15.1 Basic Principles of Drug Action
15.2 Role of Learning in Drug Tolerance
15.3 Five Commonly Abused Drugs
15.4 Biopsychological Approaches to Theories of Addiction
15.5 Intracranial Self-Stimulation and the Pleasure Centers of the Brain
15.6 Early Studies of Brain Mechanisms of Addiction: Dopamine
15.7 Current Approaches to Brain Mechanisms of Addiction
15.8 A Noteworthy Case of Addiction
Drug addiction is a serious problem in most parts of the world. For example, in the United States alone, over 60 million people are addicted to nicotine, alcohol, or both; 5.5 million are addicted to illegal drugs; and many millions more are addicted to prescription drugs. Pause for a moment and think about the sheer magnitude of the problem represented by such figures—hundreds of millions of addicted people worldwide. The incidence of drug addiction is so high that it is almost certain that you, or somebody dear to you, will be adversely affected by drugs.

This chapter introduces you to some basic pharmacological (pertaining to the scientific study of drugs) principles and concepts, compares the effects of five common addictive drugs, and reviews the research on the neural mechanisms of addiction. You likely already have strong views about drug addiction; thus, as you progress through this chapter, it is particularly important that you do not let your thinking be clouded by preconceptions. In particular, it is important that you do not fall into the trap of assuming that a drug's legal status has much to say about its safety. You will be less likely to assume that legal drugs are safe and illegal drugs are dangerous if you remember that most laws governing drug abuse in various parts of the world were enacted in the early part of the 20th century, long before there was any scientific research on the topic.

**The Case of the Drugged High School Teachers**

People’s tendency to equate drug legality with drug safety was recently conveyed to me in a particularly ironic fashion: I was invited to address a convention of high school teachers on the topic of drug abuse. When I arrived at the convention center to give my talk, I was escorted to a special suite, where I was encouraged to join the executive committee in a round of drug taking—the drug being a special high-proof single-malt whiskey. Later, the irony of the situation had its full impact. As I stepped to the podium under the influence of a psychoactive drug (the whiskey), I looked out through the haze of cigarette smoke at an audience of educators who had invited me to speak to them because they were concerned about the unhealthy impact of drugs on their students. The welcoming applause gradually gave way to the melodic tinkling of ice cubes in liquor glasses, and I began. They did not like what I had to say.

**15.1 Basic Principles of Drug Action**

This section focuses on the basic principles of drug action, with an emphasis on psychoactive drugs—drugs that influence subjective experience and behavior by acting on the nervous system.

**Drug Administration and Absorption**

Drugs are usually administered in one of four ways: by oral ingestion, by injection, by inhalation, or by absorption through the mucous membranes of the nose, mouth, or rectum. The route of administration influences the rate at which and the degree to which the drug reaches its sites of action in the body.

**Oral Ingestion** The oral route is the preferred route of administration for many drugs. Once they are swallowed, drugs dissolve in the fluids of the stomach and are carried to the intestine, where they are absorbed into the bloodstream. However, some drugs readily pass through the stomach wall (e.g., alcohol), and these take effect sooner because they do not have to reach the intestine to be absorbed. Drugs that are not readily absorbed from the digestive tract or that are broken down into inactive metabolites (breakdown products of the body’s chemical reactions) before they can be absorbed must be taken by some other route.

The two main advantages of the oral route of administration over other routes are its ease and relative safety. Its main disadvantage is its unpredictability: Absorption from the digestive tract into the bloodstream can be greatly influenced by such difficult-to-gauge factors as the amount and type of food in the stomach.

**Injection** Drug injection is common in medical practice because the effects of injected drugs are strong, fast, and predictable. Drug injections are typically made subcutaneously (SC), into the fatty tissue just beneath the skin; intramuscularly (IM), into the large muscles; or intravenously (IV), directly into veins at points where they run just beneath the skin. Many addicts prefer the intravenous route because the bloodstream delivers the drug directly to the brain. However, the speed and directness of the intravenous route are mixed blessings; after an intravenous injection, there is little or no opportunity to counteract the effects of an overdose, an impurity, or an allergic reaction. Furthermore, many addicts develop scar tissue, infections, and collapsed veins at the few sites on their bodies where there are large accessible veins.

**Inhalation** Some drugs can be absorbed into the bloodstream through the rich network of capillaries in the lungs. Many anesthetics are typically administered by inhalation, as are tobacco and marijuana. The two main shortcomings of this route are that it is difficult to precisely regulate the dose of inhaled drugs, and many substances damage the lungs if they are inhaled chronically.

**Absorption through Mucous Membranes** Some drugs can be administered through the mucous membranes of the nose, mouth, and rectum. Cocaine, for example, is
commonly self-administered through the nasal membranes (snorted)—but not without damaging them.

**Drug Penetration of the Central Nervous System**

Once a drug enters the bloodstream, it is carried in the blood to the blood vessels of the central nervous system. Fortunately, a protective filter, the blood–brain barrier, makes it difficult for many potentially dangerous blood-borne chemicals to pass from the blood vessels of the CNS into its neurons.

**Mechanisms of Drug Action**

Psychoactive drugs influence the nervous system in many ways (see Koob & Bloom, 1988). Some drugs (e.g., alcohol and many of the general anesthetics) act diffusely on neural membranes throughout the CNS. Others act in a more specific way: by binding to particular synaptic receptors; by influencing the synthesis, transport, release, or deactivation of particular neurotransmitters; or by influencing the chain of chemical reactions elicited in postsynaptic neurons by the activation of their receptors (see Chapter 4).

**Drug Metabolism and Elimination**

The actions of most drugs are terminated by enzymes synthesized by the liver. These liver enzymes stimulate the conversion of active drugs to nonactive forms—a process referred to as drug metabolism. In many cases, drug metabolism eliminates a drug’s ability to pass through lipid membranes of cells so that it can no longer penetrate the blood–brain barrier. In addition, small amounts of some psychoactive drugs are passed from the body in urine, sweat, feces, breath, and mother’s milk.

**Drug Tolerance**

Drug tolerance is a state of decreased sensitivity to a drug that develops as a result of exposure to it. Drug tolerance can be demonstrated in two ways: by showing that a given dose of the drug has less effect than it had before drug exposure or by showing that it takes more of the drug to produce the same effect. In essence, what this means is that drug tolerance is a shift in the dose-response curve (a graph of the magnitude of the effect of different doses of the drug) to the right (see Figure 15.1).

There are three important points to remember about the specificity of drug tolerance.

- One drug can produce tolerance to other drugs that act by the same mechanism; this is known as cross tolerance.
- Drug tolerance often develops to some effects of a drug but not to others. Failure to understand this second point can have tragic consequences for people who think that because they have become tolerant to some effects of a drug (e.g., to the nauseating effects of alcohol or tobacco), they are tolerant to all of them. In fact, tolerance may develop to some effects of a drug while sensitivity to other effects of the same drug increases. Increasing sensitivity to a drug is called drug sensitization (Robinson, 1991).
- Drug tolerance is not a unitary phenomenon; that is, there is no single mechanism that underlies all examples of it (Littleton, 2001). When a drug is administered at doses that affect nervous system function, many kinds of adaptive changes can occur to reduce its effects.

Two categories of changes underlie drug tolerance: metabolic and functional. Drug tolerance that results from changes that reduce the amount of the drug getting to its sites of action is called metabolic tolerance. Drug tolerance that results from changes that reduce the reactivity of the sites of action to the drug is called functional tolerance.

Tolerance to psychoactive drugs is largely functional. Functional tolerance to psychoactive drugs can result from several different types of adaptive neural changes (see Treistman & Martin, 2009). For example, exposure to a psychoactive drug can reduce the number of receptors for it, decrease the efficiency with which it binds to existing receptors, or diminish the impact of receptor binding on the activity

---

**FIGURE 15.1** Drug tolerance: A shift in the dose-response curve to the right as a result of exposure to the drug.
of the cell. At least some of these adaptive neural changes are caused by epigenetic mechanisms that affect gene expression (Wang et al., 2007).

**Drug Withdrawal Effects and Physical Dependence**

After significant amounts of a drug have been in the body for a period of time (e.g., several days), its sudden elimination can trigger an adverse physiological reaction called a withdrawal syndrome. The effects of drug withdrawal are virtually always opposite to the initial effects of the drug. For example, the withdrawal of anticonvulsant drugs often triggers convulsions, and the withdrawal of sleeping pills often produces insomnia. Individuals who suffer withdrawal reactions when they stop taking a drug are said to be physically dependent on that drug.

The fact that withdrawal effects are frequently opposite to the initial effects of the drug suggests that withdrawal effects may be produced by the same neural changes that produce drug tolerance (see Figure 15.2). According to this theory, exposure to a drug produces compensatory changes in the nervous system that offset the drug’s effects and produce tolerance. Then, when the drug is eliminated from the body, these compensatory neural changes, without the drug to offset them, manifest themselves as withdrawal symptoms opposite to the initial effects of the drug.

The severity of withdrawal symptoms depends on the particular drug in question, on the duration and degree of the preceding drug exposure, and on the speed with which the drug is eliminated from the body. In general, longer exposure to greater doses followed by more rapid elimination produces greater withdrawal effects.

**Addiction: What Is It?**

Addicts are habitual drug users, but not all habitual drug users are addicts. Addicts are those habitual drug users who continue to use a drug despite its adverse effects on their health and social life, and despite their repeated efforts to stop using it (see Volkow & Li, 2004).

The greatest confusion about the nature of drug addiction concerns its relation to physical dependence. Many people equate the two: They see drug addicts as people who are trapped on a merry-go-round of drug taking, withdrawal symptoms, and further drug taking to combat the withdrawal symptoms. Although appealing in its simplicity, this conception of drug addiction is inconsistent with the evidence. Addicts sometimes take drugs to prevent or alleviate their withdrawal symptoms (Baker et al., 2006), but this is not the major motivating factor in their addiction. If it were, drug addicts could be easily cured by hospitalizing them for a few days, until their withdrawal symptoms subsided. However, most addicts renew their drug taking even after months of enforced abstinence. This is an important issue, and it will be revisited later in this chapter.

It may have occurred to you, given the foregoing definition of addiction, that drugs are not the only substances to which humans are commonly addicted.

**FIGURE 15.2** The relation between drug tolerance and withdrawal effects. The same adaptive neurophysiological changes that develop in response to drug exposure and produce drug tolerance manifest themselves as withdrawal effects once the drug is removed. As the neurophysiological changes develop, tolerance increases; as they subside, the severity of the withdrawal effects decreases.
Indeed, people who risk their health by continually bingeing on high-calorie foods, risk their family life by repeated illicit sex, or risk their economic stability through compulsive gambling clearly satisfy the definition of an addict (Johnson & Kenny, 2010; Pelchat, 2009; Volkow & Wise, 2005). Although this chapter focuses on drug addiction, food, sex, and gambling addictions may be based on the same neural mechanisms.

### 15.2 Role of Learning in Drug Tolerance

An important line of psychopharmacologic research has shown that learning plays a major role in drug tolerance. In addition to contributing to our understanding of drug tolerance, this research has established that efforts to understand the effects of psychoactive drugs without considering the experience and behavior of the subjects can provide only partial answers.

Research on the role of learning in drug tolerance has focused on two phenomena: contingent drug tolerance and conditioned drug tolerance. These two phenomena are discussed in the following subsections.

#### Contingent Drug Tolerance

**Contingent drug tolerance** refers to demonstrations that tolerance develops only to drug effects that are actually experienced. Most studies of contingent drug tolerance employ the **before-and-after design**. In before-and-after experiments, two groups of subjects receive the same series of drug injections and the same series of repeated tests, but the subjects in one group receive the drug before each test of the series and those in the other group receive the drug after each test. At the end of the experiment, all subjects receive the same dose of the drug followed by the test so that the degree to which the drug disrupts test performance in the two groups can be compared.

My colleagues and I (Pinel, Mana, & Kim, 1989) used the before-and-after design to study contingent tolerance to the anticonvulsant effect of alcohol. In one study, two groups of rats received exactly the same regimen of alcohol injections: one injection every 2 days for the duration of the experiment. During the tolerance development phase, the rats in one group received each alcohol injection 1 hour before a mild convulsive amygdala stimulation so that the anticonvulsant effect of the alcohol could be experienced on each trial. The rats in the other group received their injections 1 hour after each convulsive stimulation so that the anticonvulsant effect could not be experienced. At the end of the experiment, all of the subjects received a test injection of alcohol, followed 1 hour later by a convulsive stimulation so that the amount of tolerance to the anticonvulsant effect of alcohol could be compared in the two groups. As Figure 15.3 illustrates, the rats that received alcohol on each trial before a convulsive stimulation became almost totally tolerant to alcohol’s anticonvulsant effect, whereas those that received the same injections and stimulations in the reverse order developed no tolerance whatsoever to alcohol’s anticonvulsant effect. Contingent drug tolerance has been demonstrated for many other drug effects in many species, including humans (see Poulos & Cappell, 1991; Wolgin & Jakubow, 2003).

![Contingent Tolerance](image.png)

**FIGURE 15.3** Contingent tolerance to the anticonvulsant effect of alcohol. The rats that received alcohol on each trial **before** a convulsive stimulation became tolerant to its anticonvulsant effect; those that received the same injections **after** a convulsive stimulation on each trial did not become tolerant. (Based on Pinel et al., 1989.)
Conditioned Drug Tolerance

Whereas studies of contingent drug tolerance focus on what subjects do while they are under the influence of drugs, studies of conditioned drug tolerance focus on the situations in which drugs are taken. Conditioned drug tolerance refers to demonstrations that tolerance effects are maximally expressed only when a drug is administered in the same situation in which it has previously been administered (see McDonald & Siegel, 2004; Mitchell, Basbaum, & Fields, 2000; Weise-Kelley & Siegel, 2001).

In one demonstration of conditioned drug tolerance (Crowell, Hinson, & Siegel, 1981), two groups of rats received 20 alcohol and 20 saline injections in an alternating sequence, 1 injection every other day. The only difference between the two groups was that the rats in one group received all 20 alcohol injections in a distinctive test room and the 20 saline injections in their colony room, while the rats in the other group received the alcohol in the colony room and the saline in the distinctive test room. At the end of the injection period, the tolerance of all rats to the hypothermic (temperature-reducing) effects of alcohol was assessed in both environments. As Figure 15.4 illustrates, tolerance was observed only when the rats were injected in the environment that had previously been paired with alcohol administration. There have been dozens of other demonstrations of the situational specificity of drug tolerance: The effect is large, reliable, and general.

The situational specificity of drug tolerance led Siegel and his colleagues to propose that addicts may be particularly susceptible to the lethal effects of a drug overdose when the drug is administered in a new context. Their hypothesis is that addicts become tolerant when they repeatedly self-administer their drug in the same environment and, as a result, begin taking larger and larger doses to counteract the diminution of drug effects. Then, if the addict administers the usual massive dose in an unusual situation, tolerance effects are not present to counteract the effects of the drug, and there is a greater risk of death from overdose. In support of this hypothesis, Siegel and colleagues (1982) found that many more heroin-tolerant rats died following a high dose of heroin administered in a novel environment than died in the usual injection environment. (Heroin, as you will learn later in the chapter, kills by suppressing respiration.)

Siegel views each incidence of drug administration as a Pavlovian conditioning trial in which various environmental stimuli (e.g., bars, washrooms, needles, or other addicts) that regularly predict the administration of the drug are conditional stimuli and the drug effects are unconditional stimuli. The central assumption of the theory is that conditional stimuli that predict drug administration come to elicit conditional responses opposite to the unconditional effects of the drug. Siegel has termed these hypothetical opposing conditional responses conditioned compensatory responses. The theory is that as the stimuli that repeatedly predict the effects of a drug come to elicit greater and greater conditioned compensatory responses, they increasingly counteract the unconditional effects of the drug and produce situationally specific tolerance.

Alert readers will have recognized the relation between Siegel’s theory of drug tolerance and Woods’s theory of mealtime hunger, which you learned about in Chapter 12. Stimuli that predict the homeostasis-disrupting effects of meals trigger conditioned compensatory responses to minimize

![Figure 15.4](https://www.mypsychlab.com)
a meal’s disruptive effects in the same way that stimuli that predict the homeostasis-disturbing effects of a drug trigger conditioned compensatory responses to minimize the drug’s disruptive effects.

Most demonstrations of conditioned drug tolerance have employed *exteroceptive stimuli* (external, public stimuli, such as the drug-administration environment) as the conditional stimuli. However, *interoceptive stimuli* (internal, private stimuli) are just as effective in this role. For example, both the feelings produced by the drug-taking ritual and the first mild effects of the drug experienced soon after administration can, through conditioning, come to reduce the full impact of a drug (Siegel, 2005). This point about interoceptive stimuli is important because it indicates that just thinking about a drug can evoke conditioned compensatory responses.

Although tolerance develops to many drug effects, sometimes the opposite occurs, that is, drug sensitization. *Drug sensitization*, like drug tolerance, can be situationally specific (see Arvanitogiannis, Sullivan, & Amir, 2000). For example, Anagnostaras and Robinson (1996) demonstrated the situational specificity of sensitization to the motor stimulant effects of amphetamine. They found that 10 amphetamine injections, 1 every 3 or 4 days, greatly increased the ability of amphetamine to activate the motor activity of rats—but only when the rats were injected and tested in the same environment in which they had experienced the previous amphetamine injections.

Drug withdrawal effects and conditioned compensatory responses are similar: They are both responses that are opposite to the unconditioned effect of the drug. The difference is that drug withdrawal effects are produced by elimination of the drug from the body, whereas conditioned compensatory responses are elicited by drug-predictive cues in the absence of the drug. In complex, real-life situations, it is often difficult to tell them apart.

### Thinking about Drug Conditioning

In any situation in which drugs are repeatedly administered, conditioned effects are inevitable. That is why it is particularly important to understand them. However, most theories of drug conditioning have a serious problem: They have difficulty predicting the direction of the conditioned effects. For example, Siegel’s conditioned compensatory response theory predicts that conditioned drug effects will always be opposite to the unconditioned effects of the drug, but there are many documented instances in which conditional stimuli elicit responses similar to those of the drug.

Ramsay and Woods (1997) contend that much of the confusion about conditioned drug effects stems from a misunderstanding of Pavlovian conditioning. In particular, they criticize the common assumption that the unconditional stimulus in a drug-tolerance experiment is the drug and that the unconditional response is whatever change in physiology or behavior the experimenter happens to be recording. They argue instead that the unconditional stimulus (i.e., the stimulus to which the subject reflexively reacts) is the disruption of neural functioning that has been directly produced by the drug, and that the unconditional responses are the various neurally mediated compensatory reactions to the unconditional stimulus.

This change in perspective makes a big difference. For example, in the previously described alcohol tolerance experiment by Crowell and colleagues (1981), alcohol was designated as the unconditional stimulus and the resulting hypothermia as the unconditional response. Instead, Ramsay and Woods would argue that the unconditional stimulus was the hypothermia directly produced by the exposure to alcohol, whereas the compensatory changes that tended to counteract the reductions in body temperature were the unconditional responses. The important point about all of this is that once one determines the unconditional stimulus and unconditional response, it is easy to predict the direction of the conditional response in any drug-conditioning experiment: The conditional response is always similar to the unconditional response.

### 15.3 Five Commonly Abused Drugs

This section focuses on the hazards of chronic use of five commonly abused drugs: tobacco, alcohol, marijuana, cocaine, and the opiates.

#### Tobacco

When a cigarette is smoked, nicotine—the major psychoactive ingredient of tobacco—and some 4,000 other chemicals, collectively referred to as *tar*, are absorbed through the lungs. Nicotine acts on nicotinic cholinergic receptors in the brain (see Benowitz, 2008). Tobacco is the
leading preventable cause of death in Western countries. In the United States, it contributes to 400,000 premature deaths a year—about 1 in every 5 deaths (U.S. Centers for Disease Control and Prevention, 2008b).

Because considerable tolerance develops to some of the immediate effects of tobacco, the effects of smoking a cigarette on nonsmokers and smokers can be quite different. Nonsmokers often respond to a few puffs of a cigarette with various combinations of nausea, vomiting, coughing, sweating, abdominal cramps, dizziness, flushing, and diarrhea. In contrast, smokers report that they are more relaxed, more alert, and less hungry after a cigarette.

There is no question that heavy smokers are drug addicts in every sense of the word (see Hogg & Bertrand, 2004). Can you think of any other psychoactive drug that is self-administered almost continually—even while the addict is walking along the street? The compulsive drug craving, which is the major defining feature of addiction, is readily apparent in any habitual smoker who has run out of cigarettes or who is forced by circumstance to refrain from smoking for several hours. Furthermore, habitual smokers who stop smoking experience a variety of withdrawal effects, such as depression, anxiety, restlessness, irritability, constipation, and difficulties in sleeping and concentrating.

About 70% of all people who experiment with smoking become addicted—this figure compares unfavorably with 10% for alcohol and 30% for heroin. Moreover, nicotine addiction typically develops quickly, within a few weeks (DiFranza, 2008), and only about 20% of all attempts to stop smoking are successful for 2 years or more. Twin studies (Lerman et al., 1999; True et al., 1999) confirm that nicotine addiction, like other addictions, has a major genetic component. The heritability estimate is about 65%.

The consequences of long-term tobacco use are alarming. Smoker’s syndrome is characterized by chest pain, labored breathing, wheezing, coughing, and a heightened susceptibility to infections of the respiratory tract. Chronic smokers are highly susceptible to a variety of potentially lethal lung disorders, including pneumonia, bronchitis (chronic inflammation of the bronchioles of the lungs), emphysema (loss of elasticity of the lung from chronic irritation), and lung cancer. Although the increased risk of lung cancer receives the greatest publicity, smoking also increases the risk of cancer of the larynx (voice box), mouth, esophagus, kidneys, pancreas, bladder, and stomach. Smokers also run a greater risk of developing a variety of cardiovascular diseases, which may culminate in heart attack or stroke.

Many smokers claim that they smoke despite the adverse effects because smoking reduces tension. However, smokers are actually more tense than nonsmokers: Their levels of tension are reasonably normal while they are smoking, but they increase markedly between cigarettes. Thus, the apparent relaxant effect of smoking merely reflects the temporary reversal of the stress caused by the smoker’s addiction (see Parrott, 1999). Consistent with this finding is the fact that smokers are more prone than nonsmokers to experience panic attacks (Zvolensky & Bernstein, 2005).

Sufferers from Buerger’s disease provide a shocking illustration of the addictive power of nicotine. In Buerger’s disease—which occurs in about 15 of 100,000 individuals, mostly in male smokers—the blood vessels, especially those supplying the legs, become constricted.

If a patient with this condition continues to smoke, gangrene may eventually set in. First a few toes may have to be amputated, then the foot at the ankle, then the leg at the knee, and ultimately at the hip. Somewhere along this gruesome progression gangrene may also attack the other leg. Patients are strongly advised that if they will only stop smoking, it is virtually certain that the otherwise inexorable march of gangrene up the legs will be curbed. Yet surgeons report that it is not at all uncommon to find a patient with Buerger’s disease vigorously puffing away in his hospital bed following a second or third amputation operation. (Brecher, 1972, pp. 215–216)

The adverse effects of tobacco smoke are unfortunately not restricted to those who smoke. Individuals who live or work with smokers are more likely to develop heart disease and cancer than those who don’t. Even the unborn are vulnerable (see Huizink & Mulder, 2006; Thompson, Levitt, & Stanwood, 2009). Nicotine is a teratogen (an agent that can disturb the normal development of the fetus): Smoking during pregnancy increases the likelihood of miscarriage, stillbirth, and early death of the child. And the levels of nicotine in the blood of breastfed infants are often as great as those in the blood of their smoking mothers.

If you or a loved one is a cigarette smoker, some recent findings provide both good news and bad news (see West, 2007). First the bad news: Treatments for nicotine addiction are only marginally effective—nicotine patches have been shown to help some in the short term (Shiffman & Ferguson, 2008). The good news: Many people do stop smoking, and they experience major health benefits. For example, smokers who manage to stop smoking before the age of 30 live almost as long as people who have never smoked (Doll et al., 2004).

Alcohol

Alcohol is involved in over 3% of all deaths in the United States, including deaths from birth defects, ill health, accidents, and violence (see Mokdad et al., 2004). Approximately 13 million Americans are heavy users, and about 80,000 die each year from alcohol-related diseases and accidents (U.S. Centers for Disease Control and Prevention, 2008a).
Because alcohol molecules are small and soluble in both fat and water, they invade all parts of the body. Alcohol is classified as a depressant because at moderate-to-high doses it depresses neural firing; however, at low doses it can stimulate neural firing and facilitate social interaction. Alcohol addiction has a major genetic component (McGue, 1999): Heritability estimates are about 55%, and several genes associated with alcoholism have been identified (Nurnberger & Bierut, 2007).

With moderate doses, the alcohol drinker experiences various degrees of cognitive, perceptual, verbal, and motor impairment, as well as a loss of control that can lead to a variety of socially unacceptable actions. High doses result in unconsciousness; and if blood levels reach 0.5%, there is a risk of death from respiratory depression. The telltale red facial flush of alcohol intoxication is produced by the dilation of blood vessels in the skin; this dilation increases the amount of heat that is lost from the blood to the air and leads to a decrease in body temperature (hypothermia). Alcohol is also a diuretic; that is, it increases the production of urine by the kidneys.

Alcohol, like many addictive drugs, produces both tolerance and physical dependence. The livers of heavy drinkers metabolize alcohol more quickly than do the livers of nondrinkers, but this increase in metabolic efficiency contributes only slightly to overall alcohol tolerance; most alcohol tolerance is functional. Alcohol withdrawal often produces a mild syndrome of headache, nausea, vomiting, and tremulousness, which is euphemistically referred to as a hangover.

A full-blown alcohol withdrawal syndrome comprises three phases (see De Witte et al., 2003). The first phase begins about 5 or 6 hours after the cessation of a long bout of heavy drinking and is characterized by severe tremors, agitation, headache, nausea, vomiting, abdominal cramps, profuse sweating, and sometimes hallucinations. The defining feature of the second phase, which typically occurs between 15 and 30 hours after cessation of drinking, is convulsive activity. The third phase, which usually begins a day or two after the cessation of drinking and lasts for 3 or 4 days, is called delirium tremens (DTs). The DTs are characterized by disturbing hallucinations, bizarre delusions, agitation, confusion, hyperthermia (high body temperature), and tachycardia (rapid heartbeat). The convulsions and the DTs produced by alcohol withdrawal can be lethal.

Alcohol attacks almost every tissue in the body (see Anderson et al., 1993). Chronic alcohol consumption produces extensive brain damage. This damage is produced both directly (see Mechtcheriakov et al., 2007) and indirectly. For example, you learned in Chapter 1 that alcohol indirectly causes Korsakoff’s syndrome (a neuropsychological disorder characterized by memory loss, sensory and motor dysfunction, and, in its advanced stages, severe dementia) by inducing thiamine deficiency, and it also indirectly causes brain damage by increasing susceptibility to stroke (Rehm, 2006). Alcohol affects the brain function of drinkers in other ways, as well. For example, it reduces the flow of calcium ions into neurons by acting on ion channels; it interferes with the function of second messengers inside neurons; it disrupts GABAergic and glutaminergic transmission; and it triggers apoptosis (see Farber & Olney, 2003; Ikonomidou et al., 2000).

Chronic alcohol consumption also causes extensive scarring, or cirrhosis, of the liver, which is the major cause of death among heavy alcohol users. Alcohol erodes the muscles of the heart and thus increases the risk of heart attack. It irritates the lining of the digestive tract and, in so doing, increases the risk of oral and liver cancer, stomach ulcers, pancreatitis (inflammation of the pancreas), and gastritis (inflammation of the stomach). And not to be forgotten is the carnage that alcohol produces from accidents on our roads, in our homes, in our workplaces, and at recreational sites—in the United States, over 20,000 people die each year in alcohol-related traffic accidents alone.

Many people assume that the adverse effects of alcohol occur only in people who drink a lot—they tend to define “a lot” as “much more than they themselves consume.” But they are wrong. Several large-scale studies have shown that even low-to-moderate regular drinking (a drink or two per day) is associated with elevated levels of most cancers, including breast, prostate, ovary, and skin cancer (Allen et al., 2009; Bagnardi et al., 2001; Benedetti, Parent, & Siemiatycki, 2009).

Like nicotine, alcohol readily penetrates the placental membrane and acts as a teratogen. The result is that the offspring of mothers who consume substantial quantities of alcohol during pregnancy can develop fetal alcohol syndrome (FAS)—see Calhoun and Warren (2007). The FAS child suffers from some or all of the following symptoms: brain damage, mental retardation, poor coordination, poor muscle tone, low birth weight, retarded growth, and/or physical deformity. Because alcohol can disrupt brain development in so many ways (e.g., by disrupting neurotrophic support, by disrupting the production of...
cell-adhesion molecules, or by disrupting normal patterns of apoptosis), there is no time during pregnancy when alcohol consumption is safe (see Farber & Olney, 2003; Guerri, 2002). Moreover, there seems to be no safe amount. Although full-blown FAS is rarely seen in the babies of mothers who never had more than one drink a day during pregnancy, children of mothers who drank only moderately while pregnant are sometimes found to have a variety of cognitive problems, even though they are not diagnosed with FAS (see Korkman, Kettunen, & Autti-Ramo, 2003).

There is no cure for alcoholism; however, disulfiram (Antabuse) can help reduce alcohol consumption under certain conditions. Disulﬁram is a drug that interferes with the metabolism of alcohol and produces an accumulation in the bloodstream of acetaldehyde (one of alcohol’s breakdown products). High levels of acetaldehyde produce flushing, dizziness, headache, vomiting, and difficulty breathing; thus, a person who is medicated with disulfiram cannot drink much alcohol without feeling ill. Unfortunately, disulfiram is not a cure for alcoholism because alcoholics simply stop taking it when they return to drinking alcohol. However, treatment with disulfiram can be useful in curtailing alcohol consumption in hospital or outpatient environments, where patients take the medication each day under supervision (Brewer, 2007).

One of the most widely publicized findings about alcohol is that moderate drinking reduces the risk of coronary heart disease. This conclusion is based on the finding that the incidence of coronary heart disease is less among moderate drinkers than among abstainers. You learned in Chapter 1 about the difficulty in basing causal interpretations on correlational data, and researchers worked diligently to identify and rule out factors other than the alcohol that might protect moderate drinkers from coronary heart disease. They seemed to rule out every other possibility. However, a thoughtful new analysis has led to a different conclusion. Let me explain. In a culture in which alcohol consumption is the norm, any large group of abstainers will always include some people who have stopped drinking because they are ill—perhaps this is why abstainers have more heart attacks than moderate drinkers. This hypothesis was tested by including in a meta-analysis only those studies that used an abstainers control group consisting of individuals who had never consumed alcohol. This meta-analysis indicated that alcohol in moderate amounts does not prevent coronary heart disease; that is, moderate drinkers did not suffer less coronary heart disease than lifelong abstainers (Fillmore et al., 2006; Stockwell et al., 2007).

**Marijuana**

Marijuana is the name commonly given to the dried leaves and flowers of *Cannabis sativa*—the common hemp plant. Approximately 2 million Americans have used marijuana in the last month. The usual mode of consumption is to smoke these leaves in a **joint** (a cigarette of marijuana) or a pipe; but marijuana is also effective when ingested orally, if first baked into an oil-rich substrate, such as a chocolate brownie, to promote absorption from the gastrointestinal tract.

The psychoactive effects of marijuana are largely attributable to a constituent called **THC** (delta-9-tetrahydrocannabinol). However, marijuana contains over 80 **cannabinoids** (chemicals of the same chemical class as THC), which may also be psychoactive. Most of the cannabinoids are found in a sticky resin covering the leaves and flowers of the plant; this resin can be extracted and dried to form a dark corklike material called **hashish**. Hashish can be further processed into an extremely potent product called **hash oil**.

Written records of marijuana use go back 6,000 years in China, where its stems were used to make rope, its seeds were used as a grain, and its leaves and flowers were used for their psychoactive and medicinal effects. In the Middle Ages, cannabis cultivation spread into Europe, where it was grown primarily for the manufacture of rope. During the period of European imperialism, rope was in high demand for sailing vessels, and the American colonies responded to this demand by growing cannabis as a cash crop. George Washington was one of the more notable cannabis growers.

The practice of smoking the leaves of *Cannabis sativa* and the word **marijuana** itself seem to have been introduced to the southern United States in the early part of the 20th century. In 1926, an article appeared in a New Orleans newspaper exposing the “menace of marijuana,” and soon similar stories were appearing in newspapers all over the United States claiming that marijuana turns people into violent, drug-crazed criminals. The misrepresentation of the effects of marijuana by the news media led to the rapid enactment of laws against the drug. In many states, marijuana was legally classified a **narcotic** (a legal term generally used to refer to opiates), and punishment for its use was dealt out accordingly. Marijuana bears no resemblance to opiate narcotics.
Popularization of marijuana smoking among the middle and upper classes in the 1960s stimulated a massive program of research. One of the difficulties in studying the effects of marijuana is that they are subtle, difficult to measure, and greatly influenced by the social situation:

At low, usual “social” doses, the intoxicated individual may experience an increased sense of well-being: initial restlessness and hilarity followed by a dreamy, carefree state of relaxation; alteration of sensory perceptions including expansion of space and time; and a more vivid sense of touch, sight, smell, taste, and sound; a feeling of hunger, especially a craving for sweets; and subtle changes in thought formation and expression. To an unknowing observer, an individual in this state of consciousness would not appear noticeably different. (National Commission on Marijuana and Drug Abuse, 1972, p. 68)

Although the effects of typical social doses of marijuana are subtle, high doses do impair psychological functioning. At high doses, short-term memory is impaired, and the ability to carry out tasks involving multiple steps to reach a specific goal declines. Speech becomes slurred, and meaningful conversation becomes difficult. A sense of unreality, emotional intensification, sensory distortion, feelings of paranoia, and motor impairment are also common.

Some people do become addicted to marijuana, but its addiction potential is low. Most people who use marijuana do so only occasionally, with only about 10% of them using daily; moreover, most people who try marijuana do so in their teens and curtail their use by their 30s or 40s (see Room et al., 2010). Tolerance to marijuana develops during periods of sustained use; however, obvious withdrawal symptoms (e.g., nausea, diarrhea, sweating, chills, tremor, sleep disturbance) are rare, except in contrived laboratory situations in which massive oral doses are administered.

What are the health hazards of marijuana use? Two have been documented. First, the few marijuana smokers who do smoke it regularly for long periods (estimated to be about 10%) tend to develop respiratory problems (see Aldington et al., 2008; Brambilla & Colonna, 2008; Tetrault et al., 2007): cough, bronchitis, and asthma. Second, because marijuana produces *tachycardia* (elevated heart rate), single large doses can trigger heart attacks in susceptible individuals who have previously suffered a heart attack.

Although many people believe that marijuana causes brain damage, almost all efforts to document brain damage in marijuana users have proven negative. The one exception is an MRI study by Yücel and colleagues (2008), who studied the brains of 15 men who had an extremely high level of marijuana exposure—at least 5 joints per day for almost 20 years. These men had hippocampuses and amygdalae with reduced volumes. Because this finding is the single positive report in a sea of negative findings, it needs to be replicated. Furthermore, because the finding is correlational, it cannot prove that extremely high doses of marijuana can cause brain damage—one can just as easily conclude that brain damage predisposes individuals to pathological patterns of marijuana use.

Because it has been difficult to directly document brain damage in marijuana users, many studies have taken an indirect approach: They have attempted to document permanent memory loss in marijuana users—the assumption being that such loss would be indicative of brain damage. Many studies have documented memory deficits in marijuana users, but these deficits tend to be acute effects associated with marijuana intoxication that disappear after a few weeks of abstinence. Indeed, there seems to be a general consensus that marijuana use is not associated with substantial permanent memory problems (see Grant et al., 2003; Jager et al., 2006; Iversen, 2005). There have been reports (see Medina et al., 2007) that people who become heavy marijuana users in adolescence display memory and other cognitive deficits; however, Pope and colleagues (2003) found that adolescents with lower verbal intelligence scores are more likely to become heavy marijuana users, which likely accounts for the poorer cognitive performance.

Several correlational studies have found that heavy marijuana users are more likely to be diagnosed with schizophrenia (see Arseneault et al., 2004). The best of these studies followed a group of Swedish males for 25 years (Zammit et al., 2002); after some of the obvious confounds had been controlled, there was a higher incidence of schizophrenia among heavy marijuana users. This correlation has led some to conclude that marijuana causes schizophrenia, but, as you know, correlational evidence cannot prove causation. In this case, it is also possible that youths in the early developmental stages of schizophrenia have a particular attraction and/or susceptibility to marijuana; however, more research is required to understand the causal factors involved in this correlation (see Pollack & Reurer, 2007). In the meantime, individuals with a history of schizophrenia in their families should avoid marijuana.

THC has been shown to have several therapeutic effects (see Karanian & Bahr, 2006). Since the early 1990s, it has been widely used to suppress nausea and vomiting in cancer patients and to stimulate the appetite of AIDS patients (see DiMarzo & Mattias, 2005). THC has also been shown to block seizures; to dilate the bronchioles of asthmatics; to decrease the severity of *glaucoma* (a disorder characterized by an increase in the pressure of the fluid inside the eye); and to reduce anxiety, some kinds of pain, and the symptoms of multiple sclerosis (Agarwal et al., 2007; Nicoll & Alger, 2004; Page et al., 2003). Medical use of THC does not appear to be associated with adverse side effects (Degenhardt & Hall, 2008; Wang et al., 2008).

Research on THC changed irrevocably in the early 1990s with the discovery of two receptors for it in the brain: CB₁ and CB₂. CB₁ turned out to be the most prevalent...
G-protein–linked receptor in the brain (see Chapter 4); CB₂ is found in the brain stem and in the cells of the immune system (see Van Sickle et al., 2005). But why are there THC receptors in the brain? They could hardly have evolved to mediate the effects of marijuana smoking. This puzzle was quickly solved with the discovery of a class of endogenous cannabinoid neurotransmitters: the endocannabinoids (see Harkany, Mackie, & Doherty, 2008). The first endocannabinoid neurotransmitter to be isolated and characterized was named **anandamide**, from a word that means “internal bliss” (see Nicoll & Alger, 2004). I cannot end this discussion of marijuana (Cannabis sativa) without telling you the following story:

You can imagine how surprised I was when my colleague went to his back door, opened it, and yelled, “Sativa, here Sativa, dinner time.”

“What was that you called your dog?” I asked as he returned to his beer.

“Sativa,” he said. “The kids picked the name. I think they learned about it at school; a Greek goddess or something. Pretty, isn’t it? And catchy too: Every kid on the street seems to remember her name.”

“Yes,” I said. “Very pretty.”

### Cocaine and Other Stimulants

**Stimulants** are drugs whose primary effect is to produce general increases in neural and behavioral activity. Although stimulants all have a similar profile of effects, they differ greatly in their potency. Coca-Cola is a mild commercial stimulant preparation consumed by many people around the world. Today, its stimulant action is attributable to **caffeine**, but when it was first introduced, “the pause that refreshes” packed a real wallop in the form of small amounts of cocaine. **Cocaine** and its derivatives are the most commonly abused stimulants, and thus they are the focus of this discussion.

Cocaine is prepared from the leaves of the coca bush, which grows primarily in Peru and Bolivia. For centuries, a crude extract called **coca paste** has been made directly from the leaves and eaten. Today, it is more common to treat the coca paste and extract **cocaine hydrochloride**, the nefarious white powder that is referred to simply as **cocaine** and typically consumed by snorting or by injection. Cocaine hydrochloride may be converted to its base form by boiling it in a solution of baking soda until the water has evaporated. The impure residue of this process is **crack,** which is a potent, cheap, smokable form of cocaine. However, because crack is impure, variable, and consumed by smoking, it is difficult to study, and most research on cocaine derivatives has thus focused on pure cocaine hydrochloride. Approximately 36 million Americans have used cocaine or crack (Substance Abuse and Mental Health Services Administration [SAMSHA], 2009).

Cocaine hydrochloride is an effective local anesthetic and was once widely prescribed as such until it was supplanted by synthetic analogues such as **procaine** and **lidocaine.** It is not, however, cocaine’s anesthetic actions that are of interest to users. People eat, smoke, snort, or inject cocaine or its derivatives in order to experience its psychological effects. Users report being swept by a wave of well-being; they feel self-confident, alert, energetic, friendly, outgoing, fidgety, and talkative; and they have less than their usual desire for food and sleep.

Cocaine addicts tend to go on so-called **cocaine sprees,** binges in which extremely high levels of intake are maintained for periods of a day or two. During a cocaine spree, users become increasingly tolerant to the euphoria-producing effects of cocaine. Accordingly, larger and larger doses are often administered. The spree usually ends when the cocaine is gone or when it begins to have serious toxic effects. The effects of cocaine sprees include sleeplessness, tremors, nausea, hyperthermia, and psychotic behavior, which is called **cocaine psychosis** and has often been mistakenly diagnosed as **paranoid schizophrenia.** During cocaine sprees, there is a risk of loss of consciousness, seizures, respiratory arrest, heart attack, or stroke (Kokkinos & Levine, 1993). Although tolerance develops to most effects of cocaine (e.g., to the euphoria), repeated cocaine exposure sensitizes subjects (i.e., makes them even more responsive) to its motor and convulsive effects (see Robinson & Berridge, 1993). The withdrawal effects triggered by abrupt termination of a cocaine spree are relatively mild. Common cocaine withdrawal symptoms include a negative mood swing and insomnia.

Cocaine and its various derivatives are not the only commonly abused stimulants. **Amphetamine** (speed) and its relatives also present major health problems. Amphetamine has been in wide illicit use since the 1960s. It is usually consumed orally in the potent form called **lisdexamfetamine** (OxyContin), which has been marketed as a treatment for attention-deficit/hyperactivity disorder (ADHD). Amphetamines are potent stimulants that act on the dopamine and norepinephrine systems in the brain (see Chapter 12). Their effects include increased alertness, energy, and mood. However, they can also produce paranoid delusions, hallucinations, and other psychological effects. At high doses, amphetamines can cause severe agitation and even psychosis. The long-term use of amphetamines can lead to tolerance, dependence, and addiction. However, the effects of amphetamines are generally short-lived, and users often experience a crash, or “letdown,” after the initial high wears off. This crash can be intense and may lead to feelings of depression and fatigue. The use of amphetamines has been associated with increased risk of heart attack, stroke, and other cardiovascular diseases. Despite these risks, amphetamines remain a widely abused substance, with millions of users worldwide.
d-amphetamine (dextroamphetamine). The effects of d-amphetamine are comparable to those of cocaine; for example, it produces a syndrome of psychosis called \textit{amphetamine psychosis}.

In the 1990s, d-amphetamine was supplanted as the favored amphetamine-like drug by several more potent relatives. One is \textit{methamphetamine}, or “meth” (see Cho, 1990), which is commonly used in its even more potent, smokable, crystalline form (ice or crystal). Another potent relative of amphetamine is \textit{3,4-methylenedioxymethamphetamine} (MDMA, or ecstasy), which is taken orally (see Baylen & Rosenberg, 2006).

The primary mechanism by which cocaine and its derivatives exert their effects is the blockade of \textit{dopamine transporters}, molecules in the presynaptic membrane that normally remove dopamine from synapses and transfer it back into presynaptic neurons. Other stimulants increase the release of monoamines into synapses (Sulzer et al., 2005).

Do stimulants have long-term adverse effects on the health of habitual users? There is mounting evidence that they do. Users of MDMA have deficits in the performance of various neuropsychological tests; they have deficiencies in various measures of dopaminergic and serotonergic function; and functional brain imaging during tests of executive functioning, inhibitory control, and decision making often reveals abnormalities in many areas of the cortex and limbic system (see Aron & Paulus, 2007; Baicy & London, 2007; Chang et al., 2007; Volz, Fleckenstein, & Hanson, 2007). The strongest evidence that methamphetamine damages the brain comes from a structural MRI study that found decreases in volume of various parts of the brains of persons who had used methamphetamine for an average of 10 years (Thompson et al., 2004)—the reductions in cortical volume are illustrated in Figure 15.5. Controlled experiments on nonhumans have confirmed the adverse effects of stimulants on brain function (see McCann & Ricaurte, 2004).

Although research on the health hazards of stimulants has focused on brain pathology, there is also evidence of heart pathology—many methamphetamine-dependent patients have been found to have electrocardiographic abnormalities (Haning & Goebert, 2007). Also, many behavioral, neurological, and cardiovascular problems have been observed in infants born to mothers who have used stimulants while pregnant (see Harvey, 2004).

The \textbf{Opiates: Heroin and Morphine}

Opium—the dried form of sap exuded by the seed pods of the opium poppy—has several psychoactive ingredients. Most notable are \textit{morphine} and \textit{codeine}, its weaker relative. Morphine, codeine, and other drugs that have similar structures or effects are commonly referred to as \textit{opiates}. The opiates exert their effects by binding to receptors whose normal function is to bind to endogenous opiates. The endogenous opiate neurotransmitters that bind to such receptors are of two classes: \textit{endorphins} and \textit{enkephalins} (see Chapter 4).

The opiates have a Jekyll-and-Hyde character. On their Dr. Jekyll side, the opiates are effective as \textit{analgesics} (painkillers; see Watkins et al., 2005); they are also extremely effective in the treatment of cough and diarrhea. But, unfortunately, the kindly Dr. Jekyll brings with him the evil Mr. Hyde—the risk of addiction.
The practice of eating opium spread from the Middle East sometime before 4000 B.C. Three historic events fanned the flame of opiate addiction. First, in 1644, the Emperor of China banned tobacco smoking, and this contributed to a gradual increase in opium smoking in China, spurred on by the smuggling of opium into China by the British East India Company. Because smoking opium has a greater effect on the brain than does eating it, many more people became addicted. Second, morphine, the most potent constituent of opium, was isolated in 1803, and it became available commercially in the 1830s. Third, the hypodermic needle was invented in 1856, and soon the injured were introduced to morphine through a needle.

Until the early part of the 20th century, opium was available legally in many parts of the world, including Europe and North America. Indeed, opium was an ingredient in cakes, candies, and wines, as well as in a variety of over-the-counter medicinal offerings. Opium potions such as laudanum (a very popular mixture of opium and alcohol), Godfrey’s Cordial, and Dalby’s Carminative were very popular. (The word carminative should win first prize for making a sow’s ear at least sound like a silk purse: A carminative is a drug that expels gas from the digestive tract, thereby reducing stomach cramps and flatulence. Flatulence is the obvious pick for second prize.) There were even over-the-counter opium potions just for baby—such as Mrs. Winslow’s Soothing Syrup and the aptly labeled Street’s Infant Quietness. Although pure morphine required a prescription at the time, physicians prescribed it for so many different maladies that morphine addiction was common among those who could afford a doctor.

The Harrison Narcotics Act, passed in 1914, made it illegal to sell or use opium, morphine, or cocaine in the United States—although morphine and its analogues are still legally prescribed for their medicinal properties. However, the act did not include the semisynthetic opiate heroin. Heroin was synthesized in 1870 by the addition of two acetyl groups to the morphine molecule, which greatly increased its ability to penetrate the blood–brain barrier. In 1898, heroin was marketed by the Bayer Drug Company; it was freely available without prescription and was widely advertised as a superior kind of aspirin. Tests showed that it was a more potent analgesic than morphine and that it was less likely to induce nausea and vomiting. Moreover, the Bayer Drug Company, on the basis of flimsy evidence, claimed that heroin was not addictive; this is why it was not covered by the Harrison Narcotics Act. The consequence of omitting heroin from the Harrison Narcotics Act was that opiate addicts in the United States, forbidden by law to use opium or morphine, turned to the readily available and much more potent heroin—and the flames of addiction were further fanned. In 1924, the U.S. Congress made it illegal for anybody to possess, sell, or use heroin. Unfortunately, the laws enacted to stamp out opiate addiction in the United States have been far from successful: An estimated 136,000 Americans currently use heroin (National Survey on Drug Use and Health, 2005), and organized crime flourishes on the proceeds.

The effect of opiates most valued by addicts is the rush that follows intravenous injection. The heroin rush is a wave of intense abdominal, orgasmic pleasure that evolves into a state of serene, drowsy euphoria. Many opiate users, drawn by these pleasurable effects, begin to use the drug more and more frequently. Then, once they reach a point where they keep themselves drugged much of the time, tolerance and physical dependence develop and contribute to the problem. Opiate tolerance encourages addicts to progress to higher doses, to more potent drugs (e.g., heroin), and to more direct routes of administration (e.g., IV injection); and physical dependence adds to the already high motivation to take the drug.

The classic opiate withdrawal syndrome usually begins 6 to 12 hours after the last dose. The first withdrawal sign is typically an increase in restlessness; the addict begins to pace and fidget. Watering eyes, running nose, yawning, and sweating are also common during the early stages of opiate withdrawal. Then, the addict often falls into a fitful sleep, which typically lasts for several hours. Once the person wakes up, the original symptoms may be joined in extreme cases by chills, shivering, profuse sweating, gooseflesh, nausea, vomiting, diarrhea, cramps, dilated pupils, tremor, and muscle pains and spasms. The gooseflesh skin and leg spasms of the opiate withdrawal syndrome are the basis for the expressions “going cold turkey” and “kicking the habit.” The symptoms of opiate withdrawal are typically most severe in the second or third day after the last injection, and by the seventh day they have all but disappeared. In short, opiate withdrawal is about as serious as a bad case of the flu:

Opiate withdrawal is probably one of the most misunderstood aspects of drug use. This is largely because of the image of withdrawal that has been portrayed in the movies and popular literature for many years. . . . Few addicts . . . take enough drug to cause the . . . severe withdrawal symptoms that are shown in the movies. Even in its most severe form, however, opiate withdrawal is not as dangerous or terrifying as withdrawal from barbiturates or alcohol. (McKim, 1986, p. 199)

Although opiates are highly addictive, the direct health hazards of chronic exposure are surprisingly minor. The main direct risks are constipation, pupil constriction, menstrual irregularity, and reduced libido (sex drive). Many opiate addicts have taken pure heroin or morphine for years with no serious ill effects. In fact, opiate addiction is more prevalent among doctors, nurses, and dentists than among other professionals (e.g., Brewster, 1986):

An individual tolerant to and dependent upon an opiate who is socially or financially capable of obtaining an adequate supply of good quality drug, sterile syringes and needles, and other paraphernalia may maintain his or her...
proper social and occupational functions, remain in fairly good health, and suffer little serious incapacitation as a result of the dependence. (Julien, 1981, p. 117)

One such individual was Dr. William Stewart Halsted, one of the founders of Johns Hopkins Medical School and one of the most brilliant surgeons of his day . . . known as “the father of modern surgery.” And yet, during his career he was addicted to morphine, a fact that he was able to keep secret from all but his closest friends. In fact, the only time his habit caused him any trouble was when he was attempting to reduce his dosage. (McKim, 1986, p. 197)

Most medical risks of opiate addiction are indirect—that is, not entirely attributable to the drug itself. Many of the medical risks arise out of the battle between the relentless addictive power of opiates and the attempts of governments to eradicate addiction by making opiates illegal. The opiate addicts who cannot give up their habit—treatment programs report success rates of only about 10%—are caught in the middle. Because most opiate addicts must purchase their morphine and heroin from illicit dealers at greatly inflated prices, those who are not wealthy become trapped in a life of poverty and petty crime. They are poor, they are undernourished, they receive poor medical care, they are often driven to prostitution, and they run great risk of contracting AIDS and other infections (e.g., hepatitis, syphilis, and gonorrhea) from unsafe sex and unsterile needles. Moreover, they never know for sure what they are injecting; Some street drugs are poorly processed, and virtually all have been cut (stretched by the addition of some similar-appearing substance) to some unknown degree.

Death from heroin overdose is a serious problem—high doses of heroin kill by suppressing breathing (Megarbene et al., 2005). However, death from heroin overdose is not well understood. The following are three points of confusion:

- Medical examiners often attribute death to heroin overdose without assessing blood levels of heroin. Careful toxicological analysis at autopsy often reveals that this diagnosis is questionable (Poulin, Stein, & Butt, 2000). In many cases, the deceased have low levels of heroin in the blood and high levels of other CNS depressants such as alcohol and benzodiazepines. In short, many so-called heroin overdose deaths appear to be a product of drug interaction (Darke et al., 2000; Darke & Zador, 1996; Mirakbari, 2004).
- Some deaths from heroin overdose are a consequence of its legal status. Because addicts are forced to buy their drugs from criminals, they never know for sure what they are buying. Reports of death from heroin overdose occur when a shipment of heroin hits the street that has been cut by a toxic substance or when the heroin is more pure than normal (Darke et al., 1999; McGregor et al., 1998).
- In the United States, deaths from opiate overdose have increased precipitously in the last few years, and many people attribute this increase to heroin. However, the sharp increase is almost entirely due to legal synthetic opioid analgesics such as Oxycontin and Lorcet (Manchikanti, 2007; Paulozzi, Budnitz, & Xi, 2006).

The primary treatment for heroin addiction in most countries is methadone. Ironically, methadone is itself an opiate with many of the same adverse effects as heroin. However, because methadone produces less pleasure than heroin, the strategy has been to block heroin withdrawal effects with methadone and then maintain addicts on methadone until they can be weaned from it. Methadone replacement has been shown to improve the success rate of some treatment programs, but its adverse effects and the high drop-out rates from such programs are problematic (see Zador, 2007). Buprenorphine is an alternative treatment for heroin addiction. Buprenorphine has a high and long-lasting affinity for opiate receptors and thus blocks the effects on the brain of other opiates, without producing powerful euphoria. Studies suggest that it is as effective as methadone (see Davids & Gaspar, 2004; Gerra et al., 2004).

In 1994, the Swiss government took an alternative approach to the problem of heroin addiction—despite substantial opposition from the Swiss public. It established a series of clinics in which, as part of a total treatment package, Swiss heroin addicts could receive heroin injections from a physician for a small fee. The Swiss government wisely funded a major research program to evaluate the clinics (see Gschwend et al., 2002). The results have been uniformly positive. Once they had a reliable source of heroin, most addicts gave up their criminal lifestyles, and their health improved once they were exposed to the specialized medical and counseling staff at the clinics. Many addicts returned to their family and jobs, and many opted to reduce or curtail their heroin use. As a result, addicts are no longer a presence in Swiss streets and parks; drug-related crime has substantially declined, and the physical and social well-being of the addicts has greatly improved. Furthermore, the number of new heroin addicts has declined, apparently because once addiction becomes treated as an illness, it becomes less cool (see Brehmer & Iten, 2001; De Preux, Dubois-Arber, & Zobel, 2004; Gschwend et al., 2003; Nord & Stohler, 2006; Rehm et al., 2001).

These positive results have led to the establishment of similar experimental programs in other countries (e.g., Canada, Norway, Netherlands, and Germany) with similar success (see Skeie et al., 2008; Yan, 2009). Furthermore, safe injection facilities have managed to reduce the spread of infection and death from heroin overdose in many cities (e.g., Milloy et al., 2008). Given the unqualified success of such programs in dealing with the drug problem, it is interesting to consider why some governments have not adopted them (see Fischer et al., 2007). What do you think?

Comparison of the Hazards of Tobacco, Alcohol, Marijuana, Cocaine, and Heroin

One way of comparing the adverse effects of tobacco, alcohol, marijuana, cocaine, and heroin is to compare the prevalence of their use in society as a whole. In terms of this criterion, it is clear that tobacco and alcohol have a greater negative impact than do marijuana, cocaine, and heroin (see Figure 15.6). Another method of comparison is one based on death rates: Tobacco has been implicated in the deaths of approximately 400,000 Americans per year; alcohol, in approximately 80,000 per year; and all other drugs combined, in about 25,000 per year.

But what about the individual drug user? Who is taking greater health risks: the cigarette smoker, the alcohol drinker, the marijuana smoker, the cocaine user, or the heroin user? You now have the information to answer this question. Complete the Scan Your Brain, which will help you appreciate the positive impact that studying biopsychology is having on your understanding of important issues. Would you have ranked the health risks of these drugs in the same way before you began this chapter? How have the laws, or lack thereof, influenced the hazards associated with the five drugs?
This section of the chapter introduces two diametrically different ways of thinking about an addiction: Are addicts driven to take drugs by an internal need, or are they drawn to take drugs by the anticipated positive effects? I am sure you will recognize, after having read the preceding chapters, that this is the same fundamental question that has been the focus of biopsychological research on the motivation to eat and sleep.

**Physical-Dependence and Positive-Incentive Perspectives of Addiction**

Early attempts to explain the phenomenon of drug addiction attributed it to physical dependence. According to various physical-dependence theories of addiction, physical dependence traps addicts in a vicious circle of drug taking and withdrawal symptoms. The idea was that drug users whose intake has reached a level sufficient to induce physical dependence are driven by their withdrawal symptoms to self-administer the drug each time they attempt to curtail their intake.

Early drug addiction treatment programs were based on the physical-dependence perspective. They attempted to break the vicious circle of drug taking by gradually withdrawing drugs from addicts in a hospital environment. Unfortunately, once discharged, almost all detoxified addicts return to their former drug-taking habits—detoxified addicts are addicts who have no drugs in their bodies and who are no longer experiencing withdrawal symptoms.

The failure of detoxification as a treatment for addiction is not surprising, for two reasons. First, some highly addictive drugs, such as cocaine and amphetamines, do not produce severe withdrawal distress (see Gawin, 1991). Second, the pattern of drug taking routinely displayed by many addicts involves an alternating cycle of binges and detoxification (Mello & Mendelson, 1972). There are a variety of reasons for this pattern of drug use. For example, some addicts adopt it because weekend binges are compatible with their work schedules, others adopt it because they do not have enough money to use drugs continuously, others have it forced on them because their binges often land them in jail, and others have it forced on them by their repeated unsuccessful efforts to shake their habit. However, whether detoxification is by choice or necessity, it does not stop addicts from renewing their drug-taking habits (see Leshner, 1997).

As a result of these problems with physical-dependence theories of addiction, a different approach began to predominate in the 1970s and 1980s (see Higgins, Heil, & Lussier, 2004). This approach was based on the assumption that most addicts take drugs not to escape or to avoid the unpleasant consequences of withdrawal, but rather to obtain the drugs’ positive effects. Theories of addiction based on this premise are called positive-incentive theories of addiction. They hold that the primary factor in most cases of addiction is the craving for the positive-incentive (expected pleasure-producing) properties of the drug.

There is no question that physical dependence does play a role in addiction: Addicts do sometimes consume the drug to alleviate their withdrawal symptoms. However, most researchers now assume that the primary factor in addiction is the drugs’ hedonic (pleasurable) effects (see Cardinal & Everitt, 2004; Everitt, Dickinson, & Robbins, 2001). All drugs with addiction potential have some pleasurable effects for users.

**From Pleasure to Compulsion: Incentive-Sensitization Theory**

To be useful, positive-incentive theories of drug addiction need to offer explanations for two puzzling aspects of drug addiction. First, they must explain why there is often such a big difference between the hedonic value of drug taking and the positive-incentive value of drug taking.

---

**FIGURE 15.6** Prevalence of drug use in the United States. Figures are based on a survey of people 12 years of age and over who live in households and used the drug in question at least once in the last month. (Based on National Survey on Drug Use and Health, 2005.)
Positive-incentive value refers specifically to the anticipated pleasure associated with an action (e.g., taking a drug), whereas hedonic value refers to the amount of pleasure that is actually experienced. Addicts often report a huge discrepancy between them: Although they are compulsively driven to take their drug by its positive-incentive value (i.e., by the anticipated pleasure), taking the drug is often not as pleasurable as it once was (see Ahmed, 2004; Redish, 2004).

The second challenge faced by positive-incentive theories of drug addiction is that they must explain the process that transforms a drug user into a drug addict. Many people periodically use addictive drugs and experience their hedonic effects without becoming addicted to them (see Everitt & Robbins, 2005; Kreek et al., 2005). What transforms some drug users into compulsive users, or addicts?

The incentive-sensitization theory of drug addiction meets these two challenges (see Berridge, Robinson, & Aldridge, 2009). The central tenet of this theory is that the positive-incentive value of addictive drugs increases (i.e., is sensitized) with drug use (see Miles et al., 2004). Robinson and Berridge (2003) have suggested that in addiction-prone individuals, the use of a drug sensitizes the drug’s positive-incentive value, thus rendering such individuals highly motivated to seek and consume the drug. A key point of Robinson and Berridge’s incentive-sensitization theory is that it isn’t the pleasure (liking) of taking the drug that is the basis of addiction; it is the anticipated pleasure (wanting) of drug taking (i.e., the drug’s positive-incentive value). Initially, a drug’s positive-incentive value is closely tied to its pleasurable effects; but tolerance often develops to the pleasurable effects, whereas the addict’s wanting for the drug is sensitized. Thus, in chronic addicts, the positive-incentive value of the drug is often out of proportion with the pleasure actually derived from it: Many addicts are miserable, their lives are in ruins, and the drug effects are not that great anymore; but they crave the drug more than ever.

Relapse and Its Causes

The most difficult problem in treating drug addicts is not getting them to stop using their drug. The main problem is preventing those who stop from relapsing. The propensity to relapse (to return to one’s drug taking habit after a period of voluntary abstinence), even after a long period of voluntary abstinence, is a hallmark of addiction. Thus, understanding the causes of relapse is one key to understanding addiction and its treatment.

Three fundamentally different causes of relapse in drug addicts have been identified (see Shaham & Hope, 2005):

- Many therapists and patients point to stress as a major factor in relapse. The impact of stress on drug taking was illustrated in a dramatic fashion by the marked increases in cigarette and alcohol consumption that occurred among New Yorkers following the terrorist attacks of September 11, 2001.
- Another cause of relapse in drug addicts is drug priming (a single exposure to the formerly abused drug). Many addicts who have abstained for many weeks, and thus feel that they have their addiction under control, sample their formerly abused drug just once and are immediately plunged back into full-blown addiction.
- A third cause of relapse in drug addicts is exposure to environmental cues (e.g., people, times, places, or objects) that have previously been associated with drug taking (see Concklin, 2006; Di Ciano & Everitt, 2003). Such environmental cues have been shown to precipitate relapse. The fact that the many U.S. soldiers who became addicted to heroin while fighting in the Vietnam War easily shed their addiction when they returned home has been attributed to their removal from that drug-associated environment.

Explanation of the effects of environmental cues on relapse is related to our discussion of conditioned drug tolerance earlier in the chapter (see Kauer & Malenka, 2007). You may recall that cues that predict drug exposure come to elicit conditioned compensatory responses through a Pavlovian conditioning mechanism, and because conditioned compensatory responses are usually opposite to the original drug effects, they produce tolerance. The point here is that these same conditioned compensatory responses seem to increase craving in abstinent drug addicts and, in so doing, trigger relapse. Moreover, because interoceptive cues have been shown to function as conditional stimuli in conditioned tolerance experiments, they can also induce craving—that is why just thinking about drugs is enough to induce craving and relapse. Because susceptibility to relapse is a defining feature of drug addicts, conditioned drug responses play a major role in most modern theories of drug addiction (see Day & Carelli, 2007; Hellemans, Dickinson, & Everitt, 2006; Hyman, Malenka, & Nestler, 2006).
Intracranial Self-Stimulation and the Pleasure Centers of the Brain

Rats, humans, and many other species will administer brief bursts of weak electrical stimulation to specific sites in their own brains (see Figure 15.7). This phenomenon is known as intracranial self-stimulation (ICSS), and the brain sites capable of mediating the phenomenon are often called pleasure centers. When research on addiction turned to positive incentives in the 1970s and 1980s, what had been learned about the neural mechanisms of pleasure from studying intracranial self-stimulation served as a starting point for the study of the neural mechanisms of addiction.

Olds and Milner (1954), the discoverers of intracranial self-stimulation, argued that the specific brain sites that mediate self-stimulation are those that normally mediate the pleasurable effects of natural rewards (i.e., food, water, and sex). Accordingly, researchers studied the self-stimulation of various brain sites in order to map the neural circuits that mediate the experience of pleasure.

**Fundamental Characteristics of Intracranial Self-Stimulation**

It was initially assumed that intracranial self-stimulation was a unitary phenomenon—that is, that its fundamental properties were the same regardless of the site of stimulation. Most early studies of intracranial self-stimulation involved septal or lateral hypothalamic stimulation because the rates of self-stimulation from these sites are spectacularly high: Rats typically press a lever thousands of times per hour for stimulation of these sites, stopping only when they become exhausted. However, self-stimulation of many other brain structures has been documented.

Early studies of intracranial self-stimulation suggested that lever pressing for brain stimulation was fundamentally different from lever pressing for natural reinforcers such as food or water. Two puzzling observations contributed to this view. First, despite their extremely high response rates, many rats stopped pressing the self-stimulation lever almost immediately when the current delivery mechanism was shut off. This finding was puzzling because high rates of operant responding are generally assumed to indicate that the reinforcer is particularly pleasurable, whereas rapid rates of extinction are usually assumed to indicate that it is not. Would you stop pressing a lever that had been delivering $100 bills the first few times that a press did not produce one? Second, experienced self-stimulators often did not recommence lever pressing.

1. Drugs that affect the nervous system and behavior are called ______ drugs.
2. The most dangerous route of drug administration is ______ injection.
3. Drug tolerance is of two different types: metabolic and ______.
4. An individual who displays a withdrawal syndrome when intake of a drug is curtailed is said to be ______ on that drug.
5. The before-and-after design is used to study ______ drug tolerance.
6. The fact that drug tolerance is often ______ suggests that Pavlovian conditioning plays a major role in addiction.
7. ______ disease provides a compelling illustration of nicotine’s addictive power.
8. Convulsions and hyperthermia are symptoms of withdrawal from ______.
9. Anandamide was the first endogenous ______ to be identified.
10. Cocaine sprees can produce cocaine psychosis, a syndrome that is similar to paranoid ______.
11. Morphine and codeine are constituents of ______.
12. ______ is a semisynthetic opiate that penetrates the blood–brain barrier more effectively than morphine.
13. ______ heroin addicts were among the first to legally receive heroin injections from a physician for a small fee.
14. Many current theories of addiction focus on the ______ of addictive drugs.
when they were returned to the apparatus after being briefly removed from it. In such cases, the rats had to be **primed** to get them going again: The experimenter simply pressed the lever a couple of times, to deliver a few free stimulations, and the hesitant rat immediately began to self-stimulate at a high rate once again.

These differences between lever pressing for rewarding lateral hypothalamic or septal stimulation and lever pressing for food or water seemed to discredit Olds and Milner’s original theory that intracranial self-stimulation involves the activation of natural reward circuits in the brain. However, several lines of research indicate that the circuits mediating intracranial self-stimulation are natural reward circuits. Let’s consider three of these.

First, brain stimulation through electrodes that mediate self-stimulation often elicits a natural motivated behavior such as eating, drinking, or copulation in the presence of the appropriate goal object. Second, producing increases in natural motivation (for example, by food or water deprivation, by hormone injections, or by the presence of prey objects) often increases self-stimulation rates.

The third point is a bit more complex: It became clear that differences between the situations in which the rewarding effects of brain stimulation and those of natural rewards were usually studied contribute to the impression that these effects are qualitatively different. For example, comparisons between lever pressing for food and lever pressing for brain stimulation are usually confounded by the fact that subjects pressing for brain stimulation are nondeprived and by the fact that the lever press delivers the reward directly and immediately. In contrast, in studies of lever pressing for natural rewards, subjects are often deprived, and they press a lever for a food pellet or a drop of water, which they must then approach and consume to experience the rewarding effects. This point was illustrated by a clever experiment (Panksepp & Trowill, 1967) that compared lever pressing for brain stimulation and lever pressing for a natural reinforcer in a situation in which the usual confounds were absent. In the absence of the confounds, some of the major differences between lever pressing for food and lever pressing for brain stimulation disappeared. When nondeprived rats pressed a lever to inject a small quantity of chocolate milk directly into their mouths through an intraoral tube, they behaved remarkably like self-stimulating rats: They quickly learned to press the lever, they pressed at high rates, they extinguished quickly, and some even had to be primed.

**Mesotelencephalic Dopamine System and Intracranial Self-Stimulation**

The mesotelencephalic dopamine system plays an important role in intracranial self-stimulation. The **mesotelencephalic dopamine system** is a system of dopaminergic neurons that projects from the mesencephalon (the midbrain) into various regions of the telencephalon. As Figure 15.8 indicates, the neurons that compose the mesotelencephalic dopamine system have their cell bodies in two midbrain nuclei—the **substantia nigra** and the **ventral tegmental area**. Their axons project to a variety of telencephalic sites, including specific regions of the prefrontal neocortex, the limbic cortex, the olfactory tubercle, the amygdala, the septum, the dorsal striatum, and, in particular, the **nucleus accumbens** (nucleus of the ventral striatum)—see Zahm, 2000.

Most of the axons of dopaminergic neurons that have their cell bodies in the substantia nigra project to the dorsal striatum; this component of the mesotelencephalic dopamine system is called the **nigrostriatal pathway**. It is degeneration in this pathway that is associated with Parkinson’s disease.

Most of the axons of dopaminergic neurons that have their cell bodies in the ventral tegmental area project to various cortical and limbic sites. This component of the mesotelencephalic dopamine system is called the **mesocorticolimbic pathway**.

---

**FIGURE 15.8** The mesotelencephalic dopamine system in the human brain, consisting of the nigrostriatal pathway (green) and the mesocorticolimbic pathway (red). (Based on Klivington, 1992.)
dopamine system is called the mesocorticolimbic pathway. Although there is some intermingling of the neurons between these two dopaminergic pathways, it is the particular neurons that project from the ventral tegmental area to the nucleus accumbens that have been most frequently implicated in the rewarding effects of brain stimulation, natural rewards, and addictive drugs.

Several pieces of evidence have supported the view that the mesocorticolimbic pathway of the mesotelencephalic dopamine system plays an important role in mediating intracranial self-stimulation. The following are four of them:

- Many of the brain sites at which self-stimulation occurs are part of the mesotelencephalic dopamine system.
- Intracranial self-stimulation is often associated with an increase in dopamine release in the mesocorticolimbic pathway (Hernandez et al., 2006). See Figure 15.9.
- Dopamine agonists tend to increase intracranial self-stimulation, and dopamine antagonists tend to decrease it.
- Lesions of the mesocorticolimbic pathway tend to disrupt intracranial self-stimulation.

The positive-incentive value of drug taking had been implicated in addiction, and the experience of pleasure had been linked to the mesocorticolimbic pathway. It was natural, therefore, that the first sustained efforts to discover the neural mechanisms of drug addiction should focus on the mesocorticolimbic pathway.

In considering the neural mechanisms of drug addiction, it is important to appreciate that specific brain mechanisms could not possibly have evolved for the purpose of mediating addiction—drug addiction is not adaptive. Thus, the key to understanding the neural mechanisms of addiction lies in understanding natural motivational mechanisms and how they are co-opted and warped by addictive drugs (Nesse & Berridge, 1997).

### Two Key Methods for Measuring Drug-Produced Reinforcement in Laboratory Animals

Most of the research on the neural mechanisms of addiction has been conducted in nonhumans. Because of the presumed role of the positive-incentive value of drugs in addiction, methods used to measure the rewarding effects of drugs in the nonhuman subjects have played a key role in this research. Two such methods have played particularly important roles: the drug self-administration paradigm and the conditioned place-preference paradigm (see Aguilar, Rodríguez-Arias, & Miñarro, 2008; Sanchis-Segura & Spanagel, 2006). They are illustrated in Figure 15.10.

In the drug self-administration paradigm, laboratory rats or primates press a lever to inject drugs into themselves through implanted cannulas (thin tubes). They readily learn to self-administer intravenous injections of drugs to which humans become addicted. Furthermore, once they have learned to self-administer an addictive drug, their drug taking often mimics in major respects the drug taking of human addicts (Deroche-Gamonet, Belin, & Piazza, 2004; Louk Vanderschuren & Everitt, 2004; Robinson, 2004). Studies in which microinjections have been self-administered directly into particular brain structures have proved particularly enlightening.

In the conditioned place-preference paradigm, rats repeatedly receive a drug in one compartment (the drug compartment) of a two-compartment box. Then, during the test phase, the drug-free rat is placed in the box, and the
proportion of time it spends in the drug compartment, as opposed to the equal-sized but distinctive control compartment, is measured. Rats usually prefer the drug compartment over the control compartment when the drug compartment has been associated with the effects of drugs to which humans become addicted. The main advantage of the conditioned place-preference paradigm is that the subjects are tested while they are drug-free, which means that the measure of the incentive value of a drug is not confounded by other effects the drug might have on behavior.

**Early Evidence of the Involvement of Dopamine in Drug Addiction**

In the 1970s, following much research on the role of dopamine in intracranial self-stimulation, experiments began to implicate dopamine in the rewarding effects of natural reinforcers and addictive drugs. For example, in rats, dopamine antagonists blocked the self-administration of, or the conditioned preference for, several different addictive drugs; and they reduced the reinforcing effects of food. These findings suggested that dopamine signaled something akin to reward value or pleasure.

**The Nucleus Accumbens and Drug Addiction**

Once evidence had accumulated linking dopamine to natural reinforcers and drug-induced reward, investigators began to explore particular sites in the mesocorticolimbic dopamine pathway by conducting experiments on laboratory animals. Their findings soon focused attention on the nucleus accumbens. Events occurring in the nucleus accumbens and dopaminergic input to it from the ventral tegmental area appeared to be most clearly related to the experience of reward and pleasure.

The following are four kinds of findings from research on laboratory animals that focused attention on the nucleus accumbens (see Deadwyler et al., 2004; Nestler, 2005; Pierce & Kumaresan, 2006):

- Laboratory animals self-administered microinjections of addictive drugs (e.g., cocaine, amphetamine, and morphine) directly into the nucleus accumbens.
- Microinjections of addictive drugs into the nucleus accumbens produced a conditioned place preference for the compartment in which they were administered.
- Lesions to either the nucleus accumbens or the ventral tegmental area blocked the self-administration of drugs into general circulation or the development of drug-associated conditioned place preferences.
- Both the self-administration of addictive drugs and the experience of natural reinforcers were found to be associated with elevated levels of extracellular dopamine in the nucleus accumbens.
Support for the Involvement of Dopamine in Addiction: Evidence from Imaging Human Brains

With the development of brain-imaging techniques for measuring dopamine in human brains, considerable evidence began to emerge that dopamine is involved in human reward in general and human addiction in particular (see O’Doherty, 2004; Volkow et al., 2004). One of the strongest of the early brain-imaging studies linking dopamine to addiction was published by Volkow and colleagues (1997). They administered various doses of radioactively labeled cocaine to addicts and asked the addicts to rate the resulting “high.” They also used positron emission tomography (PET) to measure the degree to which the labeled cocaine bound to dopamine transporters. As you learned earlier in this chapter, cocaine has its agonistic effects on dopamine by binding to these transporters, blocking reuptake, and thus increasing extracellular dopamine levels. The intensity of the “highs” experienced by the addicts was correlated with the degree to which cocaine bound to the dopamine transporters—no high at all was experienced unless the drug bound to 50% of the dopamine transporters.

Brain-imaging studies have also indicated that the nucleus accumbens plays an important role in mediating the rewarding effects of addictive behavior. For example, in one study, healthy (i.e., nonaddicted) human subjects were given an IV injection of amphetamine (Drevets et al., 2001). As dopamine levels in the nucleus accumbens increased in response to the amphetamine injection, the subjects reported a parallel increase in their experience of euphoria.

In general, brain-imaging studies have shown that dopamine function is markedly diminished in human addicts—see Figure 15.11 (Volkow et al., 2009). However, when addicts are exposed to their drug or to stimuli associated with their drug, the nucleus accumbens and some of the other parts of the mesocorticolimbic dopamine pathway tend to become hyperactive.

Dopamine Release in the Nucleus Accumbens: What Is Its Function?

As you have just learned, substantial evidence links dopamine release, particularly in the nucleus accumbens, to the rewarding effects of addictive drugs and other reinforcers (see Kelley, 2004; Nestler & Malenka, 2004). But, reward is a complex process, with many different psychological components (see Berridge & Robinson, 2003): What exactly is the role in reward of dopamine release in the nucleus accumbens?

Several studies have found increases in extracellular dopamine levels in the nucleus accumbens following the presentation of a natural reward (e.g., food), rewarding brain stimulation (Hernandez et al., 2007), or an addictive drug (see Joseph, Datla, & Young, 2003; Ungless, 2004). Even stronger evidence for the idea that increased dopamine levels in the nucleus accumbens are related to the experience of reward came from the finding that ventral tegmental neurons, which release their dopamine into the nucleus accumbens, fire in response to a stimulus at a rate proportional to its reward value. Other studies have suggested that dopamine released in the nucleus accumbens is related to the expectation of reward, rather than to its experience. For example, some studies have shown that neutral stimuli that signal the impending delivery of a reward (e.g., food or an addictive drug) can trigger dopamine release in the nucleus accumbens (e.g., Fiorino, Coury, & Phillips, 1997; Weiss et al., 2000).

A third theory about dopamine release in the nucleus accumbens encompasses and extends the experience-of-reward and expectation-of-reward theories (Caplin & Dean, 2008). The theory was proposed by Tobler, Forillo, and Schultz (2005). They found that dopaminergic neurons with their cell bodies in the ventral tegmental area...
fire at a rate related to the value of the reward. When the expected reward was delivered, there was no change in firing rate; when a greater than expected reward was delivered, firing increased; and when a less than expected reward was delivered, firing decreased. Thus, dopamine release in the nucleus accumbens reflected both the experience and expectation of reward, but not in a straightforward fashion: It seemed to reflect discrepancies between expected and actual rewards (see Fiorillo, Newsome, & Schultz, 2008; Schultz, 2007).

15.7 Current Approaches to Brain Mechanisms of Addiction

The previous three sections of the chapter have brought us from the beginnings of research on the brain mechanisms of addiction to current research, which will be discussed in this section. Figure 15.12 summarizes the major shifts in thinking about the brain mechanisms of addiction that have occurred over time.

Figure 15.12 shows that two lines of thinking about the brain mechanisms of addiction both had their origins in classic research on drug tolerance and physical dependence. One line developed into physical-dependence theories of addiction, which though appealing in their simplicity, proved to be inconsistent with the evidence, and these inconsistencies led to the emergence of positive-incentive theories. In turn, the positive-incentive approach to addiction, in combination with research on dopamine and pleasure centers in the brain, led to a focus on the mesocorticolimbic pathway and the mechanisms of reward. The second line of thinking about the brain mechanisms of addiction also began with early research on drug tolerance and physical dependence. This line moved ahead with the discovery that drug-associated cues come to elicit conditioned compensatory responses through a Pavlovian conditioning mechanism and that these conditioned responses are largely responsible for drug tolerance. This finding gained further prominence when researchers discovered that conditioned responses elicited by drug-associated cues were major factors in drug craving and relapse.

These two lines of research together have shaped modern thinking about the brain mechanisms of addiction, but this is not the end of the story (see Koob, 2006). In this, the final section of the chapter, you will learn about issues that are the focus of current research on the brain mechanisms of addiction and about new areas of the brain that have been linked to drug addiction.

Current Issues in Addiction Research

The early decades of research on addiction and its neural mechanisms clarified a number of issues about addiction, but it raised others that are the focus of current research. The following are four of these issues:

Addiction Is Psychologically Complex  Studies of addicted patients have found that drug addicts differ psychologically from healthy controls in a variety of ways. Drug addicts have been found to make poor decisions, to engage in excessive risk taking, and to have deficits in self control (see Baler & Volkow, 2011).
Addiction Is a Disturbance of Decision Making  There has been an increasing appreciation that the primary symptom of addiction is a disturbance of decision making: Why do addicts decide to engage in harmful behaviors? This has had two beneficial effects: It has led investigators who study drug addiction to consider research on decision making from other fields (e.g., economics and social psychology), and it has led investigators in these other fields to consider research on drug addiction (e.g., Cardinal & Everitt, 2004; Lieberman & Eisenberger, 2009; Sanfey, 2007).

Addiction Is Not Limited to Drugs  There has been a growing consensus that drug addiction is a specific expression of a more general problem and that other behaviors exhibit the defining feature of drug addiction: the inability to refrain from a behavior despite its adverse effects. A lot of attention has recently been paid to overeating as an addiction because of its major adverse health consequences (e.g., Di Chiara & Bassareo, 2007; Trinko et al., 2007), but compulsive gambling, compulsive sexual behavior, kleptomania (compulsive shoplifting), and compulsive shopping also seem to share some brain mechanisms with drug addiction (see Grant, Brewer, & Potenza, 2006; Tanabe et al., 2007).

Addiction Involves Many Neurotransmitters  The evidence implicating dopamine in addiction is diverse and substantial, but it is not possible for any complex behavior to be the product of a single neurotransmitter. Some evidence has pointed to a role for glutamate in addiction (Kalivas, 2004)—of particular interest are prefrontal glutamnergic neurons that project into the nucleus accumbens. Also of interest to researchers are endogenous opioids, norepinephrine, GABA, and endocannabinoids (see Koob, 2006; Weinshenker & Schroeder, 2007).

Brain Structures That Mediate Addiction: The Current View  Although researchers do not totally agree about the neural mechanisms of drug addiction, there seems to be an emerging consensus that areas of the brain other than the nucleus accumbens are involved in its three stages (see Everitt & Robbins, 2005; Koob, 2006): (1) initial drug taking, (2) the change to craving and compulsive drug taking, and (3) relapse.

Initial Drug Taking  Initial taking of potentially addictive drugs is thought to be mediated in much the same way as any pleasurable activity, with the mesocorticolimbic pathway—in particular, the nucleus accumbens—playing a key role. But the nucleus accumbens does not act alone; its interactions with three other areas of the brain are thought to be important. The prefrontal lobes are thought to play a major role in the decision to take a drug (Grace et al., 2007); the hippocampus and related structures are assumed to provide information about previous relevant experiences; and the amygdala is thought to coordinate the positive or negative emotional reactions to the drug taking.

Change to Craving and Compulsive Drug Taking  The repeated consumption of an addictive drug brings major changes in the motivation of the developing addict. Drug taking develops into a habit and then to a compulsion; that is, despite its numerous adverse effects, drug taking starts to dominate the addict’s life. Earlier in this chapter, you learned that this change has been described as an increase in the positive-incentive value of taking the drug that occurs in the absence of any increase in its hedonic effects. It is not yet known why this change occurs and why it occurs in some drug takers but not in others. The change may be a direct neural response to the repeated experience of drug-induced pleasure; it could be a product of the myriad conditioned responses to drug-associated cues (Cardinal & Everitt, 2004; Kenny, 2007); or, more likely, it could be a product of both of these influences.

Several changes in the brain’s responses appear to contribute to the development of addiction. First, there is a change in how the striatum reacts to drugs and drug-associated cues. As addiction develops, striatal control of addiction spreads from the nucleus accumbens (i.e., the ventral striatum) to the dorsal striatum, an area that is known to play a role in habit formation and retention (see Chapter 11). Also, at the same time, the role of the prefrontal cortex in controlling drug-related behaviors apparently declines, and stress circuits in the hypothalamus (see Chapter 17) begin to interact with the dorsal striatum. In essence, the development of addiction is a pathological neuroplastic response that some people show with repeated drug taking (see Kalivas, 2005; Koob & Le Moal, 2005).

Relapse  As you learned in an earlier section of this chapter, three factors are known to trigger relapse in abstinent addicts: priming doses of the drug, drug-associated cues, and stress. Each cause of relapse appears to be mediated by interaction of a different brain structure with the striatum. Evidence from research on drug self-administration in laboratory animals suggests that the prefrontal cortex mediates priming-induced relapse, the amygdala mediates conditional cue-induced relapse, and the hypothalamus mediates stress-induced relapse.
Two of this book’s themes—thinking creatively and clinical implications—received strong emphasis in this chapter because they are integral to its major objective: to sharpen your thinking about the effects of addiction on people’s health. You were repeatedly challenged to think about drug addiction in ways that may have been new to you but are more consistent with the evidence. The evolutionary perspective theme was also highlighted frequently in this chapter, largely because of the nature of biopsychological research into drug addiction. Because of the risks associated with the administration of addictive drugs and the direct manipulation of brain structures, the majority of biopsychological studies of drug addiction involve nonhumans—mostly rats and monkeys. Also, in studying the neural mechanisms of addiction, there is a need to maintain an evolutionary perspective. It is important not to lose sight of the fact that brain mechanisms did not evolve to support addiction; they evolved to serve natural adaptive functions and have somehow been co-opted by addictive drugs.

The Case of Sigmund Freud

In 1883, a German army physician prescribed cocaine, which had recently been isolated, to Bavarian soldiers to help them deal with the demands of military maneuvers. When Freud read about this, he decided to procure some of the drug.

In addition to taking cocaine himself, Freud pressed it on his friends and associates, both for themselves and for their patients. He even sent some to his fiancée. In short, by today’s standards, Freud was a public menace.

Freud’s famous essay “Song of Praise” was about cocaine and was published in July 1884. Freud wrote in such glowing terms about his own personal experiences with cocaine that he created a wave of interest in the drug. But within a year, there was a critical reaction to Freud’s premature advocacy of the drug. As evidence accumulated that cocaine was highly addictive and produced a psychosis-like state at high doses, so too did published criticisms of Freud.

Freud continued to praise cocaine until the summer of 1887, but soon thereafter he suddenly stopped all use of cocaine—both personally and professionally. Despite the fact that he had used cocaine for 3 years, he seems to have had no difficulty stopping.

Some 7 years later, in 1894, when Freud was 38, his physician and close friend ordered him to stop smoking because it was causing a heart arrhythmia. Freud was a heavy smoker; he smoked approximately 20 cigars per day.

Freud did stop smoking, but 7 weeks later he started again. On another occasion, Freud stopped for 14 months, but at the age of 58, he was still smoking 20 cigars a day—and still struggling against his addiction. He wrote to friends that smoking was adversely affecting his heart and making it difficult for him to work...yet he kept smoking.

In 1923, at the age of 67, Freud developed sores in his mouth. They were cancerous. When he was recovering from oral surgery, he wrote to a friend that smoking was the cause of his cancer...yet he kept smoking.

In addition to the cancer, Freud began to experience severe heart pains (tobacco angina) whenever he smoked...still he kept smoking.

At 73, Freud was hospitalized for his heart condition and stopped smoking. He made an immediate recovery. But 23 days later, he started to smoke again.

In 1936, at the age of 79, Freud was experiencing more heart trouble, and he had had 33 operations to deal with his recurring oral cancer. His jaw had been entirely removed and replaced by an artificial one. He was in constant pain, and he could swallow, chew, and talk only with difficulty...yet he kept smoking.

Freud died of cancer in 1939 (see Sheth, Bhagwate, & Sharma, 2005).

Themes Revisited
Although the neuroplasticity theme pervades this chapter, the neuroplasticity tag appeared only once—where the text explains that the development of addiction is a pathological neuroplastic response. The main puzzle in research on addiction is how the brain of an occasional drug user is transformed into the brain of an addict.

Think about It

1. There are many misconceptions about drug addiction. Describe three. What factors contribute to these misconceptions? In what ways is the evidence about drug addiction often misrepresented?
2. A doctor who had been a morphine user for many years was found dead of an overdose at a holiday resort. She appeared to have been in good health, and no foul play was suspected. Explain how conditioned tolerance may have contributed to her death.
3. If you had an opportunity to redraft current laws related to drug use in light of what you have learned in this chapter, what changes would you make? Do you think that all drugs, including nicotine and alcohol, should be illegal? Explain.
4. Speculate: How might recent advances in the study of the mesotelencephalic dopamine system eventually lead to effective treatments?
5. Does somebody you love use a hard drug such as nicotine or alcohol? What should you do?
6. One of my purposes in writing this chapter was to provide you with an alternative way of thinking about drug addiction, one that might benefit you. Imagine my dismay when I received an e-mail message suggesting that this chapter was making things worse for addicts. According to this message, discussion of addiction induces craving in addicts who have stopped taking drugs, thus encouraging them to recommence their drug taking. Discuss this point, and consider its implications for the design of antidrug campaigns.

Key Terms

Pharmacological (p. 384)

15.1 Basic Principles of Drug Action
Psychoactive drugs (p. 384)
Drug metabolism (p. 385)
Drug tolerance (p. 385)
Cross tolerance (p. 385)
Drug sensitization (p. 385)
Metabolic tolerance (p. 385)
Functional tolerance (p. 385)
Withdrawal syndrome (p. 386)
Physically dependent (p. 386)
Addicts (p. 386)

15.2 Role of Learning in Drug Tolerance
Contingent drug tolerance (p. 387)
Before-and-after design (p. 387)
Conditioned drug tolerance (p. 388)
Conditioned compensatory responses (p. 388)
Exteroceptive stimuli (p. 389)

15.3 Five Commonly Abused Drugs
Nicotine (p. 389)
Smoker's syndrome (p. 390)
Buergers disease (p. 390)
Teratogen (p. 390)
Depressant (p. 391)
Delirium tremens (DTs) (p. 391)
Korsakoffs syndrome (p. 391)
Cirrhosis (p. 391)
Fetal alcohol syndrome (FAS) (p. 391)
Disulfiram (p. 392)
Cannabis sativa (p. 392)
THC (p. 392)
Hashish (p. 392)
Narcotic (p. 392)
Anandamide (p. 394)
Stimulants (p. 394)
Cocaine (p. 394)

Crack (p. 394)
Cocaine sprees (p. 394)
Cocaine psychosis (p. 394)
Amphetamine (p. 394)
Dopamine transporters (p. 395)
Opium (p. 395)
Morphine (p. 395)
Codeine (p. 395)
Opiates (p. 395)
Analgesics (p. 395)
Harrison Narcotics Act (p. 396)
Heroin (p. 396)

15.4 Biopsychological Approaches to Theories of Addiction
Physical-dependence theories of addiction (p. 399)
Detoxified addicts (p. 399)
Positive-incentive theories of addiction (p. 399)
Positive-incentive value (p. 400)
Hedonic value (p. 400)
Incentive-sensitization theory (p. 400)

Relapse (p. 400)
Drug priming (p. 400)

15.5 Intracranial Self-Stimulation and the Pleasure Centers of the Brain
Intracranial self-stimulation (ICSS) (p. 401)
Primed (p. 402)
Mesotelencephalic dopamine system (p. 402)
Substantia nigra (p. 402)
Ventral tegmental area (p. 402)
Nucleus accumbens (p. 402)

15.6 Early Studies of Brain Mechanisms of Addiction: Dopamine
Drug self-administration paradigm (p. 403)
Conditioned place-preference paradigm (p. 403)
Test your comprehension of the chapter with this brief practice test. You can find the answers to these questions as well as more practice tests, activities, and other study resources at www.mypsychlab.com.

1. Tolerance to psychoactive drugs is largely
   a. nonexistent.
   b. metabolic.
   c. functional.
   d. sensitization.
   e. cross tolerance.

2. Which drug is thought to lead to about 400,000 deaths each year in the United States alone?
   a. heroin
   b. cocaine
   c. alcohol
   d. nicotine
   e. marijuana

3. Delirium tremens can be produced by withdrawal from
   a. heroin.
   b. morphine.
   c. alcohol.
   d. amphetamines.
   e. both a and b

4. Animals that have been previously trained to press a lever to deliver rewarding electrical stimulation to their own brains will often not begin pressing unless they have been
   a. primed.
   b. extinguished.
   c. fed.
   d. frightened.
   e. punished.

5. A method of measuring drug-produced reinforcement or pleasure in laboratory animals is the
   a. drug self-administration paradigm.
   b. conditioned place-preference paradigm.
   c. conditioned tolerance paradigm.
   d. all of the above
   e. both a and b