11

Psychomotor Stimulants

The drugs known as psychomotor stimulants have one effect in common: They stimulate transmission at synapses that use epinephrine (E), norepinephrine (NE), dopamine (DA), or serotonin (5-HT) as a transmitter. These transmitters are called *monoamines* (MAs) or *biogenic amines*. The first three—E, NE, and DA—are very similar. In fact, the body manufactures E from NE in one chemical step, and NE is made by changing the structure of DA slightly. Together, these three are called *catecholamines* (CAs). The odd monoamine is 5-HT. It is an *indoleamine*, which is chemically different from the CAs but is influenced by many of the same drugs and destroyed by many of the same enzymes (see Chapter 4).

The term *sympathomimetic* is sometimes used to refer to this class of drugs. This term is used because epinephrine is the primary transmitter in the sympathetic nervous system, and these drugs stimulate sympathetic synapses to some extent and mimic sympathetic arousal.

SOURCES

Some psychomotor stimulants occur naturally and have been used for centuries, and some are very new synthetic drugs. The *amphetamines* are synthetic and do not occur naturally, *d-amphetamine* (dextro-amphetamine, or dex-amphetamine) and *l-amphetamine* (levo-amphetamine) have exactly the same chemical structure, but the molecules are mirror images of each other (technically, they are called *optical isomers*). In the amphetamines, the d- isomer is more potent than the l- isomer for most central effects. When the term *dl-amphetamine* or just *amphetamine* is used, it refers to a mixture of the two isomers. The most common trade name of dl-amphetamine was Benzedrine, but neither Benzedrine nor dl-amphetamine is currently in use in the United States or Canada. Dexedrine is a common trade name of d-amphetamine. Another similar drug is *methamphetamine,* which differs slightly in structure and effect from the other two. It was sold under the trade names Methedrine or Desoxyn. Methamphetamine can be synthesized from material legally available, which includes cold medication that contains ephedrine or pseudoephedrine, iodine, hydrochloric acid, ether, and ammonia. It is currently manufactured in large quantities in illegal laboratories and sold in a waxy form known as base or paste or in a tablet or powder. When the powder is recrystalized, it is sold as "crystal," "ice," or "crystal meth." Only

slightly different chemically from the amphetamines are two synthetic drugs, *methylphenidate* (Ritalin) and *pipradrol*.

Another psychomotor stimulant is a naturally occurring drug, *ephedrine*. Ephedrine comes from the herb *ma huang* (*Ephedra vulgaris*), which has been used as a medicine in China for centuries. There are also North American varieties of *Ephedra*.

Cocaine is extracted from the leaf of a small tree known as the *coca bush* (*Erythroxylum coca*), which is native to South America. It prefers high elevations and thrives on the slopes of the Andes Mountains. It grows in both wild and cultivated forms from northwestern Argentina to Ecuador.

Cathinone is another naturally occurring cocaine-like drug found in the leaves and shoots of *Catha edulis*, a shrub-like plant that grows in the countries of eastern Africa and southern Arabia. It is called *khat* in Yemen (also spelled *quat* or *qat* and pronounced "cat"). It is also known as *tscaht* in Ethiopia and *miraa* in Kenya (Kalix, 1994). Cathinone is not stable; it degrades shortly after the plant is harvested. For this reason, the plant is used primarily in the area where it is grown, and, unlike cocaine, it is not exported for use elsewhere (United Nations, 1980). However, *methcathinone* (the cathinone equivalent of methamphetamine) is an established abused drug in some countries. In Russia, it is known as *ephedrone* or referred to as *jeff, Jee-cocktail,* or *cosmos,* and abuse of it has been a problem since the early 1980s. In the early 1990s, it appeared in the illicit drug market and was found in clandestine labs in the United States as *cat*. In 1992, it was classified as a Schedule-1 substance (the highest restriction a drug can receive) under the Emergency Scheduling Act (Glennon, Young, Martin, & Dal Cason, 1994).

HISTORY

Cocaine

For centuries, coca leaves have been chewed by various Indian tribes in South America. No one knows how long the coca plant has been used, but it is of great antiquity. Legends of some tribes of Colombian Indians tell how their people came from the Milky Way in a canoe drawn by an anaconda. In addition to a man and a woman, the canoe contained several psychoactive plants, including coca (Schultes, 1987, p. 229). Coca leaves have been found in burial middens in Peru that date back to 2500 B.C. Large stone monolithic idols found in Colombia and dating to 500 B.C. have the puffed-out cheeks of the coca chewer. The Incas started to use the plant when they conquered the region in about the tenth century. Under the Incas, coca became sacred. It was used primarily by the priests and nobility for special ceremonies and was not consumed daily by the common folk.

When the Spanish conquered the Incas, at first they banned coca use, considering it to be idolatrous and pagan, but they changed their minds when they found out how useful it could be. The Spanish did not use coca themselves, but they learned that it had great value as payment for labor in the gold and silver mines in the Andes. In addition to finding coca an item of commerce, the Spanish realized that the Indians could work harder and longer and required less food if they were given coca.

As the Spanish grew more interested in the plant, attempts were made to classify it. In 1749, samples were sent to Europe, where Linnaeus gave the plant its own family, Erythroxylaceae. In 1786, Lamarck named the most important species *Erythroxylon coca* (M. R. Aldrich & Baker, 1976).

Europeans remained unaware of either the medicinal or the psychological effects of the plant, probably because samples sent from South America had deteriorated from age. It is also likely that Europeans were averse to chewing the leaves in the manner of the South Americans. Not until the form of the drug was changed did they show any interest in coca. The first change involved identifying the active ingredient. Earlier attempts had been made with partial success, but the credit for isolating and naming cocaine goes to Albert Niemann of the German university town of Göttingen, who published his results in 1860.

For several years, cocaine was a drug without a medical use until Sigmund Freud became interested and proposed many uses of cocaine, including the treatment of addictions and depression, but it was one of his colleagues, Karl Koller, who discovered the only real medical use of cocaine—it was the world's first local anesthetic.

The isolation of cocaine not only stimulated a search for medical uses for the drug but also made it available in a form that the upper middle class could inject along with morphine, which was popular at the time (see Chapter 12). Around the turn of the twentieth century, cocaine gained favor with writers and intellectuals. Robert Louis Stevenson is reported to have written *The Strange Case of Dr. Jekyll and Mr. Hyde* with the aid of cocaine. Sherlock Holmes, the fictional detective created by Sir Arthur Conan Doyle, was a prototype of the intellectual cocaine user of the time. Over the cautions and objections of the good Dr. Watson, he injected the drug to keep his keen mind stimulated.

In 1863, Angelo Mariani, a Corsican chemist, patented a wine containing coca that became exceedingly popular and made Mariani a very wealthy man. It was probably Mariani's success that inspired a Georgia pharmacist, John S. Pemberton, to produce an American version called "French Wine of Cola, Ideal Tonic." Later, in 1886, he removed the alcohol and replaced it with a kola nut extract, added soda water, and called it Coca-Cola. In its early days, Coca-Cola was promoted as a remedy and a health drink, and it is probably for this reason that soda fountains developed in drugstores in the United States. In 1906, the Pure Food and Drug Act outlawed cocaine, and it was removed from the drink. To this day, Coca-Cola is made from coca leaves from which the cocaine has been removed.

The passage of the Pure Food and Drug Act was a manifestation of a growing backlash against cocaine and other drugs in the early part of the twentieth century in the United States. Cocaine was being injected by professionals and intellectuals, but the drug was associated with corruption and crime in the popular mind. It was no surprise that cocaine was included with morphine and opium in the Harrison Narcotic Act of 1914, which effectively banned its use. As a result of this inclusion of cocaine in the U.S. law and the influence of the United States on the development of international narcotics control, cocaine was also included with morphine in all international treaties aimed at the control of narcotics and in the internal legislation of many other countries.

The Harrison Act drove cocaine underground, where it was used by the "unconventional rich and the unconventional poor": partygoing, decadent, wealthy whites, and gamblers, musicians, and artists of all colors. For decades, cocaine was not a part of the lives of the vast majority of the population of the United States. Then, during World War II, amphetamines were introduced, so the idea of a stimulant or an "upper" was no longer new and foreign. In the 1960s, things started to change. The use of cocaine increased along with a general increase in the use of other drugs, including marijuana and hallucinogens, at the time (Grinspoon & Bakalar, 1976, p. 49).

Amphetamines

Ephedrine, in the herb ma huang, has been used in China for more than 5,000 years. Legend has it that its medicinal properties were first identified by the emperor Chen Nung, who was also credited with the discovery of tea. Ephedrine was isolated from the herb in the 1880s, but not until 1924 were its properties investigated by two Americans, Ko Kuei Chen and C. F. Schmidt. They pointed out that the structure and actions of ephedrine were similar to those of the neurotransmitter epinephrine, which was known to be a stimulant of the sympathetic nervous system. Epinephrine was used at the time to treat asthma because one of its effects was to dilate the airways in the lungs and make breathing easier. Epinephrine, however, was very unstable; it had to be administered by injection, and its effects were very brief. Ephedrine was far superior because it could be taken in pill form, had a longer duration of action, and was less toxic.

The use of ephedrine became so widespread that there were fears that supplies would run out, and a search was begun for a synthetic substitute. As it happened, such a substitute had already been discovered, but no one knew it. Many years earlier, in 1887, L. Edealeno had synthesized what we now know as amphetamine, but he had failed to explore its properties, and it remained untested until 1910, when G. Barger and Sir H. H. Dale (the proposer of Dale's law; see Chapter 4) published a technical paper showing the effects of amphetamine and other sympathomimetic drugs on the body. The significance of Barger and Dale's paper was not grasped until 1927, when Gordon Alles, a young chemist at a research laboratory in Los Angeles, suggested that amphetamine would probably be the best and cheapest substitute for ephedrine.

In 1937, the American Medical Association sanctioned the use of amphetamine for the treatment of the sleep disorder narcolepsy and as a mild "pick-me-up" or stimulant for depression. By 1943, at least half the sales of the drug were prescribed for weight reduction and diet control, antidepressant or stimulant effects, or extended periods of alertness. Amphetamine was also marketed in inhalers for the treatment of asthma and sold over the counter without a prescription. The pharmaceutical company Smith, Kline, and French held the patents of amphetamine and was doing so well that other companies wanted some of the market, too. It was not long before the Ciba company started marketing methylphenidate as a "nonamphetamine" stimulant (Grinspoon & Hedblom, 1975). To control the indiscriminate prescribing of amphetamines by physicians, most countries now limit the medical conditions for which amphetamines may be prescribed. These conditions are narcolepsy and the treatment of hyperactivity in children and do not include obesity or the need to stay awake. The production and marketing of amphetamines are now carefully monitored.

As medicinal sources of amphetamines dried up, more amphetamine and methamphetamine were being made in illicit labs, which are now the primary source. Apart from illegally manufactured methamphetamine, most stimulant abuse in Western countries is confined to cocaine.

Cathinone (Khat)

Khat use has been known since antiquity. Alexander the Great sent khat to General Harrar to cure his melancholia, and it has been mentioned repeatedly by Arab physicians as a remedy for a variety of disorders. Amda Sion, a fourteenth-century ruler of Ethiopia, was the first recorded khat addict. Khat has been known in Europe since the early 1600s but has only recently been used there because of difficulties transporting the leaf.

The first case of khat psychosis in the United States was reported in 1982. Since then, cases have been reported in the United Kingdom (Giannini, Miller, & Turner, 1992), Europe (Kalix, 1994), and Canada (Kalix, 1994). Public awareness of khat has increased as a result of reports emanating from the UN Mission in Somalia. There has been some concern that U.S. soldiers, after being exposed to khat use because of the interdiction of alcohol in Muslim countries, may have brought the habit back to the United States. There are, however, no reports of such cases.

ROUTES OF ADMINISTRATION AND ABSORPTION

The amphetamines are weak bases and have a pKa of between 9 and 10. When taken orally, they tend to be ionized in the digestive system, which slows the rate of absorption. The drug is more potent when administered by injection, inhalation, or snorting. When given for medicinal purposes or to prevent sleep and fatigue, amphetamines are always taken orally, and the decrease in potency can be compensated for by increasing the dose. The oral route has the advantage that blood levels may be kept fairly constant without too much variation over time. When amphetamines are taken for the rush they produce, they are administered by injection, which causes the sudden high blood levels required for this effect.

The same is true for cocaine, which has a pKa of 8.7. Traditionally, the Indians of the Andes rolled coca leaves into a ball, stuck a wad in the cheek, and sucked it. It is also common for those who take coca in this manner to mix the leaves with lime in the form of wood ashes (Schultes, 1987, p. 225) or ground shells; this practice raises the pH of the saliva and the digestive system and, consequently, reduces ionization and increases absorption. It is very unusual for pure cocaine to be taken orally. It is nearly always injected or sniffed to improve absorption, but recently it has become popular to smoke cocaine, both as a hydrochloride salt and as a freebase.

Most of the cocaine sold in the United States is the salt cocaine hydrochloride (cocaine HCl). It may contain various impurities from the refining process and be deliberately diluted or "cut." One method that was used to determine the purity of this drug was to place some of the powder on a sheet of tinfoil and heat it until it vaporized; pure cocaine HCl leaves little residue. It soon became apparent to those who performed this test that inhaled cocaine has an effect similar to injected cocaine. Soon this method of smoking, called *tooting*, became popular, as did other methods, such as mixing cocaine with tobacco or marijuana.

Freebasing is a process that separates the cocaine molecule from the HCl. It is rather risky because it involves heating highly combustible chemicals. The freebase vapor that is produced has a much stronger effect than the cocaine HCl because of the increased lipid solubility of the freebase form of the drug. Freebasing's popularity was greatly facilitated by the advertising and sale of special pipes and chemical kits for converting the cocaine HCl into the freebase (R. K. Siegel, 1982b). The older and more dangerous methods of making cocaine freebase have now been replaced by making crack cocaine.

Crack is cocaine HCl mixed with a solution of baking soda (sodium bicarbonate). The water is evaporated, leaving crystalline chunks or "rocks" that are heated in pipes or other devices, and the vapors are inhaled. This process accomplishes the same effect as freebasing and is considerably cheaper and safer.

After oral administration of amphetamines, the absorption rate is determined by factors such as the presence of food in the stomach and the degree of physical activity. Peak blood levels may be reached in 30 minutes to 4 hours (Brauer, Ambre, & de Wit, 1996; Vree & Henderson, 1980). After intranasal administration (sniffing) of cocaine, peak blood levels are achieved in 10 to 20 minutes (Javid, Musa, Fischman, Schuster, & Davis, 1983). The rate of absorption of vaporized cocaine HCl and cocaine from vaporized freebase or crack has not been studied, but it is likely extremely rapid because both processes release the cocaine molecule in un-ionized form, making it highly lipid soluble. In fact, crack is a variation on the ancient technique used by the Incas, who mixed coca leaves with lime. This made the saliva basic and enhanced the absorption of the cocaine from the coca leaves using the same chemical principle.

Traditionally, cathinone is taken orally by chewing the leaves of the khat plant in much the same manner as the natives of the Andes have used coca. In Russia, methcathinone is usually administered by injection, but in the United States, sniffing of methcathinone powder seems to be preferred (Glennon et al., 1994).

DISTRIBUTION

The amphetamines, cocaine, and other drugs in this class cross the blood–brain barrier and are concentrated in the spleen, kidneys, and brain.

EXCRETION

The excretion of the amphetamines depends to a very great extent on the pH of the urine. Because it is ionized at acid pHs, amphetamine is not reabsorbed from the nephron in acid urine, but as the urine becomes more basic, more of the drug is reabsorbed and more of the burden of excretion is carried by metabolism in the liver. The half-life of amphetamine may be as short as 7 to 14 hours when the urine is acidic. When the urine is basic,

excretion is shifted to metabolic processes, and the half-life may be 16 to 34 hours (Creasey, 1979, p. 180). Amphetamine is also excreted in sweat and saliva (Britton, El-Wardney, Brown, & Bianchine, 1978; Vree & Henderson, 1980).

Amphetamines that are not excreted unchanged are metabolized through several routes that use a variety of enzymes. Many of the metabolites are also behaviorally active and have very long half-lives (Brookes, 1985, p. 265).

Cocaine is excreted much faster than the amphetamines. It has a half-life of about 40 minutes (Javid et al., 1983), although this also depends on the pH of the urine. Cathinone has a half-life of about 90 minutes, intermediate between cocaine and amphetamine (Kalix, 1994).

NEUROPHYSIOLOGY

All the drugs in this chapter are grouped together because they have a common effect on synapses that use a monoamine (MA) as a transmitter, but the mechanisms by which they stimulate these synapses differ. (It may be useful at this point to review the discussion of MA synapses in Chapter 4.)

The amphetamines, cathinone, and methcathinone primarily affect synapses that use serotonin and the catecholamines, epinephrine, norepinephrine, and dopamine (DA) as transmitters or modulators. They have a threefold effect on these synapses: (a) They cause the transmitter to leak spontaneously out of the synaptic vesicles into the synaptic cleft, (b) they increase the amount of transmitter released in response to the arrival of an action potential at the synapse, and (c) they block the reuptake of the transmitter into the presynaptic cells and prolong the duration and intensity of their effect. All these actions greatly stimulate the synapse (Carlsson, 1969; Glennon et al., 1994).

Cocaine does not produce the first two of amphetamine's effects, but it is a reuptake blocker and stimulates the synapse this way (Groppetti & Di Giulio, 1976; Wolverton & Johnson, 1992). Cocaine blocks the reuptake of the neurotransmitter by working at a receptor site on the transporter molecule (Izenwasser, 1998). Photon emission tomographic (PET) studies suggest that between 60 and 77 percent of dopamine transporters are blocked by doses of cocaine commonly abused by humans and that at least 47 percent of transporters must be blocked for users to experience a cocaine-induced high (Volkow et al., 1997).

In the peripheral nervous system, these drugs stimulate synapses that use epinephrine, the transmitter in the sympathetic nervous system, and cause sympathetic arousal (the fight-or-flight response).

In the central nervous system (CNS), all monoamine systems are known to be affected by the psychomotor stimulants, but most of the behavioral effects appear to be a result of their effect on dopamine systems (see Chapter 13). One is the nigrostriatal system between the substantia nigra and the striatum (basal ganglia), which is important in the control of motor activity. Psychomotor stimulants are known to increase the release of dopamine in the nucleus accumbens, part of the mesolimbic dopamine system, which controls reinforcement and motivation (see Chapter 4 and Kalix, 1994). Another DA system exerts some control over the secretions of the pituitary gland. This DA system inhibits the secretion of *prolactin*, a hormone that controls the release of milk during breast feeding, and also suppresses male sexual activity.

In addition to its abilities as an MA stimulant, cocaine has the ability to block sodium ion channels in membranes. This blocks the conduction of action potentials along nerve axons and is the basis of cocaine's ability to act as a local anesthetic. The local anesthetic action, however, has nothing to do with the MA-stimulating effect of the drug and requires much higher concentrations. Cocaine is seldom used for this purpose today. Procaine (novocaine), a synthetic substitute that has the local anesthetic action of cocaine without its stimulant properties, was developed for this purpose. Even though procaine lacks the stimulant properties of cocaine, it nevertheless acts as a positive reinforcer in rats and monkeys (Ford & Balster, 1977; Yokel, 1987).

The influence of cocaine is still felt in the naming of local anesthetic drugs. It is common to use the ending *-caine* in the formulation of generic and trade names to indicate that the drug has local anesthetic action.

EFFECTS OF PSYCHOMOTOR STIMULANTS

Effects on the Body

Because the psychomotor stimulants activate the sympathetic nervous system, they cause an increase in heart rate and blood pressure and *vasodilation* (a dilation of the blood vessels) and *bronchodilation* (dilation of the air passages in the lungs). Bronchodilation is medically useful for people suffering from asthma. This was the primary motivation for the invention and development of the amphetamines in the first place. However, most of the sympathetic effects are not considered pleasant by people who inject amphetamines for psychological effects. They generally prefer methamphetamine, which has stronger CNS effects and fewer peripheral effects than d- or l-amphetamine.

Studies of laboratory animals have shown that some of the effects of amphetamine are greater if animals are tested in groups rather than alone. One study with humans showed that amphetamine has a tendency to cause higher increases in blood pressure and body temperature in humans tested in groups rather than alone (de Wit, Clark, & Brauer, 1997).

Some patients receiving amphetamines for medical reasons report headaches, dry mouth, stomach disturbances, and weight loss due to depression of appetite.

Effects on Sleep

One reason for the widespread use of amphetamines during World War II and in the 1950s was that they prevented sleep. Amphetamines were used by truck drivers on long trips and by students staying awake to cram for exams. Systematic studies have shown that amphetamine use does cause insomnia.

EFFECTS ON THE BEHAVIOR AND PERFORMANCE OF HUMANS

Subjective Effects

When cocaine and amphetamine are given intravenously, their effects are identical (Fischman et al., 1976).

One of the most noticeable effects of the amphetamines is that they make people feel good; they improve the mood. From the earliest occasions when amphetamines were given to humans, positive mood changes were recorded. There were reports that the drug caused "a sense of well-being and exhilaration," feelings of "high spirits," and "bubbling inside." Most subjects felt a decrease in fatigue and an increase in energy; a clear, organized mind; and a desire to get to work and accomplish things (Grinspoon & Hedblom, 1975, p. 62). Later, systematic double-blind studies confirmed these reports. Figure 11-1 shows the results of such a study. Subjects were given a low dose (5 mg) of d-amphetamine or a placebo and were asked to fill out the Profile of Mood States (POMS) questionnaire. They filled in the POMS again 1, 3, and 6 hours after the drug was taken. As can be seen in Figure 11.1, the drug caused an increase in vigor, friendliness, elation, and positive mood (Johanson & Uhlenhuth, 1980). These effects were greatest 3 hours after administration, and some of the mood changes lasted as long as 6 hours. These euphoric feelings were followed several hours later by a feeling of depression (Gunne & Anggard, 1972). PET studies using radioactive glucose have shown that cocaine-induced euphoria is correlated with a 14 percent global reduction in glucose metabolism in all areas of the neocortex as well as in the basal ganglia, thalamus, midbrain, and hippocampus (London et al., 1990) and that glucose metabolism rebounds to above-normal levels during the first week of withdrawal (Volkow et al., 1991).

Some of the subjective effects of amphetamine are greater if the subject is expecting to receive the drug (Mitchell, Laurent, & de Wit, 1996), but the effects appear to be similar in subjects tested alone or in social groups (de Wit et al., 1997).

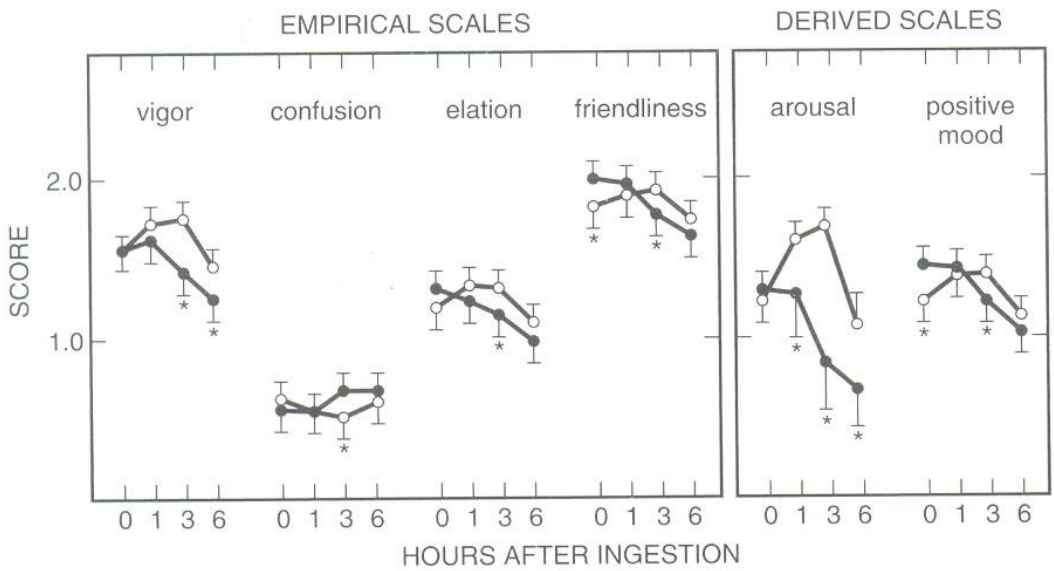

Figure 11-1 Changes in mood after 5 mg of amphetamine. Subjects were given the amphetamine orally and then filled out the POMS after 0, 1, 3, and 6 hours. Statistically significant differences between the drug (open circles) and a placebo (solid circles) are indicated with an asterisk (*). (Adapted from Johanson & Uhlenhuth, 1980, p. 277)

Higher acute doses produce a more intense subjective effect, but acute tolerance to pleasurable effects occurs with one administration or with repeated doses within a single session. Subjective effects tend to be greater when blood levels are rising than when they are falling (Brauer et al., 1996). In one study, humans were permitted to administer cocaine intravenously every 10 minutes for 1 hour. Feelings of positive mood increased after the first infusion but did not increase throughout the session, even though the blood levels of cocaine rose steadily with repeated infusions (Fischman & Schuster, 1982).

In addition to making people feel good, amphetamine at high doses after intravenous or intranasal administration produces intense feelings of euphoria and pleasure, called *rushes*. Rushes are not exclusive to intravenous administration, but this route is extremely efficient at delivering high drug levels to the brain and increasing their intensity. The rush has been described as "being lifted into the air with feelings of extreme happiness." Another account claims, "The heart starts beating at a terrible speed and his respiration is very rapid. Then he feels as if he was ascending into the cosmos, every fiber of his body trembling with happiness." Many people report that the rush has a strong sexual component. "The shot goes straight from the head to the scrotum," as one user put it (Rylander, 1969, p. 254).

The effects of cocaine are similar but shorter acting. Within a couple of minutes after cocaine is snorted, there is a numbing sensation called the *freeze*, which is followed after 5 minutes by a feeling of exhilaration and well-being. As with amphetamine, there is a feeling of energy and a sensation of clear thoughts and perceptions. This lasts for 20 to 30 minutes and is followed by a mild depression called the *comedown* or *letdown*.

When cocaine is injected, there is also a rush that may be felt within seconds and lasts about 45 seconds. This is illustrated in the following experiment. Electroencephalographic (EEG) recordings allow researchers to correlate subjective reports with neurophysiological changes. Since head movements can interfere with EEG recordings, participants were asked to use a microswitch-equipped joystick to report when the effects of

cocaine could be detected and when the participant was experiencing cocaine-induced euphoria or dysphoria. Using this technique, researchers discovered that whereas cocaine was "detected" for approximately 75 minutes postinjection, cocaine-induced euphoria occurred only during the first 10 to 15 minutes and correlated with increased alpha activity over the parietal and occipital lobes. During the 20 to 30 minutes postinjection, euphoria was replaced with dysphoria and correlated with a below-baseline level of activity in these brain regions (Lukas, 1991). These findings are shown in Color Plate C.

As with amphetamine, the rush associated with cocaine injection is almost universally described in sexual terms, namely, the orgasm. Unlike snorting, the effects of injected or inhaled are far from subtle and gradual; they take hold of the user immediately. The experience is so intense that it tends to encompass and engross the shooter totally and cuts him or her off from other people who might be nearby (Waldorf, Murphy, Renarman, & Joyce, 1977, p. 35).

With repeated administrations, cocaine-produced rushes show rapid tolerance. When intravenous injections of cocaine were given 70 minutes apart, reports of rushes disappeared over the session, but other measures, such as "feeling good," were unchanged (Kumor, Sherer, Muntander, Jaffee, & Herning, 1988).

It is generally assumed that the feelings of pleasure and euphoria result from the direct effects of these drugs on the mesolimbic dopamine system and that the direct stimulation of this system is also responsible for the powerful reinforcing effects of the psychomotor stimulants (Wolverton & Johanson, 1984). Recent evidence, however, has shown that things may not be quite that simple. For example, drugs that block both D_1 and D_2 receptors do not block amphetamine-induced euphoria, and other drugs known to mimic the effects of cocaine on dopamine synapses do not cause euphoria. Other brain systems are clearly involved in the subjective effects of psychomotor stimulants (Brauer, Goudie, & de Wit, 1997).

Stereotyped Behavior

In 1965, a Swedish psychiatrist, Gosta Rylander, described a peculiar behavior shown by high-dosage users of phenmetrazine, an amphetamine-like drug used for weight reduction. These users ground up phenmetrazine pills and injected them intravenously to experience the rush. The behavior Rylander noticed was what the users called *punding*—the repetitive performance of some (usually useless) act for an extended period. Typical acts were taking apart and putting together a watch or a telephone, sorting and resorting things in a handbag, or cleaning an apartment. When users are punding, they will usually not eat or drink or even go to the bathroom, and they become annoyed if the activity is interrupted (Rylander, 1969). Similar behavior is common among amphetamine users. Punding is considered the human equivalent of stereotyped behavior seen in laboratory animals after high-dose injections of amphetamines. (Stereotyped behavior of nonhumans will be described in detail shortly.)

It is quite likely that both punding and stereotyped behavior are caused by stimulation of the nigrostriatal DA system, which has input into the extrapyramidal motor system (see Chapter 4).

Amphetamine Psychosis

High doses of the amphetamines can cause psychotic behavior in otherwise normal people (Bowers, 1987, p. 820). The psychosis is virtually indistinguishable from true, full-blown paranoid schizophrenia. The symptoms of amphetamine psychosis include auditory and visual hallucinations, delusions of persecution, delusions of grandeur, and, sometimes, hostility and violence triggered by a paranoid belief that danger is imminent.

Amphetamine psychosis can occur in individuals who have no history of psychotic behavior. It usually clears in several days without residual effects (Angrist & Sudilovsky, 1978).

At high doses, cocaine and cathinone are also capable of causing psychotic episodes. Such a cocaine-induced psychosis convinced Sigmund Freud that cocaine was not a wonder drug after all. Freud had been giving cocaine to a friend,

+ euforia ≠ reforzamiento

Dr. von Fleischl-Marxow, to treat pain from neural tumors. During the course of treatment, Fleischl found it necessary to increase the dose to high levels, and he started showing the signs that are now known to be typical of a psychosis caused by both cocaine and amphetamines. One of the most distressing symptoms Fleischl experienced was the feeling of creatures—in his case, white snakes—crawling over him. Others have described the feeling as bugs crawling around just under the skin (Brecher & the Editors of *Consumer Reports*, 1972, p. 275). These are known as *cocaine bugs* (crank bugs, if they are caused by amphetamine). This phenomenon is formally called *formication*, from the Latin *formica*, meaning "ant."

Schizophrenia is thought to be, at least in part, a result of excessive DA functioning in the mesolimbic system (see Chapter 13). Drugs such as amphetamine worsen the psychotic symptoms of schizophrenics and create psychotic symptoms in normal persons. We also know that the effectiveness of the antipsychotic drugs (drugs that reduce the symptoms of psychosis) appears to arise from their ability to block DA receptors (Post, Cutler, Jimmerson, & Bunney, 1981) (see Chapter 13). Antipsychotics also diminish psychotic behavior caused by excessive amphetamine.

Violence. Violent behavior has been associated with continued amphetamine use. The violent behavior usually results from changes in the user's personality, which becomes hostile, paranoid, and defensive. Although violent episodes are not especially frequent, they are unpredictable and sudden. Rylander (1969, p. 263) described one such case:

> One addict who had just taken a shot stopped his car in a street, not feeling well, leaned backwards and put his feet up on the instrument panel. A bypasser asked if he was sick and offered his help. The addict drew a knife, got out and chased the helpful man. He stumbled and fell just when the addict tried to slash his back.

Sensory Effects

Amphetamines have been reported to raise the critical frequency of fusion threshold, indicating an increase in visual acuity (Simonson & Brozek, 1952). Slight improvements have been reported in auditory flicker fusion as well (Besser, 1967). The passage of time is underestimated; 1 second seems longer than it really is (Goldstone, Boardman, & Lhamon, 1958).

Effects on Performance

The Spanish conquistadores may not have believed the claims of the South American Indians that coca made them stronger, but there seems to be little doubt that amphetamines and cocaine can improve performance on a number of tasks and skills. Most of the early work of this nature was done by the armed forces of several countries during World War II. They found that endurance could be increased and the effects of fatigue could be diminished by amphetamines. In fact, amphetamines are still used in the military for this purpose. They are commonly referred to as *go pills*.

It does not appear that amphetamine will improve reaction time under normal circumstances, but it has been demonstrated many times that the drug will eliminate the effects of fatigue on reaction time, restoring it to normal. This finding also appears to be true for most measures of motor coordination and control. Improvements are more likely to be seen in complex motor tasks than in simple tasks.

Amphetamine has the ability to improve performance in tasks that require vigilance or prolonged attention. One measure of vigilance is the *clock test*. In this test, the subject faces a large dial around which a pointer moves in discrete steps. Every once in a while, the pointer moves two steps rather than one, and the task of the subject is to detect when such events occur. Over a period of 2 hours, the performance of normal subjects deteriorates from 95 to 80 percent accuracy. Subjects given 10 mg of amphetamine prior to this test show no deterioration in accuracy over the 2-hour period (Weiss, 1969). Amphetamine can also overcome deterioration in performance caused by other factors, such as decreased oxygen levels.

Not only does amphetamine return performance to normal levels, but other studies have also shown that in some situations, amphetamine can actually improve performance over normal levels. In a simplified simulated flying task, where subjects are required to move a joystick in order to keep dials from moving off center, it was found that the performance of subjects given a placebo deteriorated over a 4-hour period, but the scores of subjects given 5 mg of amphetamine actually stayed above their normal levels for the test (Weiss, 1969).

Although these drugs can improve performance, this improvement may be limited to overlearned and overpracticed tasks. Some investigators have suggested that stimulants may actually impair performance requiring flexibility and the ability to adopt new strategies (Judd, Squire, Butters, Salmon, & Paller, 1987, p. 1471).

Athletic Performance. In one early study, G. M. Smith and Beecher (1959) gave amphetamine to competitive swimmers who were then timed while performing in the event for which they were training. They found that amphetamine could produce a 1 percent improvement in their best drug-free times. Although 1 percent does not sound like much, in the highly competitive sport of swimming, athletes may train many months to reduce their times by 1 percent. Similar improvements have been seen in such track events as the 600- and 1,000-yard runs and the mile and in such field events as the shot put.

Because the psychomotor stimulants improve athletic performance, their use by athletes is banned by most national sports federations, and urine samples supplied by athletes at sporting events are screened for these drugs. As mentioned earlier, ephedrine is a psychomotor stimulant closely related to amphetamine. Ephedrine and similar drugs act as *bronchodilators* and are found in many cold preparations, cough syrups, and decongestants. Athletes undergoing such testing should be aware of the contents of these medicines before they take them because they could make their urine test positive for a banned substance. Some banned substances found in cold medicines include norpseudoephedrine, methoxphenamine, isoprenaline, isoproterenol, and methylephedrine.

EFFECTS ON THE BEHAVIOR OF NONHUMANS

Unconditioned Behavior

At low and intermediate doses, amphetamines increase spontaneous locomotor and exploratory activity in rats. At higher doses, there is an increase in locomotion at first, but after about an hour, the animals start to show increased sniffing and a variety of stereotyped behavior. The stereotyped behavior is usually some simple, short act with no particular function; it is repeated over and over to the exclusion of other behavior. In rodents, it may take the form of bobbing the head up and down, sniffing in a corner, rearing on the hind legs, or gnawing and biting.

In monkeys, there is a decrease in locomotor activity, and the stereotyped behavior is generally more complex than in rodents. It is also different in different subjects. One monkey may examine its hands; another may move sideways. These behaviors will reappear in the same animals when the drug is given at a later date. In humans, stereotyped behaviors, described earlier as punding, are more complex.

After high doses of amphetamines and cocaine, it is common for both rodents and monkeys to chew and bite at their own bodies. This self-directed biting is called *automutilation*. Animals may sometimes bite off their fingers, toes, or paws. It is likely that automutilation is a form of stereotyped behavior because it appears to be repetitious, but it may also be a result of formication. A sensation of bugs crawling under or on the skin is a symptom of amphetamine or cocaine psychosis in humans. The same sensation, experienced by animals, could cause them to pick at or cut their skin in an attempt to let the bugs out.

Even at low doses, amphetamines and cocaine decrease consumption of both food and water in most species. This is probably a combination of

(a) the effect of the drug on the part of the brain that controls appetite and (b) the fact that the drug increases other behavior sequences and reduces the time available for eating and drinking. We know that appetite suppression is not related to the reinforcing effects of these drugs because fenfluramine, a drug very similar to amphetamine, is very effective in suppressing appetite but does not appear to have any reinforcing effects (Brady et al., 1987).

Conditioned Behavior

In one of the earliest experiments on the effects of amphetamines on operant behavior, Peter Dews (1958) gave methamphetamine to pigeons responding on several schedules of reinforcement for food. Dews found that the drug increased responding on the fixed interval (FI) schedule but decreased fixed ratio (FR) responding at exactly the same dose. In his paper, Dews first demonstrated a relationship between the effect of amphetamine and the rate at which the pigeon was responding. He noticed that methamphetamine increased the rate of responding if it was low, as in the FI, but slowed responding that was normally fast, as in the FR. This effect became known as the *rate dependency effect*. It has since been demonstrated that this rule applies across all amphetamine-type drugs and many others, across many species, and across many types of behavior and schedules of reinforcement (Dews & Wenger, 1977). The significance of this observation cannot be overestimated. It was one of the first demonstrations that a drug interacts dynamically with ongoing behavior. It also showed that it was not appropriate to understand the effect a drug might have by simply classifying it as a "psychomotor stimulant." Whether the drug stimulates or depresses motor activity is a result of the behavior being observed and not entirely determined by the properties of the drug alone.

The rate dependency principle appears not to apply to the effect of amphetamine on behavior suppressed by punishment. Punishment-suppressed behavior usually occurs at a low rate, but most amphetamines and cocaine do not increase the rate.

The effects of cocaine are similar to those of amphetamine, but the rate-increasing effects of cocaine are not as great (C. G. Smith, 1964).

DISSOCIATION AND DRUG STATE DISCRIMINATION

It has been demonstrated that amphetamine causes dissociation; animals trained under the influence of amphetamine cannot completely remember what they learned when the amphetamine has worn off. This may be bad news for people who use amphetamines to help them stay awake and cram for exams (Roffman & Lal, 1972).

Rats can learn to discriminate amphetamine and cocaine from saline with moderate ease, although they are not as easily discriminable as barbiturates or benzodiazepines (Overton, 1982). Animals generalize the amphetamine response to cocaine, methylphenidate, cathinone, and some monoamine oxidase (MAO) inhibitors (see Chapter 14) (Glennon, 1987, p. 1630; Glennon et al., 1994; Huang & Ho, 1974; Porsolt, Pawelec, & Jalfre, 1982; Schechter & Glennon, 1985). In rats, amphetamine responses do not generalize to caffeine, nicotine, the barbiturates, chlorpromazine, atropine, or any of the common hallucinogens (Seiden & Dykstra, 1977, p. 416). Humans can also readily learn to discriminate amphetamine from a placebo (Chait, Uhlenhuth, & Johanson, 1986).

The discriminative effects of amphetamine can be blocked by dopamine D_2 receptors and, in some cases, by D_1 receptors, showing that dopamine systems are involved. It does not appear that norepinephrine or serotonin plays a significant role in amphetamine discrimination (Brauer et al., 1997).

TOLERANCE

Acute Tolerance

As described earlier, with continuous use of cocaine sniffing every 20 or 30 minutes for 10 or 12 hours, cocaine quickly loses its ability to cause rushes and gradually becomes unable to improve mood. This phenomenon, sometimes known as

a *coke-out*, is usually why runs come to an end (see the section on self-administration of cocaine later in this chapter). This acute tolerance dissipates rapidly and may be gone within 24 hours (Waldorf et al., 1977). Even though acute tolerance develops to the subjective effects, it does not appear to develop to the effects on blood pressure and heart rate. This suggests that people who increase the frequency of dose of amphetamine or cocaine to maintain a subjective effect may be in danger of reaching levels that could be toxic (Brauer et al., 1996).

Chronic Tolerance and Sensitization

Some effects of cocaine and amphetamines become tolerated with repeated administration. In humans, the appetite-suppressing effect usually disappears in about 2 weeks, and the effects on the heart and blood pressure also diminish. The lethal effects also show tolerance, and chronic amphetamine users are able to increase their dose to extremely high levels. In one such case, a 15,000-mg dose of amphetamine was administered in a 24-hour period; this was 1,000 times the normal therapeutic dose and several times the estimated LD_{50} for nontolerant humans. Some effects, such as the blocking of sleep, show no tolerance.

For some effects, reverse tolerance or sensitization takes place. Stereotyped behavior and psychotic behavior appear more frequently after repeated doses in humans. In rats, chronic administration of cocaine lowers the threshold for convulsions, and some electrical activity within the brain increases with continued use (Stripling & Ellinwood, 1976). With continued administration of cocaine, stereotyped behavior and spontaneous motor activity also increase in frequency and intensity (Post, Weiss, Pert, & Uhde, 1987). As described in Chapter 3, this sensitization is a result of increased sensitivity of the mesolimbic dopamine system (R. C. Pierce & Kalivas, 1997).

WITHDRAWAL

Amphetamine and cocaine are not associated with a severe or medically serious withdrawal when use is discontinued. Depression seems to be the most prominent characteristic of psychomotor stimulant withdrawal.

After a single dose of amphetamine or cocaine, the high is usually followed by a *letdown*—a period of depression and lethargy that can be thought of as a withdrawal symptom. The depression is immediately relieved by another administration of the drug. The letdown occurs within half an hour with cocaine, but its appearance is delayed for a number of hours with amphetamines. The severity of the depression is related to the dose and the duration of the intake period. If the intake period has been long enough to interfere with sleep and eating, there will also be a compensatory increase in sleeping and eating. The nature of the sleep will also change because there will be a rebound of REM sleep that the drug suppressed.

After continuous long-term use of cocaine, a permanent depression in mood may arise from changes in the functioning of the monoamine systems in the brain. These changes appear to be similar to the changes associated with depression and can be treated with antidepressant drugs (Gawin & Kleber, 1987).

When high levels of amphetamine have been continuously used for an extended time, the depression that results may be quite severe and may be accompanied by suicidal thoughts and suicide attempts. Amphetamine withdrawal depression is similar to psychiatric depression except that the latter is characterized by insomnia and decreased appetite, whereas the opposite is true for the amphetamine-induced depression (Angrist & Sudilovsky, 1978).

Withdrawal from psychomotor stimulants can also disrupt performance. In the early stages of abstinence, methamphetamine addicts demonstrate decision-making dysfunctions on tasks that require switching from a losing to a winning strategy in a two-choice procedure. This performance deficit correlates with reduced dorsolateral prefrontal cortex activation and failure to activate the ventromedial cortex, as measured by functional magnetic resonance imaging (fMRI) (Paulus et al., 2002). Following at least 1 year of amphetamine abstinence, PET imaging continued

to demonstrate decreased dorsolateral prefrontal cortex activation in association with decision making in risky situations (Ersche et al., 2005).

SELF-ADMINISTRATION IN HUMANS

Cocaine

Cocaine has a long history of self-administration, starting with the native people of South America, who consumed the drug orally, as noted earlier in this chapter. Their pattern of use was very different from the modern North American patterns of self-administration of pure cocaine or amphetamines. With pure cocaine, continuous use is rare. When snorted or injected, cocaine is usually taken in large quantities for brief periods of time that are followed by periods of abstinence. It is usually consumed, with some ceremony and ritual, at parties and in social settings.

Cocaine is often taken in conjunction with other drugs. The most usual mix is the *speed ball*, a combination of cocaine (or amphetamine) and heroin. Users claim that the heroin reduces the jitteriness that cocaine arouses by stimulating the sympathetic nervous system, and the cocaine diminishes the sleepiness or nod caused by heroin. Cocaine is also regularly mixed with depressants such as benzodiazepines or with ketamine or PCP for the same reason.

Amphetamines

Like cocaine, amphetamines are self-administered sporadically rather than continuously, but the pattern may depend on the effect for which the drug is taken. Because it is longer lasting than cocaine, amphetamine allows constant blood levels to be maintained more easily for an extended period of time—for example, when the drug is used by truck drivers or students cramming for finals to enhance behavior or prevent sleep. When the need is over, the drug is usually discontinued, and the person then recovers by making up for the lost sleep.

When amphetamines are used for their euphoric effects, usually much higher doses are taken, and the administration is frequently intravenous. In the 1960s, this type of use was characterized by the *peak user* or *speed freak* who typically injected amphetamine every few hours for days at a time. During such *runs*, users do not sleep, they eat very little, and they may show symptoms of amphetamine psychosis, such as punding and paranoia. Eventually, when they are too exhausted to continue or they run out of the drug, they *crash*—they sleep for an extended period (24 to 48 hours). When they wake up, they are very hungry and will eat ravenously before going out to search for more drugs in order to begin another run. This pattern is now seen with crack addicts.

SELF-ADMINISTRATION IN NONHUMANS

In 1968, Roy Pickens and Travis Thompson, then at the University of Minnesota, published the first detailed account of cocaine self-administration in nonhumans. (The first cocaine self-administration experiments were actually done by G. A. Deneau and his colleagues at the University of Michigan, but these were not published until 1969.) Pickens and Thompson, using two rats implanted with intravenous catheters, showed that the rats would bar press on an FR schedule for cocaine. (This experiment is described in Chapter 5.) For several reasons, this was an important milestone. It was the first demonstration of self-administration of a drug other than morphine, and it established that a drug with no apparent withdrawal symptoms could be a reinforcer, confirming that the reinforcing effect of drugs was not a result of fear of withdrawal. Since the time of this experiment, there have been many demonstrations of cocaine self-administration in many species.

In fact, cocaine may have a more robust reinforcing effect than almost any other drug. Animals learn to self-administer cocaine more easily than any other drug, and they work harder for it. In an experiment reported by Yanagita (1975), the reinforcing potency of cocaine was

compared with that of a number of other drugs, using the progressive ratio procedure. In four of six monkeys, cocaine was the most reinforcing drug tested. (One monkey worked the ratio up to 6,400 before stopping.) Cocaine tied for first in a fifth monkey, and the sixth found amphetamine more reinforcing than cocaine.

Figure 11-2 shows data published by Deneau, Yanagita, and Seevers (1969) and demonstrates the erratic pattern of cocaine self-administration in monkeys when the drug is freely available 24 hours a day. A monkey learns quickly to give itself the drug and is soon administering the drug at levels high enough to cause convulsions. The record shows that there is considerable fluctuation from day to day. On some days, no drug is taken; on others, massive quantities are infused. Often, if monkeys are given unlimited access to the drug, they will administer to the point of killing themselves (Bozarth & Wise, 1984).

Figure 11-2 also shows the typical run–abstinence cycle that is characteristic of human stimulant use. In this case, the monkey actually stopped responding for a 28-hour period on day 17 before resuming injections on day 18.

The pattern of self-administration is quite different when daily access to cocaine is limited. Under these conditions, laboratory animals self-administer cocaine in a steady and regular manner, precisely controlling the amount of drug they receive on any given day (Amed & Koob, 1998). If the work required for each infusion or the dose

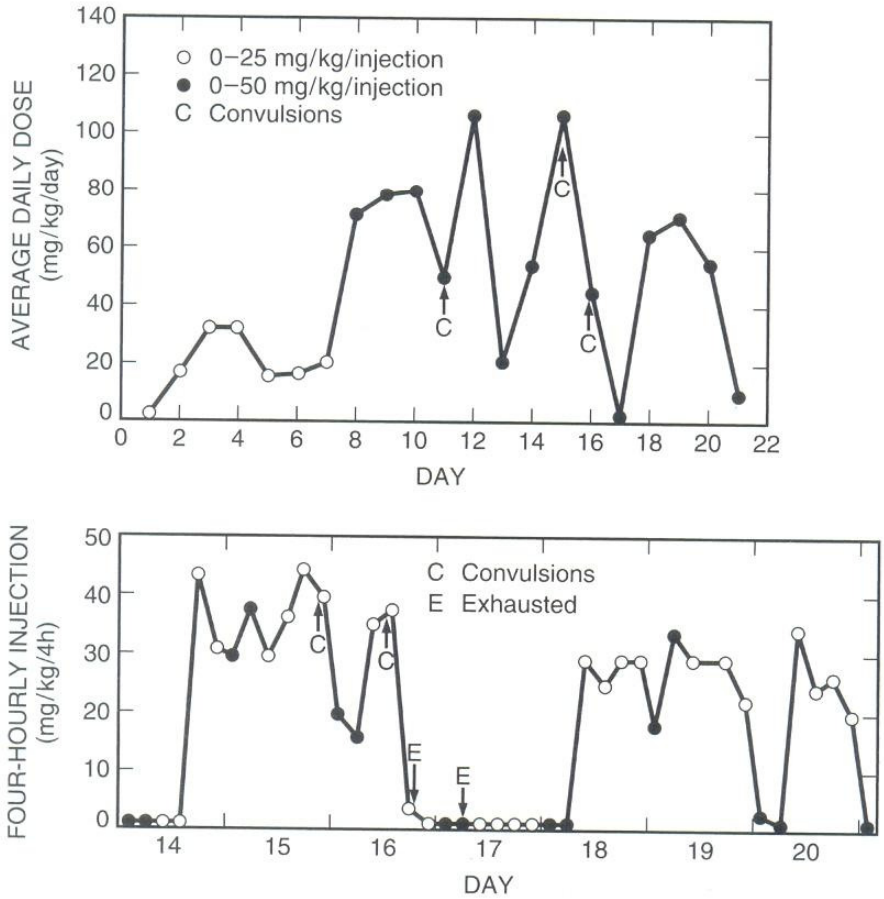

Figure 11-2 The pattern of cocaine self-administration in the monkey. *Top*: Daily intake for 21 days. *Bottom*: Intake in 4-hour periods from day 14 to day 21, illustrating the cycles of intake and abstinence. (Adapted from Deneau, Yanagita, & Seevers, 1969)

per infusion is changed, the behavioral output changes exactly as needed to keep the daily dose constant.

Behavioral economics studies show that the demand for cocaine, like the demand for most drugs, is inelastic when cost is low but becomes elastic when cost is very high (Carroll & Bickel, 1998; Yokel, 1987, p. 15).

Nonhumans readily self-administer all the psychomotor stimulants, using a variety of routes of administration. The patterns and rates are similar to those for cocaine. Cocaine self-administration can be primed by other psychomotor stimulants and by other drugs such as morphine and caffeine. In addition, cocaine self-administration is enhanced by stress, previous experience with cocaine, and the concurrent administration of caffeine, heroin, and alcohol. Self-administration is decreased by the concurrent availability of alternative reinforcers such as sweetened water (Carroll & Bickel, 1998).

HARMFUL EFFECTS

Direct Effects

When methylphenidate is given chronically at low levels in the treatment of hyperactivity in children, it sometimes causes a reduction in growth velocity (Brookes, 1985, p. 267).

There are reports that the Andean Indians who chew the coca leaf regularly seem to have few health problems. It has been noted, however, that these and other regular users of cocaine have a sallow or yellowish complexion, which may be attributable to mild jaundice caused by liver disease. Chronic cocaine use has also caused liver damage in experimental animals (Caldwell, 1976). Chronic cocaine sniffing can also cause inflammation and ulceration of the mucous membranes in the nose. This damage can even progress to the extent that openings appear in the septum (the membrane separating the nostrils). Because cocaine is a local anesthetic, this discomfort in the nose will be relieved by sniffing more cocaine, and in this way it will contribute to the motivation to continue sniffing the drug.

Cocaine sniffing, smoking, or injecting can lead to an intense compulsion to continue until the drug runs out or the user becomes exhausted. During such runs, it is not unusual for vast sums to be spent on the drug (R. K. Siegel, 1982a). People have been known to sell their houses and cars to finance continuous intake. Not only do such binges consume personal finances, but many users report disturbing physiological and psychological symptoms: paranoid feelings, visual hallucinations, cravings, antisocial behavior, attention and concentration problems, blurred vision, and weight loss.

The use of oral amphetamine for short periods (e.g., to stay awake while driving or studying) can have undesirable effects that include restlessness, excessive talking, confusion, and dizziness. If use is continued for too long, paranoid psychotic behavior starts to appear, which is complicated by the lack of sleep. Punding and irrational thinking may also emerge, and these are not likely to improve driving or studying. In susceptible individuals, the increased blood pressure can cause strokes (Rumbaugh, Bergeron, Fang, & McCormack, 1971). In addition, when the drug is stopped, the period of recovery is characterized by depression with suicidal tendencies and lethargy, and the REM rebound will cause sleep disturbances.

High-level chronic use, especially if associated with intravenous administration, is potentially quite harmful. The effects are both direct and indirect. Amphetamines have a strong direct effect on the heart and circulatory system; the irregular heartbeat and increased blood pressure they cause can result in internal bleeding and strokes (Grinspoon & Bakalar, 1979a). Irreversible brain damage has also been reported as a result of deterioration and rupturing of small blood vessels in the brain (Rumbaugh et al., 1971).

In addition, amphetamine appears to have a neurotoxic effect on some parts of the brain, especially those cells in the brain that release dopamine. Nonhuman primate studies demonstrate that damage to brain dopamine neurons can result, not from excessive use but from only four administrations of methamphetamine at doses comparable to those

used recreationally by humans. PET imaging with a radiolabeled dopamine transporter ligand revealed that total doses of 2, 4, or 8 mg/kg of methamphetamine injected into baboons over 8 hours on a single day resulted in significant reductions in dopamine transporter density in the caudate and putamen 2 to 3 weeks later. This indicates the death of dopamine cells (Villemagne et al., 1998). The results of this study are shown in Color Plate D.

Indirect Effects

As with so many drugs used excessively, many of the harmful effects of amphetamine are indirect and arise from the user's lifestyle. Because intravenous users rarely use sterile injection apparatus, they frequently contract diseases, particularly hepatitis and AIDS. Their ability to fight diseases is reduced by (a) the poor diet caused by the appetite-suppressing effects of the drug and (b) the fact that they seldom sleep. High-dose amphetamine users are suspicious, antisocial, and prone to violence (Rylander, 1969). The death rate among intravenous amphetamine users is much higher than expected in the general population, but it is about the same as among chronic alcoholics and heroin addicts of the same age group (H. Kalant & Kalant, 1979).

Reproduction

Both amphetamine and cocaine have been used to enhance sexual activity. It has been reported that low doses prolong erections and delay ejaculation in males and enhance desire and enjoyment of orgasms in females. These changes, along with the decrease in sexual inhibitions that is caused by the drug, sometimes lead to changes in sexual orientation and practices while taking these drugs. People who would not normally do such things sometimes engage in marathon sexual acts, group sex, and homosexuality (D. E. Smith, Buxton, & Dammann, 1979). Continuous high doses of cocaine by inhalation of crack or freebase or by injection often lead to a disruption in sexual activity in males and periods of disinterest in sex (R. K. Siegel, 1982a).

Like cocaine, khat initially increases sex drive in males, but continued use can cause decreased sexual interest and impotency (Giannini, Burge, Shaheen, & Price, 1986). It can also inhibit milk production in nursing mothers who continuously abuse the plant.

There have been some studies of the effects of amphetamine-like drugs on fetal abnormalities. Most of these studies were done on women who used these drugs to control their appetite during pregnancy. They provided some evidence linking this chronic, oral, low-dose use with a higher-than-average incidence of birth abnormalities. Evidence from animal studies also indicates that amphetamine used during pregnancy can cause behavioral and physical problems in offspring (Grinspoon & Hedblom, 1975, pp. 146–147).

There is mounting evidence that cocaine use by a pregnant woman is detrimental to the fetus, but the media presentation of *crack babies* was somewhat of an exaggeration. Many studies have found that maternal cocaine use does retard fetal growth; babies are smaller and more likely to be premature (Zuckerman & Frank, 1994). Other studies, however, have found that babies born to mothers who reported using cocaine while pregnant were not more likely to be born prematurely or to have smaller birth weights but were almost 10 times more likely to have *abruptio placentae* (the placenta detaches prematurely; Shiono et al., 1995). Studies of possible long-term developmental and behavioral effects of prenatal exposure to cocaine are plagued with methodological difficulties, not the least of which is accurately measuring cocaine exposure and separating its effect from other concurrent factors such as the use of other drugs and the quality of pre- and postnatal care (Zuckerman & Frank, 1994). It is now becoming clear that such exposure does not necessarily lead to reduced intelligence, as was once thought. Several studies, however, have concluded that children whose mothers used cocaine while pregnant have more behavioral problems, including a decreased ability to pay attention and stay focused, increased aggression, and irritability (G. Vogel, 1997).

Overdose

Cocaine users who take large doses commonly experience muscle weakness and respiratory depression. The user may be unable to stand up or may collapse but not lose consciousness (Crowley, 1987, p. 202).

The lethal dose of cocaine depends to a large extent on the route of administration. Individuals vary greatly, but the LD_{50} in a 150-pound man is about 500 mg. When the drug is taken intranasally, the LD_{50} may be as low as 30 mg. The absolute dose may not be the important variable in determining the lethality; rather, what seems to be important is the sudden increase in drug levels in the brain.

The cocaine-related deaths of several prominent athletes have emphasized that cocaine has intense cardiovascular effects that can be fatal when the drug is injected or inhaled in concentrated form, causing the cocaine sudden-death syndrome. As noted earlier, it is not unusual for laboratory animals to self-administer lethal doses of cocaine. F. R. George and Goldberg (1989) showed that between individual strains of rats and mice, there is considerable variability in sensitivity to various effects of cocaine. One strain of rats, for example, seemed insensitive to the reinforcing effects of usual doses of cocaine but was very sensitive to the lethal effects of cocaine on the heart. If there are similar genetic variations in humans, it is possible that certain individuals might be highly resistant to the euphoric effects of the drug. Such people would be at a considerable risk from cocaine because attempts to reach euphoric doses could easily drive blood levels into the lethal range. Such genetic variations in sensitivity may account for the cocaine sudden-death syndrome (F. R. George & Goldberg, 1989).

The cocaine overdose or *caine reaction* has two phases. An initial excitement is followed by severe headache, nausea, vomiting, and then severe convulsions. This phase is followed by a loss of consciousness, respiratory depression, and cardiac failure causing death. Death may be very rapid, within 2 to 3 minutes, or it may take as long as half an hour. Someone who survives the first 3 hours is likely to recover, but if breathing has been depressed too long, there may be brain damage from loss of oxygen (Gay & Inaba, 1976).

Seizures caused by cocaine overdose can be treated with diazepam, and respiratory depression or arrest can be treated with artificial respiration. Chlorpromazine, an antipsychotic, is also very effective as an antagonist of the toxic effects of cocaine (Crowley, 1987, p. 203).

TREATMENT

The first stage in the treatment of a cocaine abuser involves a period of detoxification during which the direct effects of cocaine are treated. The Haight-Ashbury Free Medical Clinic in San Francisco (Gay & Inaba, 1976) has developed a procedure whereby the acute toxic effects of cocaine are treated directly until the patient is out of danger, and then, for the next 3 to 12 days, depressant drugs are given and are slowly tapered off. For the less seriously afflicted, a period of hospitalization may not be essential.

Following detoxification or for users wishing to stop who are not under the influence of the drug, there are a number of possible long-term treatments. Some of these depend on treatment with other drugs, and some do not.

The initial concern with cocaine abusers seeking treatment is that they will resume using the drug very quickly, before treatment has had a chance to have any effect. Because of drug priming (see Chapter 3), it is particularly important to prevent the patient from using cocaine again, even once. The craving for cocaine increases considerably just 15 minutes after a single cocaine injection (Jaffe, Cascella, Kumor, Sherer, 1989). This fact makes a relapse extremely likely.

A recently developed approach makes use of positive reinforcement in the form of a monetary reward for providing clean urine samples. The reward increases with each succeeding drug-free test. In addition to the money, a relative, spouse, or friend who is involved in the program participates

in some previously agreed-on enjoyable activity. These incentives are combined with counseling to help the user avoid situations where there is a risk of relapse, employment counseling, and encouragement to pursue educational or recreational goals. In a test of this strategy, 11 of 13 cocaine users admitted for outpatient treatment remained drug free for a 12-week period of treatment. Only five of 12 patients in a control group that was offered 12-steps counseling remained drug free for the 12 weeks (Higgins et al., 1991). Other cognitive-behavioral techniques are now being developed for methamphetamine users. These techniques combine social support, family education, individual counseling, and urine testing (Rawson et al., 2004).

In addition to these treatments, some drugs, primarily antidepressants, have been found to be helpful. There is some evidence that a period of prolonged cocaine use will cause permanent biochemical changes in the brain that are similar to the biochemical changes associated with depression (see Chapter 14). This depression may be responsible for the craving that ex-users have for cocaine. Relieving the depression with antidepressant drugs could also diminish the craving. In fact, antidepressants have been reported to diminish the craving for cocaine in ex-users with a delay of about 2 weeks after beginning treatment. This is, in fact, the same delay that is often seen with the antidepressants in their therapeutic effect on depression (Gawin & Kleber, 1987).

More recently, a new drug has been tried with some initial success. Topiramate is a drug used to prevent seizures. It works by both stimulating gamma-aminobutyric acid and blocking glutamate. This combination of effects also seems to reduce cocaine craving (Kampman et al., 2004). Drug craving can be experimentally induced and correlated with changes in regional blood flow using PET scanning. Researchers recorded 1-minute audio scripts of cocaine addicts describing detailed personal experiences and subjective effects of cocaine use and replayed the script to the addicts during a PET scanning session. Compared to control conditions in which the scripts described a personal experience in nature, cocaine-related scripts induced sensations of drug craving that correlated with increased cerebral blood flow in the nucleus accumbens, dorsal and ventral regions of the anterior cingulate cortex, and the frontal cortex (Kilts, Gross, Ely, & Drexler, 2004). Topiramate's effects may therefore decrease craving by inhibiting increases in cerebral blood flow in reward-related brain regions.

Another drug that appears to be useful in treating cocaine addicts and preventing early relapse during treatment is modafinil (Dackis et al., 2005). Modafinil is a stimulant drug used to treat narcolepsy. It works by increasing activity of the glutamate and dopamine. It has been described as a "mood brightener." The drug may be reversing the dopamine and glutamate depletion caused by excessive cocaine use and thereby blocking the mood depression caused by cocaine withdrawal.

Substitution therapies do not seem to be effective. Attempts to use methylphenidate and phenmetrazine (an appetite suppressant) as maintenance drugs for cocaine abusers, in the same way that methadone is used with heroin users (see Chapter 12), were unsuccessful. A similar technique was tried with amphetamine abusers in the 1960s, but this failed as well (Bergsman & Jarpe, 1969; Gawin & Kleber, 1987, p. 175; Gorelick, 1995). It is possible that modafinil may be able to fulfill this function.

CHAPTER SUMMARY

- All the drugs covered in this chapter—amphetamines (including crystal meth), ephedrine, cocaine, and cathinone—have a similar effect on the nervous system; they all increase activity at synapses that use a monoamine (MA) as a transmitter.
- Cocaine, ephedrine, and cathinone are derived from plant material, but the amphetamines are synthetic.
- Amphetamine and cocaine are weak bases. Although they can be absorbed from the digestive system, they are much more effective when injected, sniffed, or smoked and inhaled. They are easily distributed throughout the body and are extensively

metabolized by the liver and excreted in the urine. Cocaine has a much shorter half-life than the amphetamines.

- Crack cocaine is a mixture of cocaine and baking soda. As a consequence, it is not ionized and rapidly absorbed and distributed.
- The amphetamines and cathinone increase activity at MA synapses by stimulating leakage of the transmitter, increasing the amount of transmitter released, and blocking reuptake of the transmitter. Cocaine works by blocking uptake of the transmitter.
- MA systems in the brain are closely related to the mesolimbic dopamine system, which governs reinforcement, and the basal ganglia of the nigrostriatal system, which regulate body movement.
- The psychomotor stimulants improve mood. When amphetamine and cocaine are taken in high doses by inhaling or intravenous injection, they cause intense feelings of pleasure called rushes. After the effects of the psychomotor stimulants have worn off, a period of depression usually ensues.
- When taken continuously at high doses, by humans or nonhumans, the psychomotor stimulants cause stereotyped behavior—the senseless repetition of a meaningless act. In humans, high doses may also cause paranoid behavior and psychosis.
- At low doses, the amphetamines and cocaine can improve performance in certain activities and can eliminate the effect of fatigue on most cognitive and perceptual tasks and on athletic activity.
- The amphetamines can cause dissociation and are readily discriminated from saline. All the psychomotor stimulants and antidepressants will generalize to each other but do not generalize to any other type of drug.
- The discriminative stimulus effects of cocaine and amphetamine appear to be controlled by DA receptors.
- Withdrawal from amphetamines and cocaine is characterized by intense depression, and fMRI and PET studies have detected changes in frontal cortex activity associated with disruption of decision-making capabilities even after a year of abstinence from amphetamine.
- The psychomotor stimulants are readily self-administered by both humans and nonhumans, and the pattern of self-administration is similar in most species. It consists of a run of self-administration lasting for days or hours during which there is very little eating or sleeping, followed by a period of abstinence and recovery. This period is followed by another run. Cocaine and amphetamine are probably more powerful reinforcers than any other drug.
- Excessive cocaine use and the associated lifestyle can be unhealthy. Many who inject cocaine do not use sterile needles, and this contributes to the spread of AIDS. Continuous use of high doses of psychomotor stimulants can make people paranoid and psychotic, retard the development of unborn children, and cause sudden death in susceptible individuals.
- Among the treatments being developed for cocaine and psychomotor stimulant abuse are antidepressant drugs that reduce withdrawal depression. Other drugs that seem to be helpful are modafinil and Topiramate. Alternate therapies offer social and monetary rewards for remaining abstinent.