like drug that appears to have no effect on any opiate receptor. Many years ago it was tested for abuse potential by comparing it with opiates and was found to be very dissimilar to the opiates and, therefore, considered safe. Recently, however, there have been numerous reports of people consuming large quantities of Robitussin (in Canada, cough medicines that contain dextromethorphan often end with a "-DM") and other over-the-counter cough medicines for their psychological effects, a practice sometimes called *roboing* (Darboe, Keenan, & Richards, 1996). This has led to a more careful reexamination of dextromethorphan's behavioral pharmacology (Nicholson, Hayes, & Balster, 1999). Also of interest is *dextrophan*, a metabolite of dextromethorphan.

Neurophysiology

Although it has no effect on opiate receptors, dextromethorphan and dextrophan have been shown to bind with low affinity to the PCP receptor of the NMDA receptor complex, where they also act as channel blockers in a manner similar to alcohol and the dissociative anesthetics (see Chapter 4). This means that they have pharmacological properties similar to the dissociative anesthetics, PCP, and ketamine. Dextrophan has a 5-fold to 10-fold greater affinity for the receptor than dextromethorphan and, consequently, has a much greater PCP-like effect.

Pharmacokinetics

In most cases, dextromethorphan is converted rapidly to dextrophan during first pass through the liver. Because the effects of dextrophan are greater than dextromethorphan, the most intense effects of consuming dextromethorphan may be delayed until this transformation occurs. Since first-pass metabolism is greatest after oral administration, oral consumption may be the most effective route of administration.

Population studies have shown that there is considerable individual variation in the ability to metabolize dextromethorphan to dextrophan. Some are rapid metabolizers and should be able to experience the effects of dextrophan rapidly, but others are slow metabolizers, so the metabolite will not reach high levels, and the effects will be diminished. About 5 to 10 percent of Caucasians and around 4 percent of African Americans are poor metabolizers (He, Daniel, Hajiloo, & Shockley, 1999). Such differences in metabolism can cause considerable individual variation in the effects of taking dextromethorphan.

Discriminative Stimulus Properties

Rats and, to some extent, rhesus monkeys trained to discriminate PCP will generalize fully to dextrophan and partially to dextromethorphan. Generalization is dose and training specific, and this has led researchers to believe that dextromethorphan and dextrophan are not identical to PCP and other full NMDA receptor blockers. They may have their effect on a different subset of NMDA receptors.

Self-Administration

It appears that rats and monkeys will readily self-administer both dextromethorphan and dextrophan.

Behavioral Effects

Nonhumans. The effects of dextromethorphan and dextrophan have been investigated in rats. Dextromethorphan caused a decrease in locomotor activity, whereas dextrophan caused an increase along with stereotyped behavior at higher doses. Some memory impairment was seen with dextromethorphan but not with dextrophan. The two drugs appeared to have different effects, with dextromethorphan's effect resembling that of sedatives and dextrophan resembling PCP (Dematteis, Lallement, & Mallaert, 1998).

Humans. Dextromethorphan has been used as a cough suppressant for over 30 years. At normal therapeutic doses, it has few side effects and no PCP-like effects, but at higher doses, its effects are similar to PCP and ketamine and include ataxia, dizziness, euphoria, and tactile and visual hallucinations.

GHB

GHB (gamma-hydroxybutyrate) occurs naturally in the body as a metabolite of gamma-aminobutyric acid (GABA) and appears to be a neurotransmitter or neuromodulator. It has its own receptor site. GHB is now being developed to be sold under the trade name Xyrem as a treatment for narcolepsy (Nicholson & Balster, 2001).

GHB was initially isolated and investigated in 1960 by Henri Laborit (the researcher credited with the discovery of the antipsychotic drugs; see Chapter 13). It has been widely used in Europe as a medicine and in the United States as a dietary supplement. It received little attention from public health officials until the early 1990s, when its use became more widespread as a growth promoter among bodybuilders, as a sedative, and as a recreational drug used along with ecstasy and ketamine (see Chapter 16) as a club drug at raves and dance parties. It also gained a reputation as a date rape drug. In 1993, the actor River Phoenix collapsed and died outside the Viper Room in Los Angeles. Although it was never confirmed, the rumor that GHB was responsible created a lot of interest in the drug (O'Connell, Kay, & Plosay, 2000).

In 1990, the U.S. Food and Drug Administration declared GHB unsafe and banned it from public sale. This effort was not entirely effective because GHB continued to be sold on the Internet and in some stores. To get around the legislation, kits were sold that contained GBL, a metabolic precursor of GHB, along with instructions on how to convert it into GHB. GHB has many street names, including *liquid X, GBH* (grievous bodily harm), *scoop, cherry meth, blue nitro, easy lay*, and more than 30 others (O'Connell, et al., 2000).

The legal status of GHB remains unclear. In February 2000, the U.S. attorney general was voted authority by the U.S. Congress to make GHB a Schedule I drug; that is, it has abuse potential but no medical use. GHB products now being tested for medical purposes were to be classed as Schedule III drugs. This is similar to the classification of Marinol, a preparation containing THC (the active ingredient in marijuana) that has medical use (see Chapter 15). This ambiguity has not yet been resolved. GHL and kits for making GHB, however, are now illegal in the United States.

Pharmacokinetics and Dose

GHB and GBL, its precursor, are considered to be pharmacologically equivalent except that GBL is more readily absorbed. GHB is rapidly absorbed orally and its effects begin in 15 to 30 minutes and peak between 25 and 45 minutes. It has a half-life of 30 to 50 minutes. Endogenous GHB is taken into cells via an active reuptake mechanism from the synaptic cleft, where it is rapidly metabolized.

A minimum dose is about 10 mg/kg body weight and will produce muscle relaxation. A therapeutic dose for sleep is in the range of 15 to 30 mg/kg, and a high dose of 60 mg/kg will cause unarousable sleep or coma lasting for 1 to 5 hours. A lethal dose may be anywhere between 300 and 900 mg/kg. This gives it a therapeutic index of between 20 and 60.

GHB-associated deaths have been reported, but most have involved the coadministration of another drug, such as heroin or ecstasy

Neuropharmacology

GHB binds to its own receptors, which are located in the CNS. Even though there are high levels of endogenous GHB outside the CNS, all GHB receptors appear to be inside the CNS. The GHB receptor is part of a complex that has its effect by releasing a second messenger inside the membrane.

GHB acts both presynaptically and postsynaptically to modulate activity of other neurotransmitters. Its main effect seems to be on dopamine synapses, where it inhibits dopamine release and causes the accumulation of excess dopamine in the presynaptic neuron. It has also been reported that after a period of inhibition or at higher doses, there is a surge in dopamine activity.

GABA does not bind to the GHB receptor, but GHB does bind to the $GABA_B$ receptor. This appears to happen only at GHB concentrations higher than those that occur naturally in the body. GHB also appears to have a modulatory effect on GABA levels, in some cases decreasing GABA, and, because it is also a GABA precursor, it can also increase GABA levels.

Effects on Behavior

Nonhumans. GHB has sedative properties and at high doses acts as an anesthetic, but there are significant differences between GHB and the other drugs discussed in this chapter. The anesthetic state it induces appears to be more similar to a cataleptic state than anesthesia; the EEG shows seizure-like activity that can be blocked with anticonvulsant drugs like valproic acid. The nonresponsive state achieved at high levels of GHB is more similar to a petit mal seizure than anesthesia. At higher doses, jerks and seizure-like activity can be seen.

Humans. Users report that GHB causes alcohol-like intoxication without a hangover. They report increased feelings of relaxation and euphoria. GHB is sometimes used in conjunction with alcohol and various club drugs like ketamine and ecstasy to enhance their effects. It is also reputed to be an aphrodisiac, increasing libido and increasing and enhancing sexual pleasure.

Amnesia for events both during and after drug use have also been reported (Miotto et al., 2001). At higher doses, before passing out, people show many of the signs of alcohol intoxication, they appear confused, speech is incoherent, and they have poor balance and coordination. Driving ability is clearly impaired (Couper & Logan, 2001).

Effects on Sleep. Unlike the barbiturates and benzodiazepines (or almost any other drug for that matter), GHB normalizes sleep patterns and increases stage 3 and 4 and REM sleep. This effect is the basis for its development as a treatment for *narcolepsy*. In narcolepsy, normal sleep does not occur at night, so the narcoleptic falls into uncontrollable sleep during the day. The benzodiazepine and barbiturate hypnotics alter normal nighttime sleep patterns and are consequently not useful, but GHB appears to be an effective treatment.

Anxiolytic Properties. There is conflicting evidence that GHB has anxiolytic effects. Some studies report that it increases punished responding, but others do not. It is clear, however, that GHB is not as effective an anxiolytic as the barbiturates or benzodiazepines.

Drug State Discrimination

Animals trained to discriminate GHB from saline only partially generalize to morphine, LSD, and chlordiazepoxide and generalize even less to amphetamine and ethanol and do not generalize at all to barbital and PCP-like compounds, indicating a unique subjective effect.

Any generalization to other drugs seems to be highly dose specific. At high training doses of GHB, animals will generalize to drugs that are $GABA_B$ agonists, suggesting that this effect is probably responsible for its subjective effect, but

at low doses, the subjective effect appears to be mediated by its activity at its own receptor. Similarly, alcohol-trained rats only generalize to GHB at a very narrow range of intermediate doses.

Self-Administration

Nonhumans. GHB will create a place preference in rats, but it requires more trials than with cocaine. There are no convincing studies that show rats or monkeys will reliably self-administer GHB. On the other hand, there is evidence that GHB will reduce the self-administration of alcohol in both rats and humans, with humans reporting a reduction in craving for alcohol. This may be a result of the dopamine-blocking effect of GHB, but this effect needs further study.

Human Epidemiology. Clearly GHB is used by humans, but little data are available on the extent of its use. The Drug Abuse Warning Network is a system that tracks drug use by frequency of the number of times it is mentioned in cases seen in hospital emergency rooms in the United States and Canada. In 1992 there were 20 mentions of GHB, but in 1998 it was mentioned on nearly 1,300 occasions. This cannot be taken as an indication of how often the drug is used, but it does suggest a drastic increase in use. It remains to be seen whether the newly introduced legislation will be able to reduce its availability and the extent of its use (Nicholson & Balster, 2001).

Prevalence of GHB use among high school students in the United States does not appear to have changed much since 2000. In 2004, 2 percent of grade 12 students reported using GHB (Johnston et al., 2005).

Tolerance and Withdrawal

Tolerance develops to the motor-impairing effects of GHB in rats following high doses for 9 days. These rats were cross-tolerant with alcohol on the same effect. Tolerance has also been demonstrated to the sedating and anesthetic effects of GHB.

Case reports suggest that many chronic users report insomnia that lasts for no more than 3 days after discontinuing using GHB. Anxiety has also been reported. One study, however, has reported more severe cases of withdrawal after continuous consumption every 3 to 4 hours. Initially, patients reported anxiety and tremor. This developed into severe delirium with auditory and visual hallucinations that took 5 to 15 days to resolve (Dyer, Roth, & Hyma, 2001).

GHB will alleviate withdrawal symptoms of alcohol in humans and nonhumans, and it has been used in treating alcoholics who report reduced use of alcohol and reduced craving. GHB is also effective in reducing withdrawal effects from opiates.

CHAPTER SUMMARY

- Hallucinogens are a class of drugs that cause hallucinations. Other drugs discussed in this chapter may be called many names depending on why they are taken. These include phantasticants, psychedelics (mind manifesters), entactogens (touching within), and empathogens (empathy creators). Many are used as club drugs.
- The indoleamine-like drugs include LSD, psilocybin, and DMT, and the catecholamine-like drugs include mescaline and ecstasy.
- LSD is an extremely potent hallucinogen that resembles serotonin. It was synthesized in 1943 but did not become popular until the 1960s, when it was extensively used.
- LSD is sold on the street as hits in blotters, gelatin, and sugar cubes. It is effective orally.
- The indoleamine-like and catecholamine-like drugs all are agonists at a specific serotonin receptor, and this increases the responses of glutaminergic neurons in the cortex.
- In general, the hallucinatory experience starts out with colored visions of tunnel, spiral, and lattice shapes that move. Meaningful images start to become incorporated into these images, and finally there is a rapid succession of meaningful scenes.
- LSD also has empathogenic effects, and people often experience profound feelings of a mystical or religious nature.

- Tolerance develops and dissipates rapidly to the effects of LSD and psilocybin.
- Indeolamine-like hallucinogens are only rarely self-administered by nonhumans, but human use is widespread among many cultures. In the United States, its use has been dropping since 1996.
- There are a large number of synthetic drugs that combine the properties of catecholamine-like drugs and amphetamine. The best known is ecstasy, also known as MDMA.
- Ecstasy enhances social intimacy and is considered an empathogen and entactogen and is widely used as a club drug.
- Ecstasy is taken orally, is absorbed in 2 hours, and has a half-life of about 8 hours. It enhances the release and blocks the reuptake of catecholamines, primarily serotonin.
- Ecstasy is self-administered by nonhumans. Its use among young people in the United States is declining.
- Heavy use of ecstasy causes a depletion of serotonin in the brain and the effects of this last for months and cause sleep disorders, depression, and anxiety. Acute doses at raves cause a loss of heat regulation accompanied by dehydration and heatstroke symptoms.
- Phencyclidine (PCP) and ketamine are dissociative anesthetics. They can be snorted, injected, or taken orally. Their effects are felt within minutes.
- The dissociative anesthetics block NMDA receptors for glutamate in the cortex. They can block memories for events during their effect and can induce thought disorders. They induce numbness, relaxation, and analgesia. With continuous use, tolerance develops, and there are withdrawal symptoms.
- Nonhumans self-administer dissociative anesthetics. The use of PCP by young people in the United States has declined, but ketamine use is staying steady at a low level.
- Psychosis caused by the dissociative anesthetics can sometimes last long after the drug has been used, and there have been a number of accidental deaths reported.
- Dextromethorphan is widely used in over-the-counter cough suppressants. Both it and its metabolite dextrophan block the NMDA receptor for glutamate and have effects similar to the dissociative anesthetics.
- Dextrophan is more potent than dextromethorphan, so speeded metabolism enhances its effect.
- Nonhumans readily self-administer dextromethorphan.
- GHB is a metabolite of GABA. It was used as a medicine in Europe and became available in health food stores as a dietary supplement. It was made illegal in the United States in 1990, but it also has a legitimate medical use. Its legal status has not been resolved.
- GHB is taken orally. Its effects begin in 15 to 30 minutes and peak between 25 and 45 minutes. It has a half-life of 30 to 50 minutes. Low doses cause relaxation and sleep. High doses cause unarousable sleep or coma.
- GHB has its own receptor in the CNS and modifies the activity of many other neurotransmitters.
- GHB acts like an anesthetic, but it seems to be causing a cataleptic state. It causes an alcohol-like intoxication with amnesia. At therapeutic doses it causes normal sleep with normal EEG patterns and can be used to treat narcolepsy.
- GHB is not self-administered by nonhumans. In the United States, its use increased in the 1990s but appears to have leveled off. Tolerance and withdrawal effects have been reported.