How Do Drugs and Hormones Influence Behavior?

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Japanese and Chinese fishermen are credited with discovering that seaweed can be used as a medicine. They may have observed that flies die after alighting on seaweed washed up on the shore, so they tried rubbing seaweed onto the skin as an insect repellent. It worked. They also found that, when eaten, seaweed kills intestinal worms, so they used extracts from it to treat worms in children. These folk remedies led scientists to analyze the chemical composition of the seaweed *Chondria armata* and identify two chemically similar insecticidal compounds in it: domoic acid and kainic acid. Purified doses of these acids were given to large numbers of children as a treatment for worms, with no reported side effects. Physicians therefore concluded that these substances weren’t toxic to humans. Unfortunately, they were wrong.

On November 22, 1987, two people in Moncton, New Brunswick, Canada, were hospitalized after suffering from gastroenteritis and mental confusion. Soon more reports of the illness came from Quebec, and, by December 9, five people had died. In all, more than 200 cases of this mysterious disorder were reported. The severity of symptoms varied greatly, but the worst cases included marked confusion and memory loss. For some of those who survived, the memory impairments were permanent. Autopsies revealed extensive cell loss in the hippocampus, amygdala, and surrounding cortex and in the thalamus (Hynie & Todd, 1990).

The only experience common to the victims was to have eaten mussels. To find out whether the mussels were responsible, scientists injected mussel extracts into mice. Soon after, the mice started scratching behind one ear and then convulsed and died. Apparently, the mussels did contain a toxin, but the curious scratching behavior indicated that the toxin was unlike any other known shellfish poison. Chemical analysis of the mussels showed that they contained large amounts of domoic acid. Investigators were surprised. How did the mussels become contaminated with domoic acid, and why was it suddenly acting like a poison in humans?

To answer the first question, the investigators traced the mussels. They found that they came from two Prince Edward Island cultured-mussel farms. Cultured-mussel farming began in 1975 and by the 1980s had grown into a large, successful industry, producing as much as 3.2 million pounds of mussels annually. Mussel farmers release mussel sperm and eggs into the water, where the resulting zygotes attach themselves to long ropes suspended there. The mussels feed by siphoning from 2 to 6 liters of water per hour to extract small sea organisms called phytoplankton. More than 90 percent of the phytoplankton that the Prince Edward Island mussels consumed were single-cell diatoms called *Nitzschia pungens*, shown in Figure 6-1. When analyzed, the diatoms were found to contain domoic acid. Because there had been no evidence of domoic acid in diatoms before 1987, a search for the origins of the contamination began. Apparently, a dry climate in 1987 produced a buildup of domoic acid–containing seaweed in the streams and along the shoreline. By feeding on seaweed, the diatoms had accumulated large quantities of domoic acid, which was then passed on to the mussels as they fed on the diatoms.

But the discovery that domoic acid was the toxic agent in this episode only partly solved the mystery with which investigators were confronted. Remember that domoic acid had been thought to be harmless. It had been widely used to rid children of worms. How had it now

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**Figure 6-1**

Diatoms have a variety of shapes and sizes. They are ubiquitous in the ocean and common in fresh water, where they are frequently present in great numbers. *Nitzschia pungens*, shown here, is a diatom that can accumulate domoic acid.
resulted in sickness, brain damage, and death? And why were only some people affected? Certainly more than 200 people had eaten the contaminated mussels. These two questions will be answered in the following sections, where domoic acid poisoning is used to illustrate some of the principles of drug action. Many of those principles also apply to the action of hormones, which are drugs that we make in our own bodies. Hormones are the topic of the last section of this chapter. Before we begin to tell how drugs produce their effects on the brain, we must make an admission. The sheer number of neurotransmitters, receptors, and possible sites of drug action is astounding. The science of drug research has made important advances, but we do not know everything there is to know about any drug.

**PRINCIPLES OF DRUG ACTION**

A drug is a chemical compound that is administered to bring about some desired change in the body. Drugs are usually used to diagnose, treat, or prevent illness, to relieve pain and suffering, or to improve some adverse physiological condition. The kinds of drugs that we will be concerned with in this chapter are psychoactive drugs—those substances that act to alter mood, thought, or behavior and that are used to manage neuropsychological illness. Many psychoactive drugs are also abused substances. That is, they are taken for nonmedical reasons to the point at which they impair the user’s functioning and may produce addiction. Some psychoactive drugs can also act as toxins, producing sickness, brain damage, or death.

In this chapter you will learn that the effects of many drugs depend on how they are taken, in what quantities, and under what circumstances. We begin by looking at the major ways that psychoactive drugs are administered, what routes they take to reach the central nervous system, and how they are eliminated from the body. We then consider how drugs act on neurons and why different people may respond differently to the same dose of a drug.

**How Psychoactive Drugs Get into the Nervous System**

To be effective, a psychoactive drug has to reach its nervous system target. The way that a drug enters and passes through the body to reach that target is called its route of administration. Many drugs are administered orally because it is a natural and safe way to consume a substance. Drugs can also be inhaled into the lungs, administered through rectal suppositories, absorbed from patches applied to the skin, or injected into the bloodstream, into a muscle, or even into the brain. Figure 6-2 illustrates the various routes of drug administration.

These different routes pose different barriers between the drug and its target. Taking a drug by mouth is easy and convenient, but not all drugs can pass the barriers of the digestive-tract contents and walls. Generally, there are fewer barriers between a drug and its target if the drug is inhaled rather than swallowed, and fewer still if it is injected into the blood. The fewest obstacles are encountered if a psychoactive drug is injected directly into the brain. Figure 6-2 also summarizes the characteristics of drugs that allow them to pass through various barriers to reach their targets.

Let us look more closely at the barriers that an orally taken drug must pass to get to the brain. To reach the bloodstream, an ingested drug must first be absorbed through the lining of the stomach or small intestine. If the drug is liquid, it is absorbed more readily. Drugs taken in solid form are not absorbed unless they can be dissolved by the stomach's gastric juices. In either form, liquid or solid, absorption is
affected by the physical and chemical properties of the drug, as well as by the presence of other stomach or intestinal contents. In general, if a drug is a weak acid, such as alcohol, it is readily absorbed across the stomach lining. If it is a weak base, it cannot be absorbed until it passes through the stomach and into the intestine—a process that may destroy it.

After it has been absorbed by the stomach or intestine, the drug must next enter the bloodstream. This part of the journey requires additional properties. Because blood has a high water concentration, a drug must be hydrophilic to be carried in the blood. A hydrophobic substance will be blocked from entering the bloodstream. If it makes its way into the blood, a drug is then diluted by the approximately 6 liters of blood that circulate through an adult person’s body.

To reach its target, a drug must also travel from the blood into the extracellular fluid, which requires that molecules of the drug be small enough to pass through the pores of capillaries, the tiny vessels that carry blood to the body’s cells. And, even if the drug makes this passage, it may encounter still other obstacles. For one thing, the extracellular fluid’s roughly 35 liters of water dilute it even further. For another, the drug is at risk of being modified or destroyed by various metabolic processes taking place in cells.

At the brain, the passage of drugs across capillaries is much more difficult because of the blood-brain barrier. It is not that the brain is deficient in capillaries. The brain has a rich capillary network. In fact, none of its neurons is farther than about 50 micrometers (µm, one-millionth of a meter) away from a capillary. But capillaries to the brain are impermeable to many substances, which is what creates the blood-brain barrier.

Figure 6-3 shows the structure of brain capillaries and why they are impermeable to many substances. As you can see, like all capillaries, brain capillaries are composed of a single layer of endothelial cells. In most parts of the body, the walls of capillary endothelial cells are not fused together, so substances can pass through the clefts between the cells. In contrast, in the brain (at least in most parts of it), endothelial cell walls are fused to form tight junctions, so molecules of most substances cannot squeeze between them.
Capillaries in the brain are not leaky, have tight junctions, and are covered with astrocyte feet. These properties prevent materials from moving in and out easily, and are the basis of the blood–brain barrier.

Small, uncharged molecules are able to pass through the endothelial membrane and reach the brain.

Certain other molecules are carried across the membrane by active transport.

Large and electrically charged molecules are unable to pass out of the capillary.

Figure 6-3 also shows that the endothelial cells of a brain capillary are surrounded by the end feet of astrocyte glial cells, which are attached to the capillary wall and cover about 80 percent of it. The glial end feet play only minor roles in the blood–brain barrier. The glial cells provide a route for the exchange of food and waste between capillaries and the brain’s extracellular fluid and from there to other cells. They may also play a role in maintaining the tight junctions between endothelial cells and in making capillaries dilate to increase blood flow to areas of the brain in which neurons are very active.

You may wonder why endothelial cells form tight junctions only in most parts of the brain, not in all of it. The cells of capillary walls in a few brain regions lack tight junctions, and so these regions, shown in Figure 6-4, lack a blood–brain barrier. One is the pituitary of the hypothalamus, which allows the passage of hormones into the pituitary gland. Another is the area postrema of the lower brainstem. The absence of a blood–brain barrier here allows toxic substances in the blood to trigger a vomiting response. The pineal gland also lacks a blood–brain barrier, enabling hormones to reach it and modulate the day–night cycles that this structure controls.

The rest of the brain needs certain substances to carry out its work, and these substances must be able to cross the blood–brain barrier. For instance, oxygen, glucose, and amino acids (the building blocks of proteins) must routinely travel from the blood to brain cells, just as carbon dioxide and other waste products must routinely be excreted from brain cells into the blood. There are two ways that molecules of these substances cross the blood–brain barrier. First, small molecules such as oxygen and carbon dioxide, which are not ionized and so are fat soluble, can pass right through the endothelial membrane. Second, molecules of glucose, amino acids, and other food components can be carried across the membrane by active-transport systems. An active-transport system is a pump, such as the sodium/potassium pump, that is specialized for the transport of a particular substance. When a substance has passed from the capillaries into the brain’s extracellular fluid, it can move readily into neurons and glia.
But the blood–brain barrier halts more substances than it lets through. In most cases, the barrier is beneficial. For example, because the electrical activity of neurons depends on certain extracellular concentrations of ions, it is important that ionic substances not cross the blood–brain barrier and upset the brain’s electrical activity. It is also important that neurochemicals from the rest of the body not pass into the brain and disrupt the communication between neurons. In addition, the blood–brain barrier protects the brain from many circulating hormones and from various toxic and infectious substances. Injury or disease can sometimes rupture the blood–brain barrier, thereby letting pathogens through. For the most part, however, the brain is very well protected from substances potentially harmful to its functioning.

The blood–brain barrier has special relevance for understanding drug actions on the nervous system. A drug can reach the brain only if its molecules are small and not ionized, enabling them to pass through endothelial cell membranes, or if the drug has a chemical structure that allows it to be carried across the membrane by an active-transport system. Because very few drugs are small or have the correct chemical structure, very few can gain access to the central nervous system. For example, the neurotransmitter dopamine, although a small molecule, is unable to cross the blood–brain barrier because of its chemical composition. Therefore it cannot be used as a drug for Parkinson’s disease, even though, once in the brain, it could be very effective. In contrast, L-dopa, the precursor from which dopamine is made, has a slightly different chemical makeup, crosses the blood–brain barrier through an active-transport system, and so can be used to treat Parkinson’s disease. Because the blood–brain barrier works so well, it is extremely difficult to find new drugs to use as treatments for brain diseases.

To summarize, drugs that can make the entire trip from the mouth to the brain have some special chemical properties. The most effective ones are small in size, weak acids, water and fat soluble, potent in small amounts, and not easily degraded. Do-moic acid is such a drug. Because it is a weak acid, it is easily absorbed through the stomach. It is potent in small amounts, so it survives dilution in the bloodstream and in the extracellular fluid. Finally, it is a small molecule that is similar in structure to those of food substances that are transported across the blood–brain barrier and so it, too, is transported.

**Figure 6-4**

The following three sites in the brain have no blood–brain barrier: the medial eminence (pituitary), which is a target for many blood-borne hormones, the pineal gland, which is a target for hormones that affect behavioral rhythms, and the area postrema, which initiates vomiting in response to noxious substances.
Considering the many obstacles that psychoactive drugs encounter on their journey from the mouth to the brain, it is clear why inhaling a drug or injecting it into the bloodstream has advantages. These alternative routes of administration bypass the obstacle of the stomach. In fact, with each obstacle eliminated on the route to the brain, the dosage of a drug can be reduced by a factor of 10 without reducing the effects of the drug. For example, 1 milligram (1000 micrograms) of amphetamine, a psychomotor stimulant, produces a noticeable behavioral change when ingested orally. However, if inhaled into the lungs or injected into the blood, thereby circumventing the stomach, 100 micrograms (1000 micrograms ÷ 10) of the drug produces the same results. Similarly, if amphetamine is injected into the cerebrospinal fluid, thus bypassing both the stomach and the blood, 10 micrograms is enough to produce an identical outcome, as is 1 microgram if dilution in the cerebrospinal fluid is skirted also and the drug is injected directly onto target neurons. These numbers are well known to users of illicit drugs. Drugs that can be inhaled or injected intravenously are much cheaper to use because the doses required are less than those needed for drugs taken by mouth.

After a drug has been administered, the body soon begins to remove it. Drugs are metabolized throughout the body, including in the kidneys, liver, and bile. They are excreted in urine, feces, sweat, breast milk, and exhaled air. Drugs that are developed for therapeutic purposes are usually designed not only to increase their chances of reaching their targets but also to enhance their survival in the body.

There are some substances that, if ingested, the body has trouble removing. Such substances are potentially dangerous because, if large doses of them are taken, they can build up in the body and become poisonous. For instance, certain metals, such as mercury, are not easily eliminated from the body; when they accumulate there, they can produce severe neurological conditions. Interestingly, when researchers studied the medical histories of patients with severe domoic acid poisoning, they found that all the patients had preexisting kidney problems. This finding suggests that the kidneys play an important role in eliminating domoic acid. Because these patients had kidneys that did not function normally, domoic acid reached toxic levels in their bodies.

**Individual Differences in Response to Drugs**

There are vast individual differences in responses to drugs due to differences in age, sex, body size, and other factors that affect sensitivity to a particular substance. For instance, large people are generally less sensitive to a drug than smaller people are, because of greater dilution of the drug in their body fluids. Females are about twice as sensitive to drugs as males. This difference is due in part to their relatively smaller body size, but it is also due to hormonal differences between females and males. Old people may be twice as sensitive to drugs as young people are. The elderly often have less-effective barriers to drug absorption as well as less-effective processes for metabolizing and eliminating drugs from their bodies.

Individual differences in sensitivity to domoic acid were observed among people who ate toxic mussels. Only 1 in 1000 became ill, and only some of those who were ill suffered severe memory impairments, with even fewer dying. The three patients with memory impairments were men age 69, 71, and 84. All of those who died were men older than 68. Apparently, domoic acid is either more readily absorbed or more poorly excreted, or both, in older men. Subsequent studies of mice confirmed the greater sensitivity of older animals to the toxic effects of domoic acid.
Drugs and Synapses

Drugs have their effects by initiating chemical reactions in the body or by influencing the body’s ongoing chemical activities. As you know, many chemical reactions take place in the nervous system’s neurons, especially at synapses. Most drugs that have psychoactive effects do so by influencing these chemical reactions at synapses. So, to understand how drugs work, we must explore the ways in which they modify synaptic actions.

Figure 6-5 summarizes the seven major steps in neurotransmission at a synapse. Synthesis of the neurotransmitter can take place in the cell body, the axon, or the terminal. The neurotransmitter is then stored in storage granules or in vesicles until it is released from the terminal’s presynaptic membrane. The amount of transmitter released into the synapse is regulated in relation to previous experience. When released, the transmitter acts on a receptor embedded in the postsynaptic membrane. It is then either destroyed or taken back up into the terminal from which it came for reuse. The synapse also has mechanisms for degrading excess neurotransmitter and removing unneeded by-products from the synapse.

Each of these steps in neurotransmission includes a chemical reaction that a drug can potentially influence in one of two ways: either by increasing the effectiveness of neurotransmission or by diminishing it. Drugs that increase the effectiveness of neurotransmission are called agonists, whereas those that decrease its effectiveness are called antagonists. Agonists and antagonists can work in a variety of ways, but their end results are always the same. For example, drugs that stimulate the release of the neuro-
transmitter dopamine, that block the reuptake of this transmitter, or that block its inactivation are all considered dopamine agonists because they all increase the amount of dopamine available in the synapse. Conversely, drugs that block the synthesis of dopamine or its release from the presynaptic membrane or that block dopamine receptors or speed up its inactivation are all considered dopamine antagonists because they all decrease the biochemical effect of this transmitter in the synapse.

An Acetylcholine Synapse: Examples of Drug Action

Using the acetylcholine synapse between motor neurons and muscles as an example, Figure 6-6 shows how several drugs and toxins affect neurotransmission. Some of these drugs will be new to you, but you have probably heard of others. Knowing their effects at the synapse will allow you to understand the behavioral effects that they produce.

Figure 6-6 shows two toxins that influence the release of acetylcholine from the axon terminal: black widow spider venom and botulin toxin. **Black widow spider venom** is an agonist because it promotes the release of acetylcholine—an excess amount of it. For the insects that are prey of black widow spiders, the excitation caused by this excess acetylcholine at neuromuscular synapses is sufficient to paralyze and kill them. A black widow spider bite does not contain enough toxin to similarly affect a human. **Botulin toxin** is the poisonous agent in tainted foods, such as canned goods that have been improperly processed. It acts as an antagonist because it blocks the release of acetylcholine. The effects of botulin toxin can last from weeks to months. A severe case of poisoning from it can result in paralysis of both movement and breathing and so cause death. It might surprise you to know that, despite being a poison, botulin toxin has medical uses. If injected into a muscle, it can selectively paralyze that muscle. This selective action makes it useful in blocking excessive and enduring muscular twitches or contractions. It is also used cosmetically to paralyze facial muscles that cause facial wrinkling.

Figure 6-6 also shows two drugs that act on receptors for acetylcholine: nicotine and curare. **Nicotine**, a chemical contained in cigarette smoke, acts as an agonist to stimulate cholinergic receptors. Its molecular structure is similar enough to that of acetylcholine to allow it to fit into the receptors' binding sites. **Curare** acts as an antagonist by occupying cholinergic receptors and so preventing acetylcholine from binding to them. When curare binds to these receptors, it does not cause them to function; instead, it simply blocks them. After being introduced into the body, curare acts quickly, and it is cleared from the body in a few minutes. Large doses of it, however, arrest movement and breathing for a sufficient period of time to result in death. Early European explorers of South America discovered that the Indians along the Amazon River killed small animals by using arrows coated with curare prepared from the seeds of a plant. The hunters themselves did not become poisoned when eating the animals, because ingested curare cannot pass from the gut into the body. Many curare-like drugs have been synthesized. Some are used to briefly paralyze large animals so that they can be tagged for iden-
tification or examination. You have probably seen this use of these drugs in wildlife programs on television. Skeletal muscles are more sensitive to curare-like drugs than are respiratory muscles, so an appropriate dose will paralyze an animal’s movement but still allow it to breathe.

A fifth drug action shown in Figure 6-6 is that of **physostigmine**, a drug that inhibits cholinesterase, which is the enzyme that breaks down acetylcholine. Physostigmine therefore acts as an agonist to increase the amount of acetylcholine available in the synapse. Physostigmine is obtained from an African bean and was used as a poison by native peoples in Africa. Large doses of physostigmine can be toxic because they produce excessive excitation of the neuromuscular synapse and so disrupt movement and breathing. In small doses, however, physostigmine is used to treat myasthenia gravis, a condition of muscular weakness mentioned previously, in which muscle receptors are less than normally responsive to acetylcholine. The action of physostigmine is short lived, lasting only a few minutes or, at most, a half hour. But another class of compounds called **organophosphates** bind irreversibly to acetylcholinesterase and consequently are extremely toxic. Many insecticides are organophosphates. Organophosphates are also used in chemical warfare.

Many hundreds of other drugs can act on acetylcholine neuromuscular synapses, and thousands of additional substances can act on other kinds of synapses. A few that are neurotoxins are listed in Table 6-1. Despite their varied effects, all these substances act as either agonists or antagonists. If you understand the opposing actions of agonists and antagonists, you will also understand how some drugs can be used as antidotes for poisoning by other drugs.

If a drug or toxin that is ingested affects neuromuscular synapses, will it also affect acetylcholine synapses in the brain? That depends on whether the substance can cross the blood–brain barrier. Some of the drugs that act on acetylcholine synapses at the muscles can also act on acetylcholine synapses in the brain. For example, physostigmine and nicotine can readily pass the blood–brain barrier and affect the brain, whereas curare cannot. Thus, whether a cholinergic agonist or antagonist has psychoactive action depends on the size and structure of its molecules, which determine whether that substance can manage to reach the brain.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Origin</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrodotoxin</td>
<td>Puffer fish</td>
<td>Blocks membrane permeability to Na(^+) ions</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Natural element</td>
<td>Blocks Ca(^{2+}) channels</td>
</tr>
<tr>
<td>Reserpine</td>
<td>Tree</td>
<td>Destroys storage granules</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Crocus plant</td>
<td>Blocks microtubules</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Coffee bean</td>
<td>Blocks adenosine receptors, blocks Ca(^{2+}) channels</td>
</tr>
<tr>
<td>Spider venom</td>
<td>Black widow spider</td>
<td>Stimulates ACh release</td>
</tr>
<tr>
<td>Botulin toxin</td>
<td>Food poisoning</td>
<td>Blocks ACh release</td>
</tr>
<tr>
<td>Curare</td>
<td>Plant berry</td>
<td>Blocks ACh receptors</td>
</tr>
<tr>
<td>Rabies virus</td>
<td>Infected animal</td>
<td>Blocks ACh receptors</td>
</tr>
<tr>
<td>Ibotenic acid</td>
<td>Mushroom</td>
<td>Similar to domoic acid</td>
</tr>
<tr>
<td>Strychnine</td>
<td>Plant</td>
<td>Blocks glycine</td>
</tr>
<tr>
<td>Apamin</td>
<td>Bees and wasps</td>
<td>Blocks Ca(^{2+}) channels</td>
</tr>
</tbody>
</table>
Psychoactive drugs are substances that produce changes in behavior by acting on the nervous system. These drugs encounter various barriers between their entry into the body and their action at a central nervous system target. One of the most important of these obstacles is the blood–brain barrier, which generally allows only substances needed for nourishing the brain to pass from the capillaries into the central nervous system. Most drugs that have psychoactive effects do so by crossing the blood–brain barrier and influencing chemical reactions at brain synapses. Drugs that influence communication between neurons do so by acting either as agonists or as antagonists to neurotransmission—that is, by either increasing or decreasing the effectiveness of neurotransmission. There are, however, great individual differences in people’s responses to drugs due to differences in age, sex, body size, and other factors that affect sensitivity to a particular substance.

**THE CLASSIFICATION OF PSYCHOACTIVE DRUGS**

It is difficult to devise a classification system for the many thousands of psychoactive drugs. Classifications based on a drug’s chemical structure have not been very successful, because drugs having similar structures can have quite different effects, whereas drugs having different structures can have very similar effects. Classification schemes based on receptors in the brain also have been problematic, because a single drug can act on many different receptors. The same problem arises with classification systems based on the neurotransmitter that a drug affects, because many drugs act on many different transmitters. The classification used in this book, summarized in Table 6-2, is based on the most pronounced psychoactive effect that a drug produces. That classification divides drugs into seven classes, with each class containing from a few to many thousands of different chemicals in its subcategories.

Drugs that are used to treat neuropsychological illnesses are listed again in Table 6-3, along with the dates that they were discovered and the names of their discoverers. You may be surprised to know that their therapeutic actions were originally discovered by accident. Subsequently, scientists and pharmaceutical companies developed many forms of each drug in an effort to increase its effectiveness and reduce its side effects. At the same time, experimental researchers attempted to explain each drug’s action on the nervous system. Those drug actions are what we examine here, as we consider some of the classes of drugs given in Table 6-2.

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### Table 6-2  Classification of Psychoactive Drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Sedative hypnotics and antianxiety agents</td>
<td>Barbiturates (anesthetic agents), alcohol, Benzodiazepines: diazepam (Valium)</td>
</tr>
<tr>
<td>II. Antipsychotic agents</td>
<td>Phenothiazines: chlorpromazine, Butyrophenones: haloperidol</td>
</tr>
<tr>
<td>III. Antidepressants</td>
<td>Monoamine oxidase (MAO) inhibitors, Tricyclic antidepressants: imipramine (Tofranil), Atypical antidepressants: fluoxetine (Prozac)</td>
</tr>
<tr>
<td>IV. Mood stabilizers</td>
<td>Lithium</td>
</tr>
<tr>
<td>V. Narcotic analgesics</td>
<td>Morphine, codeine, heroin</td>
</tr>
<tr>
<td>VI. Psychomotor stimulants</td>
<td>Cocaine, amphetamine, caffeine, nicotine</td>
</tr>
<tr>
<td>VII. Psychedelics and hallucinogens</td>
<td>Anticholinergics: atropine, Noradrenergics: mescaline, Serotonergics: LSD (lysergic acid diethylamide), psilocybin, Tetrahydrocannabinol: marijuana</td>
</tr>
</tbody>
</table>

Visit the Web site at [www.worthpublishers.com/kolb/chapter6](http://www.worthpublishers.com/kolb/chapter6) to learn more about the variety of psychoactive drugs.
Sedative Hypnotics and Antianxiety Agents

The effects of sedative hypnotics and antianxiety agents differ, depending on their dose. At low doses they reduce anxiety, at medium doses they sedate, and at high doses they produce anesthesia or coma. At very high doses they can kill (Figure 6-7).

The most common members of this diverse group of drugs are alcohol, barbiturates, and benzodiazepines. Alcohol is well known to most people because it is so widely consumed. Its potentially devastating effects on fetuses are explored in “Fetal Alcohol Syndrome” on page 202.

Barbiturates are a type of drug sometimes prescribed as a sleeping medication, but they are now mainly used to induce anesthesia before surgery. Benzodiazepines are also known as minor tranquilizers or antianxiety agents. An example is the widely prescribed drug Valium. Benzodiazepines are often given to people who are having trouble coping with some major life stress, such as a traumatic accident or a death in the family. Whereas both alcohol and barbiturates can produce sleep, anesthesia, and coma at doses only slightly higher than those that produce sedation, the dose of benzodiazepines that produces sleep and anesthesia is substantially higher than that which is needed to relieve anxiety.

A characteristic feature of sedative hypnotics is that they cause weaker and weaker responses in the user who takes repeated doses. A larger dose is then required to maintain the drug’s initial effect. This lessening of response to a drug over time is called tolerance. Cross-tolerance develops when the tolerance developed for one drug is carried over to a different drug. Cross-tolerance suggests that the two drugs are similar in their actions on the nervous system. Alcohol, barbiturates, and benzodiazepines show cross-tolerance, suggesting that they affect a common nervous system target. This common

### Table 6-3 Drugs Used for the Treatment of Mental Illness

<table>
<thead>
<tr>
<th>Illness</th>
<th>Drug class</th>
<th>Representative drug</th>
<th>Common trade name</th>
<th>Discoverer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>Phenothiazines</td>
<td>Chlorpromazine</td>
<td>Largactil</td>
<td>Jean Delay and Pierre Deniker (France), 1952</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thorazine</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>Butyrophenone</td>
<td>Haloperidol</td>
<td>Haldol</td>
<td>Paul Jansen (Belgium), 1957</td>
</tr>
<tr>
<td></td>
<td>Monoamine oxidase (MAO) inhibitors</td>
<td>Iproniazid</td>
<td>Marsilid</td>
<td>Nathan S. Kline and J. C. Saunders (United States), 1956</td>
</tr>
<tr>
<td>Bipolar disorders</td>
<td>Tricyclic antidepressants</td>
<td>Imipramine</td>
<td>Tofranil</td>
<td>Roland Kuhn (Switzerland), 1957</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>Selective serotonin reuptake inhibitors</td>
<td>Fluoxetine</td>
<td>Prozac</td>
<td>Eli Lilly Company, 1986</td>
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<td></td>
<td>Benzodiazepines</td>
<td>Lithium (metallic element)</td>
<td></td>
<td>John Cade (Australia), 1949</td>
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<td></td>
<td></td>
<td>Chlordiazepoxide</td>
<td>Librium</td>
<td>Leo Sternbach (Poland), 1940</td>
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<td>Meprobamate</td>
<td>Miltown</td>
<td>Frank Berger and William Bradley (Czechoslovakia), 1946</td>
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<td>Equanil</td>
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Antianxiety agent. A type of drug that reduces anxiety; benzodiazepines and sedative-hypnotic agents are of this type.

Cross-tolerance. A form of tolerance in which the response to a novel drug is reduced because of tolerance developed in response to a related drug.
The expression fetal alcohol syndrome (FAS) was coined in 1973 to describe a pattern of physical malformation and mental retardation observed in children born of alcoholic mothers. Children with FAS may have abnormal facial features, such as unusually wide spacing between the eyes. They also have a range of brain abnormalities, from small brains with abnormal gyri to abnormal clusters of cells and misaligned cells in the cortex. Related to these brain abnormalities are certain behavioral symptoms that FAS children tend to have in common. They display varying degrees of learning disability and lowered intelligence test scores, as well as hyperactivity and other social problems.

Identification of FAS stimulated widespread interest in the effects of alcohol consumption by pregnant women. The offspring of approximately 6 percent of alcoholic mothers suffer from pronounced FAS. The incidence of it in different geographic regions varies widely, depending largely on the pattern and degree of alcohol abuse in those locations. In major cities, the incidence of FAS is about 1 in 700 births. Its incidence increases to as many as 1 in 8 births on one Native American reservation in Canada.

FAS is not an all-or-none syndrome. Alcohol-induced abnormalities can vary from hardly noticeable physical and psychological effects to the complete FAS syndrome. The severity of effects is thought to be related to when, how much, and how frequently alcohol is consumed. Apparently, the effects are worse if alcohol consumption occurs in the first 3 months of pregnancy, which, unfortunately, may be a time when many women do not yet realize that they are pregnant. Severe FAS is also more likely to coincide with binge drinking, which produces high blood-alcohol levels. Other factors related to a more severe outcome are poor nutritional health of the mother and the mother’s use of other drugs, including the nicotine in cigarettes.

A major question raised by FAS is how much alcohol is too much to drink during pregnancy. The answer to this question is complex, because the effects of alcohol on a fetus depend on so many factors. To be completely safe, it is best not to drink at all in the months preceding pregnancy and during it. This conclusion is supported by findings that as little as one drink of alcohol per day during pregnancy can lead to a decrease in intelligence test scores of children.

Fetal alcohol syndrome in both its full-blown and milder forms has important lessons for us. Alcohol is a widely used drug. When taken in moderation, it is thought to have some health benefits; yet it does pose risks, although those risks are completely avoidable if alcohol is used appropriately. A major problem is that women who are most at risk for bearing FAS babies are poor and not well educated, with alcohol-consumption problems that predate pregnancy and little access to prenatal care. It is often difficult to inform these women about the dangers that alcohol poses to a fetus and to encourage them to abstain from drinking while they are pregnant.

Children who suffer from fetal alcohol syndrome do not merely look abnormal; their brains are underdeveloped and many are severely retarded. The brain of a child who suffered from fetal alcohol syndrome (lower right) lacks the convolutions characteristic of the brain of a normal child (lower left).
target is now known to be the receptor sites for the major inhibitory neurotransmitter GABA. Neurons that contain GABA are widely distributed in the nervous system and function to inhibit the activity of other neurons.

One of the receptors affected by GABA is the GABA<sub>A</sub> receptor. As illustrated in Figure 6-8, this receptor contains a chloride channel, and excitation of the receptor produces an influx of Cl<sup>-</sup> ions. Remember that an influx of Cl<sup>-</sup> ions increases the concentration of negative charges on the inside of the cell membrane, depolarizing it and making it less likely to propagate an action potential. The inhibitory effect of GABA, therefore, is to decrease a neuron's rate of firing.

The GABA<sub>A</sub> receptor is a complex molecule that has not only a binding site for GABA but also two other binding sites. One of these two binding sites accepts alcohol and barbiturates (the sedative-hypnotic site), whereas the other site accepts benzodiazepines (the antianxiety site). Drugs binding to the sedative-hypnotic site directly increase the influx of chloride ions and so act like GABA. Consequently, the higher the dose of these drugs, the greater their inhibitory effect on neurons. The effect of antianxiety drugs is different. Excitation of the antianxiety site enhances the binding of GABA to its receptor site, which means that the availability of GABA determines the potency of an antianxiety drug. Because GABA is very quickly reabsorbed by the neurons that secrete it and by surrounding glial cells, GABA concentrations are never excessive, making it hard to overdose on antianxiety drugs.

Scientists do not know what natural substances bind to the GABA<sub>A</sub> receptor binding sites other than GABA. A. Leslie Morrow and her coworkers (1999) suggest that a natural brain steroid called allopregnanolone may bind to the sedative-hypnotic site. Allopregnanolone is produced by activation of the pituitary. One mechanism by which alcohol may have its effects is by facilitating the production of allopregnanolone, which in turn activates the sedative-hypnotic site of the GABA<sub>A</sub> receptor, thus producing sedation. An explanation of the less potent effect of alcohol on human males than on females is that females have higher levels of allopregnanolone, thus making them more sensitive to the effects of alcohol and causing them to drink less and to be less likely to become alcoholic.

Because of their different actions on the GABA<sub>A</sub> receptor, sedative-hypnotic and antianxiety drugs should never be taken together. A sedative hypnotic acts like GABA, but, unlike GABA, it is not quickly absorbed by surrounding cells. Thus, by remaining on the site, its effects are enhanced by an antianxiety drug. The cumulative action of the two drugs will therefore exceed the individual action of either one. Even small combined doses of antianxiety and sedative-hypnotic drugs can produce coma or death.

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**Figure 6-8**

Sedative hypnotics bind to the GABA<sub>A</sub> receptor, which contains a chloride channel. By binding to one of the sites (the sedative-hypnotic site) on the GABA<sub>A</sub> molecule, barbiturates and alcohol mimic the effects of GABA. By binding to a different site (the antianxiety site) on the molecule, benzodiazepines enhance the action of GABA. Note that sedative hypnotics, antianxiety agents, and GABA each have different binding sites.
Antipsychotic Agents

The term psychosis refers to a number of neuropsychological conditions, such as schizophrenia, that are characterized by hallucinations or delusions. (An example of delusions is described in “Drug-Induced Psychosis” on page 224.) Drugs used to treat psychosis are known as antipsychotic agents, also called major tranquilizers or neuroleptics. The use of antipsychotic agents has greatly reduced the number of patients held in mental institutions, as Figure 6-9 shows. Improving the functioning of schizophrenics has been an important achievement because the incidence of schizophrenia is high, about 1 in every 100 people.

Although major tranquilizers have been widely used for nearly 50 years, their therapeutic actions are still not understood. They have an immediate effect in reducing motor activity, and so they alleviate the excessive agitation of some schizophrenic patients. In fact, one of their negative side effects can be to produce symptoms reminiscent of Parkinson’s disease, in which control over movement is impaired. With prolonged use, they can cause dyskinesia (involuntary movements). This condition includes rhythmical movements of the mouth, hands, and other body parts. The effects are usually reversible if the person stops taking the drug.

At least part of the action of antipsychotic drugs is to block one kind of dopamine receptor, called the D₂ receptor. This action of antipsychotic drugs has led to the dopamine hypothesis of schizophrenia. It holds that some forms of schizophrenia may be related to excessive dopamine activity, which antipsychotic drugs control. Other support for the dopamine hypothesis comes from the “schizophrenia-like” symptoms of chronic users of amphetamine, a stimulant drug. As Figure 6-10 shows, amphetamine is a dopamine agonist that fosters the release of dopamine from the presynaptic membrane of dopamine synapses and blocks the reuptake of dopamine from the synaptic cleft. If amphetamine causes schizophrenia-like symptoms by increasing dopamine activity, perhaps naturally occurring schizophrenia is related to excessive dopamine action, too.

Even though such drug effects suggest that the dopamine hypothesis of schizophrenia may have merit, experimental studies have been unable to find dopamine-
related differences between normal people and schizophrenics. Compared with the brains of normal subjects, the brains of patients with schizophrenia do not contain a greater number of dopamine synapses, do not release more dopamine from presynaptic membranes, and do not possess more D2 receptors for dopamine. Consequently, the cause of schizophrenia and the mechanism by which antipsychotic agents work currently remain unclear.

**Antidepressants**

Depression is a very common psychological disorder. At any given time, about 5 percent of the adult population suffers from it, and in the course of a lifetime, 30 percent may experience at least one episode of depression. The symptoms of this disorder are discussed in “Depression” on page 206. Most people recover from depression within a year of its onset, but, if the illness is left untreated, the incidence of suicide is high. Two different types of drugs have antidepressant effects: the **monoamine oxidase inhibitors (MAO inhibitors)** and the **tricyclic antidepressants**. The so-called **second-generation antidepressants**, which include fluoxetine (Prozac), are similar to the tricyclic antidepressants.
P. H. was a 53-year-old high school teacher who, although popular with his students, was obtaining less and less satisfaction from his work. His marriage was also foundering because he was becoming apathetic and no longer wanted to socialize or go on holidays with his wife. He was having great difficulty getting up in the morning and arriving at school on time. He eventually consulted a physician with a complaint of severe chest pains, which he thought signified that he was about to have a heart attack. He informed his doctor that a heart attack would be a welcome relief because it would end his problems. The physician concluded that P. H. was suffering from depression and referred him to a psychiatrist. The psychiatrist arranged for P. H. to come in once a week for counseling and gave him a prescription for a monoamine oxidase (MAO) inhibitor, a kind of antidepressant drug. The psychiatrist informed P. H. that many foods contain tyramine, a chemical that can raise blood pressure to dangerous levels, and, because the action of this chemical increases when taking a MAO inhibitor, he should avoid foods that contain tyramine. The psychiatrist gave him a list of foods to be avoided and especially warned him against eating cheese or drinking wine. This was standard advice given to patients for whom MAO inhibitors were prescribed. A few days later, P. H. opened a bottle of wine, took a two-pound block of cheese out of the refrigerator, and began to consume them. That evening he suffered a massive left-hemisphere stroke that left him unable to speak or to walk. It seemed clear that P. H. had attempted to commit suicide. Because of their dangers, MAO inhibitors are now seldom prescribed.

Depression is a condition that affects about 6 percent of adults and is much more common in women than in men. Approximately 64 percent of severely depressed people recover within 6 months, many without treatment. Depression is characterized by a wide range of symptoms, including emotional ones (such as feelings of emptiness and despair), motivational ones (such as lack of drive and initiative), behavioral ones (such as withdrawal from usual activities), and cognitive ones (such as considering oneself inadequate and inferior). Depressed people may also experience changes in appetite, disturbances of sleep, sexual problems, and various aches and pains, including headaches.

Since the 1950s, depression has been treated with antidepressant drugs, a variety of behavioral therapies, and electroconvulsive therapy (ECT), a treatment in which electrical current is passed briefly through one hemisphere of the brain. Of the drug treatments available, tricyclic antidepressants, including the second-generation versions, are now favored because they are safer and more effective than MAO inhibitors.

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Depression is often detected when patients go to a physician complaining about one of the many somatic symptoms that often accompany the disorder. The most common complaints made by these patients are weakness, pain, and irregular menses.

Antidepressants are thought to act by improving chemical transmission in serotonin, noradrenaline, histamine, and acetylcholine receptors and perhaps in dopamine receptors, too. Figure 6-11 shows their action at a serotonin synapse, the synapse on which most research is focused. As you can see, MAO inhibitors and the tricyclic and second-generation antidepressants have different mechanisms of action in increasing the availability of serotonin. Monoamine oxidase is an enzyme that breaks down serotonin within the axon terminal. The inhibition of MAO with an MAO inhibitor therefore provides more serotonin for release with each action potential. The tricyclic antidepressants and the second-generation antidepressants block the transporter that takes serotonin back into the axon terminal. The second-generation antidepressants are thought to be especially selective in blocking serotonin uptake, and, consequently, some are also called selective serotonin uptake blockers. Because the transporter is blocked, serotonin remains in the synaptic cleft for a longer period, thus prolonging its action on postsynaptic receptors.

There is, however, a significant problem in understanding how antidepressants function. Although these drugs begin to affect synapses very quickly, their antidepressant actions take weeks to develop. No one is sure why. Additionally, about 20 percent of patients with depression fail to respond to antidepressant drugs, and others cannot tolerate the side effects of these medications. Side effects can include increased anxiety, sexual dysfunction, sedation, dry mouth, blurred vision, and memory impairments. Although many people hoped that the second-generation antidepressants would produce fewer side effects than do the tricyclic antidepressants, that hope has not been fully realized. In fact, it is unclear how selective antidepressants are in their action on the brain. Even marketing for Prozac, one of the more selective antidepressant compounds, suggest that this drug can be used to treat not only

![Figure 6-11](image_url)

Different antidepressant drugs act on the serotonin synapse in different ways to increase the availability of serotonin. MAO inhibitors block MAO, an enzyme that breaks down serotonin within the terminal. Selective serotonin reuptake blockers block the transporter protein that takes serotonin back up into the terminal after use. Thus, both types of drugs result in increased levels of serotonin available to act on serotonin receptors.
depression but also obsessive-compulsive disorder. The major symptoms of obsessive-compulsive disorder are obsessive thoughts and behaviors, such as ideas that people cannot get out of their heads and ritual-like actions that they keep endlessly performing. Although obsessive-compulsive disorder is related to guilt and anxiety, as is depression, it is usually classified as a separate condition from depression.

**Narcotic Analgesics**

The term *narcotic analgesics* describes a group of drugs that have sleep-inducing (narcotic) and pain-relieving (analgesic) properties. Many of these drugs are derived from opium, an extract of the seeds of the opium poppy, Papaver somniferum, which is shown in Figure 6-12. Opium has been used for thousands of years to produce euphoria, analgesia, sleep, and relief from diarrhea and coughing.

In 1805, the German chemist Friedrich Sertürner synthesized two pure substances from the poppy plant, codeine and morphine. **Codeine** is often included in cough medicine and in pain relievers such as aspirin (although not in the United States). **Morphine**, which was named after Morpheus, the Greek god of dreams, is a very powerful pain reliever. Despite decades of research, no other drug has been found that exceeds morphine's effectiveness as an analgesic. Opium antagonists such as nalorphine and naloxone block the actions of morphine and so are useful in treating morphine overdoses. **Heroin**, another opiate drug, is synthesized from morphine. It is more fat soluble than morphine and penetrates the blood–brain barrier more quickly, allowing it to produce very rapid relief from pain. Although heroin is a legal drug in some countries, it is illegal in others, including the United States.

What are the effects of opiate drugs on the central nervous system? Candace Pert and Solomon Snyder provided an important answer to this question by injecting radioactive opiates into the brain and identifying special receptors to which the opiates bound. But what were these receptors doing in the brain? Opiates, such as morphine, after all, are not naturally occurring brain chemicals. This question was answered by the Scottish pharmacologists John Hughes and Hans Kosterlitz, who identified two short peptides that had opioid properties and appeared to be neurotransmitters. They called these opiate-like transmitters **endorphins**, an abridgement of the phrase endogenous morphinlike substances.

We now know that there are endorphin-containing neurons in many brain regions and that morphine is similar enough to endorphins to mimic their action in the brain. Researchers have extensively studied whether endorphins can be used to relieve pain. The answer is so far mixed. Although endorphins do alleviate pain, they are difficult to deliver to the brain. Consequently, morphine remains a preferred pain treatment.
Stimulants

Stimulants are a diverse group of drugs that increase the activity of neurons in a number of ways. They are subdivided into four groups: behavioral stimulants, convulsants, general stimulants, and psychedelic drugs.

Behavioral stimulants are drugs that increase motor behavior as well as elevate a person’s mood and level of alertness. Two examples are cocaine and amphetamine. **Cocaine** is extracted from the Peruvian coca shrub, shown in Figure 6-13. It can be taken either by sniffing (snorting) or by injection. Many cocaine users do not like to inject cocaine intravenously, so they sniff a highly concentrated form of it called “crack.” Crack is chemically altered so that it vaporizes at low temperatures, and the vapors are inhaled. The indigenous people of Peru discovered cocaine in coca leaves, which they chewed. **Amphetamine** is a synthetic compound that was discovered in attempts to synthesize the neurotransmitter epinephrine. Both amphetamine and cocaine are dopamine agonists that act by blocking the dopamine transporter, leaving more dopamine available in the synaptic cleft. Amphetamine also stimulates the release of dopamine from presynaptic membranes. Both these mechanisms increase the amount of dopamine available in synapses to stimulate dopamine receptors.

Cocaine was originally popularized as an antidepressant by the Viennese psychoanalyst Sigmund Freud. In a 1884 paper titled “In Praise of Coca,” Freud concluded: “The main use of coca will undoubtedly remain that which the Indians have made of it for centuries: it is of value in all cases where the primary aim is to increase the physical capacity of the body for a given short period of time and to hold strength in reserve to meet further demands—especially when outward circumstances exclude the possibility of obtaining the rest and nourishment normally necessary for great exertion.” Freud also recommended that cocaine could be used as a local anesthetic.

Cocaine was once widely used in soft drinks and wine mixtures, which were promoted as invigorating tonics. It is the origin of the trade name Coca-Cola, because this soft drink once contained cocaine, as suggested by the advertisement in Figure 6-14. The addictive properties of cocaine soon
became apparent, however. Freud had recommended cocaine to a close friend who, in an attempt to relieve excruciating pain after the amputation of his thumb, had become addicted to morphine. The euphoric effects of cocaine helped the friend withdraw from the morphine, but soon he required larger and larger doses of cocaine. Eventually, he experienced euphoric episodes followed by a sudden crash after each injection. He continued to use larger and larger doses and eventually became schizophrenic. Similar experiences by others led to an escalating negative view of cocaine use. Cocaine proved to be valuable as a local anesthetic, however, and many derivatives, such as Novocaine, are used for this purpose today.

Amphetamine was first used as a treatment for asthma. A form of amphetamine, Benzedrine, was sold in inhalers as a nonprescription drug through the 1940s. Soon people discovered that they could open the container and ingest its contents to obtain an energizing effect. In 1937, an article in the Journal of the American Medical Association reported that Benzedrine tablets improved performance on mental-efficiency tests. This information was quickly disseminated among students, who began to use the drug as an aid to study for examinations. Amphetamine was widely used in World War II to help keep troops and pilots alert and to improve the productivity of wartime workers. It was also used as a weight-loss aid. In the 1960s, drug users discovered that they could obtain an immediate pleasurable “rush,” often described as a whole-body orgasm, by intravenous injection of amphetamine. People who took amphetamine in this way, called “speed freaks,” would inject the drug every few hours for days, remaining in a wide-awake, excited state without eating. They would then crash in exhaustion and hunger and, after a few days of recovery, would begin the cycle again. One explanation for repeated injections was to prevent the depressive crash that occurred when the drug wore off.

General stimulants are drugs that cause a general increase in the metabolic activity of cells. Caffeine is a widely used example. Caffeine inhibits an enzyme that ordinarily breaks down cyclic adenosine monophosphate (cAMP). The resulting increase in cAMP leads to an increase in glucose production within cells, thus making available more energy and allowing higher rates of cellular activity.

The final class of stimulants consists of psychedelic drugs; they alter sensory perception and cognitive processes. There are four major types of psychedelics. One consists of acetylcholine psychedelics, which either block or facilitate transmission at acetylcholine synapses in the brain. A second is made up of norepinephrine psychedelics. This type includes mescaline, obtained from the peyote cactus, which is legal for use by Native Americans for religious practices. A third type of psychedelic drug is tetrahydrocannabinol, or THC for short. THC is the active ingredient in marijuana, which is obtained from the hemp plant Cannabis sativa. There is growing evidence that cannabis acts on endogenous THC receptors called the CB1 and CB2 receptors. They are thought by scientists to be the receptors for an endogenous neurotransmitter called anandamide. Surprisingly, a number of lines of research suggest that anandamide plays a role in enhancing forgetting. The idea is that anandamide prevents memory systems of the brain from being overwhelmed by the information to which the brain is exposed each day. Thus, THC may have a detrimental effect on memory. The fourth and last type in this drug category consists of the serotonin psychedelics. They include both lysergic acid diethylamide (LSD) and psilocybin (obtained from a certain mushroom). These substances may stimulate postsynaptic receptors of serotonin synapses or they may block the activity of serotonin neurons through serotonin autoreceptors. In addition, these drugs may stimulate other transmitter systems, including norepinephrine receptors.
Classifying psychoactive drugs by their principal effects yields seven major categories: sedative hypnotics and antianxiety agents, antipsychotic agents, antidepressants, mood stabilizers, narcotic analgesics, psychomotor stimulants, and stimulants that have psychedelic and hallucinogenic effects. Researchers are still learning how these drugs act on the nervous system. We now know that sedative hypnotics and antianxiety agents, including alcohol, barbiturates, and benzodiazepines, all affect receptor sites for the neurotransmitter GABA. Although the therapeutic actions of antianxiety agents are still not understood, one of those actions is to block a certain kind of dopamine receptor. Antidepressants, including the tricyclics and MAO inhibitors, are thought to act by improving chemical transmission in serotonin, noradrenaline, histamine, and acetylcholine receptors. The narcotic analgesics derived from opium have their effects by binding to special receptors for naturally occurring brain chemicals called endorphins. Cocaine and amphetamine are examples of psychomotor stimulants that act as dopamine agonists, making more dopamine available in synapses. As scientists continue to study the actions of psychoactive drugs, they will also learn much more about neuropsychological disorders and possible treatments of them.

DRUGS, EXPERIENCE, CONTEXT, AND GENES

Many behaviors trigger very predictable results. When you strike the same key of a piano repeatedly, you hear the same note each time. When you flick a light switch over and over again, the same bulb goes on exactly as before. This kind of cause-and-effect consistency leads some people to assume that a drug will produce the same results every time it is taken. That assumption is incorrect, however, for several reasons. For one thing, the effect of a drug may change from one administration to another because the drug is taken in different contexts with different accompanying behaviors, which cause the brain to respond to it differently. In addition, the actions of a drug on one person may be quite different from its actions on someone else. The reason is that experience and the influence of genes also determine drug reactions. Finally, with repeated use, the effect of a drug can be dramatically different from the effect obtained with the first use. The reason is that many drugs produce an enduring change in the brain that, in time, can be quite substantial and can alter what subsequent doses do. In the following sections, we will consider a number of ways in which repeated use of drugs changes the brain and behavior.

Tolerance

Two college freshman roommates, B. C. and A. S., went to a party, then to a bar, and by 3 AM were in a restaurant ordering pizza. A. S. decided that he wanted to watch the chef make his pizza, and off he went to the kitchen. A long and heated argument ensued involving A. S., the chef, and the manager. The two roommates then got into A. S.’s car and were leaving the parking lot when a police officer, called by the manager, drove up and stopped them. A. S. failed a breathalyzer test, which measures body alcohol content, and was taken into custody; but, surprisingly, B. C. passed the test, even though he had consumed the same amount of alcohol as A. S. had. Why this difference in their responses to the drinking bout?
The reason for the difference could be that B. C. had developed greater tolerance for alcohol than A. S. had. In one study, Isbell and coworkers (1955) showed how such tolerance comes about. These researchers gave subjects enough alcohol daily in a 13-week period to keep them in a constant state of intoxication. Yet they found that the subjects did not stay drunk for 3 months straight. When the experiment began, all the subjects showed rapidly rising levels of blood alcohol and behavioral signs of intoxication, as shown in Figure 6-15. Between the 12th and 20th days of alcohol consumption, however, blood-alcohol levels and the signs of intoxication fell to very low levels, even though the subjects maintained a constant alcohol intake. Interestingly, too, although blood-alcohol levels and signs of intoxication fluctuated in subsequent days of the study, one did not always correspond with the other. A relatively high blood-alcohol level was sometimes associated with a low outward appearance of being drunk. Why?

### Experiment

**Question:** Will consumption of alcohol produce tolerance?

**Procedure**

Subjects were given alcohol every day for 13 weeks—enough to keep them intoxicated.

**Results**

- When the experiment began, all the subjects increased their intake of alcohol.
- After 15–20 days of alcohol consumption, blood-alcohol levels fell...
- ...and the signs of intoxication fell, too.

### Figure 6-15

Relative changes in intoxication, blood-alcohol level, and alcohol intake in subjects after 20 days of steady drinking document the development of tolerance to alcohol. Note that, as alcohol intake increases initially, so do blood-alcohol levels and the degree of intoxication. With continued consumption, blood-alcohol levels and behavioral intoxication decrease, owing to tolerance.


**Conclusion**

Because of tolerance, much more alcohol was required by the end of the study to obtain the same level of intoxication that was produced at the beginning.
These results were likely the products of three different kinds of tolerance—metabolic tolerance, cellular tolerance, and learned tolerance. In the development of metabolic tolerance, the number of enzymes needed to break down alcohol in the liver, blood, and brain increases. As a result, any alcohol that is consumed is metabolized more quickly, and so blood-alcohol levels are reduced. In the development of cellular tolerance, the activities of brain cells adjust to minimize the effects of alcohol present in the blood. This kind of tolerance can help explain why the behavioral signs of intoxication may be very low despite a relatively high blood-alcohol level. Learned tolerance, too, can help explain a drop in the outward signs of intoxication. As people learn to cope with the daily demands of living while under the influence of alcohol, they may no longer appear to be drunk.

That learning plays a role in tolerance to alcohol may seem surprising to you, but this role has been confirmed in many studies. For instance, Wenger and his coworkers (1981) trained rats to walk on a narrow conveyor belt to avoid electric shock to their feet from a grid over which the belt slid. One group of rats received alcohol after training in walking the belt, whereas another group received alcohol before training. A third group received training only, and a fourth group alcohol only. After several days of exposure to their respective conditions, all groups were given alcohol before a walking test. The rats that had received alcohol before training performed well, whereas those that had received training and alcohol separately performed just as poorly as those that had never had alcohol before or those that had not been trained. Apparently, animals can acquire the motor skills needed to balance on a narrow belt despite alcohol intoxication. Over time, in other words, they can learn to compensate for being drunk.

The results of these experiments are relevant to our story of A. S. and B. C. A. S. came from a large city and worked for long hours assisting his father with his plumbing business. He seldom attended parties and so was unaccustomed to alcohol. B. C., in contrast, came from a small town, where he was the acclaimed local pool shark. He was accustomed to “sipping a beer” both while waiting to play and during play, which he did often. B. C.’s body, then, was prepared to metabolize alcohol, and his experience in drinking while engaging in a skilled sport had prepared him to display controlled behavior under the influence of alcohol. Enhanced metabolism and controlled behavior are manifestations of tolerance to alcohol.

Tolerance can develop not only to alcohol but also to many other drugs, such as barbiturates, amphetamine, and narcotics. In humans, for instance, a dose of 100 milligrams of morphine is sufficient to cause profound sedation and even death in some first-time users, but those who have developed tolerance to this drug have been known to take 4000 milligrams of the drug without adverse effects. Similarly, long-time users of amphetamine may take doses 100 or more times as great as the doses that they initially took to produce the same behavioral effect. In other words, with repeated administration of a drug, the effect produced by that drug may progressively diminish owing to tolerance.

**Metabolic tolerance.** Reduced sensitivity to a substance that results from the increased ability of cells to metabolize the substance.

**Cellular tolerance.** A change that takes place in a cell in which the activity of the cell adjusts to the excitatory or inhibitory effects of a drug.

**Sensitization.** Increased behavioral response to the same dose of a drug.
To demonstrate sensitization, Terry Robinson and Jill Becker (1986) isolated rats in observation boxes and recorded their reactions to an injection of amphetamine, especially reactions such as increases in sniffing, rearing, and walking, which are typical rat responses to this drug. Every 3 or 4 days, the investigators repeated the procedure. The results are given in Figure 6-16 (left). They show that the behavior of the rats was more vigorous each time they received the drug. This increased response on successive tests was not due to the animals becoming “comfortable” with the test situation. Control animals that received no drug did not display a similar escalation in sniffing, rearing, and walking. Moreover, the sensitization to amphetamine was enduring. Even when two injections of amphetamine were separated by months, the animals still showed an increased response to the drug.

Remember that amphetamine is a dopamine agonist and acts both by stimulating the release of dopamine from the axon terminals of dopamine neurons and by blocking the reuptake of dopamine into those terminals. Which of these two actions might underlie sensitization to amphetamine? One possibility is that sensitization is due to the release of dopamine. Perhaps with each successive dose of amphetamine, more dopamine is released, causing a progressively increasing behavioral response to the drug.

This explanation was confirmed by another experiment on rats, some of which had been sensitized to amphetamine and others of which had never been given the drug (Casteñeda et al., 1988). The basal ganglia, which is rich in dopamine synapses, was removed from the brain of each rat and placed in a fluid-filled container. Then the tissue was treated with amphetamine. An analysis of the fluid that bathed the tissue showed that the basal ganglia from sensitized rats released more dopamine than did the basal ganglia of nonsensitized rats. This increased release of dopamine can explain sensitization to amphetamine.

Sensitization also develops to drugs with depressant effects, such as the major tranquilizer Flupentixol, which is a dopamine antagonist that blocks dopamine receptors. Figure 6-16 (right) shows the effect of Flupentixol on the swimming behavior of rats in another study (Whishaw et al., 1989). The researchers trained the rats to swim a short distance to a platform in a swimming pool. When the rats were able to reach the platform within 1 to 2 seconds, they were given an injection of Flupentixol. On the first few swims after the injection of the drug, the rats swam normally, but then they began to slow down. After about 12 swims, they simply sank when placed in the water and had to be removed to prevent them from drowning. This effect was not just the result of administering 12 successive swimming trials on the same day. If the rats were injected with the drug and given only one trial each day for 12 days, the same results were obtained. On the first few days, the rats swam normally, but thereafter they began to slow down until, by the 12th day, they sank when placed into the water. Sensitization to the drug depended on the number of swims, regardless of the spacing between swims or the number of drug injections. Presumably, Flupentixol blocks dopamine synapses in the brain more effectively after sensitization in a way that accounts for these results.

Sensitization can be very selective with respect to the behavior affected, and it is detected only if tests are always given under the same conditions. For example, if rats are given amphetamine in their home cage on a number of occasions before a sensitization experiment starts, their behavior in the test situation does not reveal their previous drug experience. Sensitization develops as if the animals were receiving the drug for the first time. Furthermore, sensitization is difficult to achieve in an animal that is tested in its home cage. Fraioli and coworkers (1999) gave amphetamine to two groups of rats and recorded the rats’ behavioral responses to successive injections.
**EXPERIMENT**

**Question:** Does the injection of a drug always produce the same behavior?

**Procedure #1**

In the Robinson and Becker study, animals were given periodic injections of the same dose of amphetamine. Then the researchers measured the number of times the rat reared in its cage.

**Procedure #2**

In the Whishaw study, animals were given different numbers of swims after being injected with Flupentixol. Then the researchers measured their speed to escape to a platform in a swimming pool.

**Results #1**

- Number of incidents of rearing
- Number of injections

**Results #2**

- Time to platform
- Number of trials

**Conclusion #1**

Sensitization, as indicated by increased rearing, develops with periodic repeated injections.

**Conclusion #2**

Sensitization is also dependent on the occurrence of the behavior. The number of swims, not the spacing of swims or the treatment, causes an increase in the time it takes for the rat to reach the platform.

**Figure 6-16**

Experimental studies demonstrate two examples of sensitization. (Left) Amphetamine stimulates dopamine release and blocks reuptake. Each injection of the same dose of the drug given to rats produces a greater effect, as measured by an increase in the number of behaviors such as rearing. (Right) Flupentixol blocks dopamine receptors. The rat swims dower and slower in each trial until it can no longer escape from the swimming pool.

One group of rats lived in the test apparatus; so, for that group, home was the test box. The other group of rats was taken out of its normal home cage and placed in the test box for each day’s experimentation. The “home” group showed no sensitization to amphetamine, whereas the “out” group displayed robust sensitization. At least part of the explanation of the “home–out” effect is that the animals are used to engaging in a certain repertoire of behaviors in their home environment, and it is difficult to get them to change that behavior even in response to a drug. When animals are placed in novel environments and receive spaced injections of a drug, however, their response to the drug may increase, showing sensitization to it. Presumably, humans, too, show sensitization to a drug when they periodically take it in novel circumstances.

**Addiction and Dependence**

B. G. started smoking when she was 13 years old. Now a university lecturer, she has one child and is aware that smoking is not good for her own health or for the health of her family. She has quit smoking many times but always resumes the habit. Recently, she used a nicotine patch taped to her skin, which provides nicotine without the smoke. After successfully abstaining from cigarettes for more than 6 months with this treatment, she began to smoke again. Because the university where she works has a no-smoking policy, she has to leave the campus and stand across the street from the building in which she works to smoke. Her voice has developed a rasping sound, and she has an almost chronic “cold.” She says that she used to enjoy smoking but does not any more. Concern about quitting dominates her thoughts.

B. G. has a drug problem. She is one of approximately 25 to 35 percent of North Americans who smoke. Most smokers begin the habit when they are between the ages of 15 and 35, and each consumes an average of about 18 cigarettes a day. Like B. G., most smokers realize that smoking is a health hazard, have experienced unpleasant side effects from it, and have attempted to quit but cannot. B. G. is exceptional only in her occupation. Most smokers work at jobs in forestry, fishing, construction, and mining rather than teaching and medicine.

**Substance abuse** is a pattern of drug use in which people rely on a drug chronically and excessively, allowing it to occupy a central place in their lives. A more advanced state of drug abuse is **substance dependence**, also popularly known as **addiction**. People who are substance dependent have developed a **physical dependence** on a drug in addition to abusing it. This physical dependence is usually indicated by tolerance to the drug, meaning that the person using the drug requires increased doses to obtain the desired effect. The user may also experience unpleasant, sometimes dangerous **withdrawal symptoms** if he or she suddenly stops taking the drug. These symptoms can include muscle aches and cramps, anxiety attacks, sweating, nausea, and, for some drugs, even convulsions and death. Withdrawal symptoms can begin within hours of the last dose of a drug and tend to intensify over several days before they subside. B. G., although she is an abuser of the drug nicotine, is not physically dependent on it. She smokes approximately the same number of cigarettes each day (she has not developed tolerance to nicotine) and she does not get sick if she is deprived of cigarettes (she does not suffer symptoms of withdrawal from nicotine).

Many different kinds of drugs are abused or cause addiction, including sedative hypnotics, antianxiety agents, narcotics, and stimulants. Drugs that are abused have a common property: they produce **psychomotor activation** in some part of their dose range. That is, at certain levels of consumption, these drugs make the user feel energetic and in control. This common effect has led to the hypothesis that abused drugs may all act on the same target in the brain. One proposed target is dopamine neurons, because their stimulation is associated with psychomotor activity.
Three lines of evidence support a central role for dopamine in drug abuse. First, animals will press a bar for electrical stimulation of the dopamine system in the brain, and they will no longer press it if the dopamine system is blocked or damaged. This finding suggests that the release of dopamine is somehow desirable. Second, abused drugs seem to cause the release of dopamine or to prolong its availability in synaptic clefts. Even drugs that have no primary action on dopamine synapses have been found to increase dopamine. Apparently, when activated, many brain regions that contain no dopamine neurons themselves may stimulate dopamine neurons elsewhere in the brain. Third, drugs that block dopamine receptors or decrease the availability of dopamine at dopamine receptors are not substances that people abuse. For example, even though major tranquilizers are widely available for treating psychosis, they are not abused drugs.

Explaining Drug Abuse

Why do people become addicted to drugs? Historically, one explanation is the dependency hypothesis. According to this hypothesis, habitual users of a drug experience psychological or physiological withdrawal symptoms when the effects of the drug wear off. They feel anxious, insecure, or just plain sick in the absence of the drug, and so they take the drug again to alleviate those symptoms. In this way, they get “hooked” on the drug. Although this hypothesis may account for part of drug-taking behavior, it has shortcomings as a general explanation. For example, an addict may abstain from a drug for months, long after any withdrawal symptoms have abated, and yet still be drawn back to using the drug. In addition, some drugs, such as the tricyclic antidepressants, produce withdrawal symptoms when discontinued, but these drugs are not abused.

Researchers currently see addiction as being a series of stages. The first stage is the activation of pleasure by the consequences of drug taking. Using the drug produces in the person a positive subjective sensation. In other words, the user likes the experience. In the second stage, pleasure is linked through associative learning with mental representations of the objects, acts, places, and events related to taking the drug. This associative learning may be achieved through classical (also called Pavlovian) conditioning. You may recall from your introductory psychology course that classical conditioning consists of learning to associate some formerly neutral stimulus (such as the sound of a bell) with a stimulus (such as food in the mouth) that elicits some involuntary response (such as salivation). The pairing of the two stimuli continues until the formerly neutral stimulus is alone able to trigger the involuntary reaction. In drug use, the sight of the drug and the drug-taking context and equipment are repeatedly paired with administering the drug, which produces a pleasurable reaction. If you are a cat owner, you may have noticed that, when your cat wants to be petted, she may rub against your hand. She has been classically conditioned to associate the pleasure that she gets from petting with your hand. Soon the visual cues alone are enough to elicit pleasure. The third stage is attributing incentive salience to the cues associated with drug use. In other words, those cues become highly desired and sought-after incentives in their own right. Stimuli that signal the availability of these incentives also become attractive. For instance, acts that led to the drug-taking situation in the past become attractive, as do acts that the drug taker predicts will lead again to the drug. Drug users may even begin to collect objects that remind them of the drug, such as pipe collecting by pipe smokers or bottle-opener collecting by drinkers. In this sequence of events, then, a number of repetitions of the drug-taking behavior lead from liking that act to seeking it out or wanting it, regardless of its current consequences.

Incentive salience. Refers to cues that, after having been associated with drug use, become sought out.
A number of findings are in keeping with this view of drug addiction. For one thing, there is ample evidence that abused drugs initially have a pleasurable effect. There is also evidence that a habitual user continues to use his or her drug even though it no longer produces any pleasure. Street addicts using heroin sometimes report that they are miserable, that their lives are in ruins, and that the drug is not even great anymore, but they still want it. Furthermore, desire for the drug is often greatest just when the addicted person is maximally high on the drug, not when he or she is withdrawing from it, as the dependency hypothesis would predict.

To account for all the facts about drug abuse and addiction, Robinson and Berridge (1993) proposed the **incentive-sensitization theory**. This perspective is also called the wanting-and-liking theory because, according to this theory, wanting and liking a drug are affected differently, as is illustrated in Figure 6-17. Robinson and Berridge define wanting as equivalent to craving for a drug, whereas liking is defined as the pleasure that drug taking produces. The road to drug dependency begins with the initial trying out of the drug. At this time, the user may experience only a mild degree of wanting and liking the substance, because positive reactions may be mixed with some unpleasant side effects. With repeated use, liking the drug may decline from its initial level, but wanting the drug increases. Now the user may also begin to show tolerance to the drug's unpleasant effects and so may begin to increase the dosage to increase liking. Eventually, the drug produces very little liking, but wanting comes to dominate the drug user's behavior. This is because the user has become conditioned to all of the cues associated with drug taking, including needles and other drug paraphernalia, as well as drug-taking friends and locations. According to Robinson and Berridge, encounters with these cues, rather than expected pleasure from the drug, initiates wanting.

How can the wanting-and-liking theory explain B. G.'s behavior toward smoking? B. G. reports that her most successful period of abstinence from cigarettes coincided with moving to a new town. She stopped smoking for 6 months and, during that time, felt as if she were free and in command of her life again. The wanting-and-liking theory would argue that her ability to quit at this time was increased because she was separated from the many cues that had previously been associated with smoking. Then one night after going out to dinner, B. G. and a few of her new colleagues went to a bar, where some of them began to smoke. B. G. reported that her desire for a cigarette became overpowering. Before the evening was over, she bought a package of cigarettes and smoked more than half of it. On leaving the bar, she left the remaining cigarettes on the table, intending that this episode would be only a one-time lapse. Shortly thereafter, however, she resumed smoking. The wanting-and-liking theory suggests that her craving for a cigarette was strongly conditioned to certain social cues that she encountered again on her visit to the bar, which is why the wanting suddenly became overwhelming.

The neural basis for liking and wanting are not completely understood. Robinson and Berridge believe that liking may be due to the activity of opioid neurons, whereas wanting may be due to activity in a part of the dopamine system. In these dopamine pathways, called the **mesolimbic dopamine system**, the axons of dopamine neurons in the midbrain project to the nucleus...
accumbens, the frontal cortex, and the limbic system, as shown in Figure 6-18. When cues that have previously been associated with drug taking are encountered, this dopamine system becomes active, producing the subjective experience of wanting. That desire for the drug is not a conscious act. Rather, the craving derives from unconsciously acquired associations between drug taking and various cues related to it.

We can extend the wanting-and-liking explanation of drug addiction to many other life situations. Cues related to sexual activity, food, and even sports can all induce a state of wanting, sometimes in the absence of liking. For example, we frequently eat when prompted by the cue of other people eating, even though we may not be hungry and derive little pleasure from eating at that time. It is interesting that country music is dominated by songs about the opposing forces of wanting and liking.

**Behavior on Drugs**

Ellen is a healthy, attractive, and intelligent nineteen-year-old university freshman. In her high school health class, she learned about the sexual transmission of HIV and other diseases. More recently, in her college orientation, senior students presented a seminar about the dangers of having unprotected sex and provided the freshmen in her residence with free condoms and safe-sex literature. It is certain that Ellen knows the facts about unprotected sex and is cognizant of the dangers associated with this behavior. Indeed, she holds negative attitudes toward having unprotected sex, does not intend to have unprotected sex, and has always practiced safe-sex behavior: She and her former boyfriend were always careful to use latex condoms when having intercourse. At a homecoming party in her residence, Ellen has a great time, drinking and dancing with her friends, and meeting new people. She is particularly taken with Brad, a sophomore at her college, and the two of them decide to go back to her room to order a pizza. One thing leads to another, and Ellen and Brad have sex without using a condom. The next morning, Ellen wakes up, dismayed and surprised at her behavior, and very concerned that she might be pregnant, or may have contracted a sexually transmitted disease. Even worse, she is terrified that she might have contracted AIDS. (MacDonald et al., 1998)

What happened to Ellen? What is it about drugs, especially alcohol, that make people do things that they would not ordinarily do? Ellen is not alone in engaging in risky behavior under the influence of alcohol. Alcohol is associated with many harmful behaviors that are costly both to individual persons and to society. These behaviors include not only unprotected sexual activity but also drinking and driving, date rape, spousal or child abuse, and other forms of aggression and crime.
An early and still widely held explanation of the effects of alcohol is the disinhibition theory. It holds that alcohol has a selective depressant effect on the cortex, the region of the brain that controls judgment, while sparing subcortical structures, those areas of the brain responsible for more primitive instincts. Stated differently, alcohol presumably depresses learned inhibitions based on reasoning and judgment, while releasing the “beast” within. This theory often excuses alcohol-related behavior with such statements as, “She was too drunk to know better,” or “The boys had a few too many and got carried away.” Does such disinhibition explain Ellen’s behavior? Not really. Ellen had used alcohol in the past and managed to practice “safe sex” despite the effects of the drug. The disinhibition theory cannot explain why her behavior was different on this occasion. If alcohol is a disinhibitor, why is it not always so?

Craig MacAndrew and Robert Edgerton have questioned the disinhibition theory along just these lines in their book titled Drunken Comportment. They cite many instances in which behavior under the influence of alcohol changes from one context to another. People who engage in polite social activity at home when consuming alcohol may become unruly and aggressive when drinking in a bar. Even their behavior at the bar may be inconsistent. For example, while drinking one night at a bar, Joe becomes obnoxious and gets into a fight; but on another occasion he is charming and witty, even preventing a fight between two friends, whereas on a third occasion he becomes depressed and only worries about his problems. MacAndrew and Edgerton also cite examples of cultures in which people are disinhibited when sober only to become inhibited after consuming alcohol and cultures in which people are inhibited when sober and become more inhibited when drinking. How can all these differences in alcohol’s effects be explained?

MacAndrew and Edgerton suggest that behavior under the effects of alcohol represents time out from the rules of daily life that would normally apply. This time out takes into consideration learned behavior that is specific to the culture, group, and setting. Time out can help explain Ellen’s decision to sleep with Brad. In our culture, alcohol is used to facilitate social interactions, so behavior while intoxicated represents time out from more conservative rules regarding dating. But time-out theory has more difficulty explaining Ellen’s lapse in judgment regarding safe sex. Ellen had never practiced unsafe sex before and had never made it a part of her time-out social activities. So why did she engage in it with Brad?

Tara MacDonald and her coworkers (1998) suggest that alcohol myopia can explain alcohol-related lapses in judgment, such as that displayed by Ellen. Alcohol myopia (nearsightedness) is the tendency for people under the influence of alcohol to respond to a restricted set of immediate and prominent cues while ignoring more remote cues and potential consequences. Immediate and prominent cues are very strong and obvious ones that are close at hand. If there is a fight, the person with alcohol myopia will be quicker than normal to throw a punch because the cue of the fight is so strong and immediate. Similarly, if there is a raucous party, the myopic drinker will be more eager than usual to join in because the immediate cue of boisterous fun dominates the person’s view. In regard to Ellen and Brad, once they arrived at Ellen’s room, the sexual cues of the moment were far more immediate than concerns about long-term safety. As a result, Ellen responded to those immediate cues and behaved in a way that she normally would not. Such alcohol myopia can explain many other lapses in judgment that lead to risky behavior, including aggression, date rape, and reckless driving under the effects of alcohol.

Alcohol myopia. The behavior displayed after imbibing alcohol in which local and immediate cues become prominent.
Why Doesn’t Everyone Abuse Drugs?

Observing that some people are more prone to drug abuse and dependence than other people are, scientists have wondered if this difference might be genetically based. Three lines of evidence suggest a genetic contribution. First, the results of twin studies show that, if one of two twins abuses alcohol, the other is more likely to abuse it if those twins are identical (have the same genetic makeup) than if they are fraternal (have only some of their genes in common). Second, the results of studies of people adopted shortly after birth reveal that they are more likely to abuse alcohol if their biological parents were alcoholic, even though they have had almost no contact with those parents. Third, although most animals do not care for alcohol, selective breeding of mice, rats, and monkeys can produce strains that consume large quantities of it.

There are problems with all these lines of evidence, however. Perhaps identical twins show greater concordance for alcohol abuse because they are exposed to more similar environments than fraternal twins are. And perhaps the link between alcoholism in adoptees and their biological parents has to do with nervous system changes due to prebirth exposure to the drug. Finally, the fact that animals can be selectively bred for alcohol consumption does not mean that human alcoholics have a similar genetic makeup. The evidence for a genetic basis of alcohol abuse will become compelling only when a gene or set of genes related to alcoholism is found.

Another avenue of research into individual differences associated with drug abuse has been to search for personality traits that drug abusers tend to have in common. One such trait is unusual risk taking. Consider Bruno Gouvy, the Frenchman shown in Figure 6-19. He was the first person to jump out of a helicopter and surf the sky on a snowboard. He also set a world speed record on a monoski and was the first person to snowboard down Mont Blanc, the highest peak in Europe. He set a windsurfing record across the Mediterranean Sea and a free-fall speed record after jumping out of a plane. In an attempt to snowboard down three major peaks in one day, he hit black ice and fell 3000 feet to his death. Do people who love high-risk activities have a genetic predisposition toward risk-taking behavior that will also lead them to experiment with drugs (Comings et al., 1996)?

In an attempt to find out if certain behavioral traits are related to drug abuse, Pierre Piazza and his coworkers (1989) gave rats an opportunity to self-administer amphetamine. Some rats were very quick to become amphetamine “junkies,” giving themselves very large doses of it, whereas other rats avoided the drug. By examining the behavior of the rats in advance of the drug-taking opportunity, the researchers were able to identify behavioral characteristics associated with becoming an amphetamine junkie. In particular, those rats that ran around the most when placed in an open area, and so seemed less cautious and self-restrained than other rats, were also the most likely to become addicted. Perhaps, the researchers concluded, such behavioral traits make some rats more prone to drug use.

Although research on the characteristics that might influence becoming a drug user continues, there is as yet no unequivocal evidence to suggest that a specific gene determines substance abuse. Nor is there unequivocal evidence that differences in the dopamine system make some people more prone to drug abuse than others. And, even if a particular substance-abuse gene or genes could be found, that genetic factor would not provide a full explanation of drug addiction. Identical twins have all their genes in common, and yet, when one becomes a drug abuser, the other does not necessarily become one, too. Clearly, learning also plays an important role in developing drug abuse and addiction.
Can Drugs Cause Brain Damage?

Table 6-1 shows that many substances produced by plants and animals can act as neurotoxins, causing damage to neurons. Given the widespread use of psychoactive drugs in our society, it is important to ask whether these substances can do the same. In this section, we both examine the evidence that commonly used psychoactive drugs can act as neurotoxins and investigate the processes by which they might have toxic effects.

THE DOMOIC ACID STORY

Let us first consider how domoic acid acts as a toxin on the nervous system. The chemical structure of domoic acid is similar to that of the neurotransmitter glutamate. Because of its structural similarity to glutamate, domoic acid is referred to as a glutamate analogue. It is also a glutamate agonist because, like glutamate, it binds to glutamate receptors and affects them in the same way. As described in Chapter 5, each neurotransmitter can attach to a number of different types of receptors. Glutamate has three kinds of receptors and domoic acid acts to stimulate one of them, the kainate receptor, so named because the chemical substance kainate binds very potently to it. Domoic acid, it turns out, binds to the kainate receptor even more potently than kainate itself. (Because receptors are usually named for the compound that most potently binds to them, had domoic acid been discovered earlier, the kainate receptor would have been called the domoic receptor.)

The distribution of the different glutamate receptor subtypes in the brain varies from region to region. Kainate receptors are especially numerous in the hippocampus. If domoic acid reaches these receptors in high enough concentrations, it overexcites the receptors, initiating a series of biochemical reactions that results in the death of the postsynaptic neuron. Consequently, domoic acid is more toxic to the hippocampus than it is to other brain regions. Figure 6-20 shows a section through the brain of a rat that has been given an injection of domoic acid. The brain is colored with a silver stain that accumulates in damaged neurons. Tissue in the hippocampus exhibits the greatest amount of damage, although there is also sparse damage elsewhere in the brain.

It may seem surprising that a chemical that mimics a neurotransmitter can cause memory problems and brain damage. To understand how domoic acid can act as a neurotoxin requires that we temporarily turn to a different story, that of monosodium glutamate (MSG). The plot of this second story eventually links up with the plot of the domoic acid story.

In the late 1960s, there were many reports that monosodium glutamate, a salty-tasting, flavor-enhancing food additive, produced headaches in some people. In the process of investigating why this happened, scientists placed large doses of monosodium glutamate on cultured neurons and noticed that the neurons died. Subsequently, they injected monosodium glutamate into the brains of experimental animals, where it also produced neuron death. These findings raised the question of whether large doses of the neurotransmitter glutamate, which monosodium glutamate resembles structurally, might also be toxic to neurons. It turned out that it is. This finding suggested that a large dose of any substance that acts like glutamate might be toxic.

Now the toxic action of domoic acid can be explained. Domoic acid in large quantities excessively stimulates the glutamate receptors of certain brain cells, which is not to say that people should totally avoid all substances, such as domoic acid and MSG, that are similar in chemical structure to glutamate. Only very large doses of these substances are harmful, just as glutamate itself is not harmful except in large doses. Glutamate, in fact, is an essential chemical in the body. Recent findings show
that we even have taste-bud receptors for glutamate in our mouths, in addition to our receptors for sweet, salty, bitter, and sour. The taste-bud receptor for glutamate is called mGluR4, and its function is most likely to encourage us to eat foods containing glutamate. Clearly, glutamate in doses typically found in food is required by the body and is not toxic. Only excessive doses of glutamate cause harm.

THE POTENTIAL HARMFULNESS OF RECREATIONAL DRUGS

What about the many recreational drugs that affect the nervous system? Are any of them potentially harmful? The answer is not always easy to determine, as Una McCann and her coworkers (1997) found in their review of studies. For one thing, there is the problem of sorting out the effects of the drug itself from the effects of other factors related to taking the drug. For instance, although chronic alcohol use can be associated with damage to the thalamus and limbic system, producing severe memory disorders, it is not the alcohol itself that seems to cause this damage, but rather related complications of alcohol abuse, including vitamin deficiencies due to poor diet. For example, not only do alcoholics obtain reduced amounts of thiamine (vitamin B1) in their diets, but alcohol also interferes with the absorption of thiamine by the intestine. Thiamine plays a vital role in maintaining cell-membrane structure. Similarly, there are many reports of people who suffer some severe psychiatric disorder subsequent to their abuse of certain recreational drugs, but, in most cases, it is difficult to determine whether the drug initiated the condition or just aggravated an existing problem. It is also hard to determine exactly whether the drug itself or some contaminant in the drug is related to a harmful outcome. For example, cases of Parkinson's disease that developed after the use of synthetic heroin, described in Chapter 5, were caused by a contaminant (MPTP) rather than by the heroin itself. A number of cases of chronic use of marijuana have been associated with psychotic attacks, as “Drug-Induced Psychosis” on page 224 describes. But the marijuana plant contains at least 400 chemicals, 60 or more of which are structurally related to its active ingredient tetrahydrocannabinol. Clearly, it is almost impossible to determine whether the psychotic attacks are related to THC or to some other ingredient contained in marijuana.

Perhaps the best evidence that a recreational drug can cause brain damage comes from the study of MDMA, also called “ecstasy,” a widely used synthetic amphetamine. Although MDMA is structurally related to amphetamine, it produces hallucinogenic effects, giving it the name “hallucinogenic amphetamine.” The results of animal studies show that doses of MDMA approximating those taken by human users result in the degeneration of very fine serotonergic nerve terminals. In rodents, these terminals regrow within a few months after drug use is stopped, but, in monkeys, the terminal loss may be permanent, as shown in Figure 6-21. At present, no clear behavioral effects have been associated with this form of brain damage. But researchers still want to know if use of MDMA in humans is associated with the same loss of serotonergic terminals as it is in rodents and monkeys. Answering this question is complicated by the fact that many MDMA users have also used other drugs. In addition, the types of anatomical analysis used with other animals cannot...
be used with humans. There is some evidence that MDMA use is associated with memory impairments, but again it is difficult to attribute the deficits specifically to MDMA.

The finding that MDMA can be toxic to neurons has led to investigations into whether amphetamine also is toxic. The results of studies in rodents have shown that high doses of amphetamine can result in the loss of dopamine terminals, but again no behavioral deficits have been associated with this loss. Whether humans using amphetamine show similar neuron damage is not known. The drug doses used in the rodent studies are typically higher than those taken by human amphetamine users, so the implications of the rodent studies are open to question.

The psychoactive actions of cocaine are similar to those of amphetamine, and its possible deleterious effects have been subjected to intense investigation. The results of many studies show that cocaine use is related to blockage of cerebral blood flow and other changes in blood circulation. However, whether cocaine causes these abnormalities or aggravates preexisting conditions is not clear.

### Drug-Induced Psychosis

R. B. S. was a 29-year-old pilot who flew small freight aircraft into coastal communities in the Pacific Northwest. He was a heavy marijuana smoker and for years had been selectively breeding a particularly potent strain of marijuana in anticipation of the day when marijuana would become legalized. One evening, he felt that he was experiencing a sudden revelation. He was convinced that he was no longer in control of his life but, instead, was being manipulated by a small computer that had been implanted into his brain when he was 7 years old. He shared this information with a close friend, who urged him to consult a doctor. R. B. S. did so, and the doctor told him that it was unlikely that he had a computer implanted in his brain. But R. B. S. insisted that he had undergone the surgery when he participated in an experiment at a local university. He also claimed that all the other children who participated in the experiment had been murdered. The doctor called the psychology department at the university and confirmed that an experiment in which children took part had in fact been conducted years before, but the records of the study had long since been destroyed. R. B. S. believed that this information completely vindicated his story. R. B. S.’s delusion of the “brain computer” and the murdered children persisted and cost him his pilot’s license.

The delusion appeared to be completely compartmentalized in his mind. When asked why he could no longer fly, he would intently recount the story of the implant and the murders, saying that his assertion of its truth had lost him the medical certification needed for a license. Then he would happily discuss other topics in a normal way.

R. B. S. was suffering from a mild focal psychosis, a condition in which a person loses contact with reality. In some cases, this loss of contact is so severe and the capacity to respond to the environment is so impaired and distorted that the person can no longer function. People in a state of psychosis may have hallucinations (false sensory perceptions) or delusions (false beliefs), or they may withdraw into a private world that is almost totally isolated from people and events around them. A variety of drugs can produce psychosis, including LSD, amphetamine, cocaine, and, as shown by this case, marijuana. The most common form of psychosis is symptomatic of schizophrenia, a disorder in which many aspects of a person’s life that had formerly been adaptive deteriorate into a welter of distorted perceptions and disturbed thoughts.

The marijuana that R. B. S. used so heavily comes from the hemp plant Cannabis sativa, which is perhaps the oldest
Phencyclidine (PCP), or “angel dust,” is an NMDA receptor blocker that was originally developed as an anesthetic. Its use was discontinued after about half of treated patients were found to display psychotic symptoms for as long as a week after coming out of anesthesia. PCP users report perceptual changes and slurring of speech after small doses, with high doses producing perceptual disorders and hallucinations. Because there is little cross-tolerance between THC and other drugs, it seems that THC has its own brain receptor. THC may mimic a naturally occurring substance called anandamide, which acts on a THC receptor that naturally inhibits adenyl cyclase, part of one of the second-messenger systems.

Did marijuana cause R. B. S.’s delusion? His heavy use of it certainly raised the suspicion that the drug may have had some influence on his condition. R. B. S.’s doctor found a number of reports of similar conditions linked to marijuana. Although there is no evidence that marijuana use produces brain damage, there is evidence that it exacerbates the symptoms of schizophrenic patients. But, because various forms of schizophrenia are quite common (1 in 100 people), it is possible that R. B. S.’s delusions might have eventually occurred anyway, even if he had not used marijuana. Furthermore, marijuana contains about 400 compounds besides THC, any of which could have triggered his psychotic symptoms.

Marijuana has a number of beneficial effects. They include alleviating the nausea and vomiting associated with chemotherapy in cancer patients, controlling the brain seizures symptomatic of epilepsy, reducing intraocular pressure in patients with glaucoma, and relieving the symptoms of some movement disorders. However, marijuana’s effects in altering psychological functioning will likely prevent its legalization.
In Review

Behavior may change in a number of ways with the repeated use of a drug. These changes include tolerance, in which a behavioral response decreases; sensitization, in which a behavioral response increases; and addiction, in which the desire to use a drug increases as a function of experience with it. Today, many researchers believe that it is not so much avoidance of withdrawal symptoms that keeps people using a drug as it is a set of powerful learned incentives associated with drug taking. Individual differences in experience and genetic makeup, as well as the context in which a drug is taken, influence that drug’s effects on behavior. The behavior of acting in disinhibited ways while under the influence of alcohol can often be explained by the concepts of time out and alcohol myopia. Scientists are still investigating the potential deleterious effects on the brain of different psychoactive drugs. So far, their findings have been mixed, with some drugs producing brain damage and others apparently not.

HORMONES

Hormones, which are chemical messengers produced by endocrine glands, have effects on the body by traveling through the bloodstream to various target cells. In 1849, Swedish scientist A. A. Berthold performed the first experiment to demonstrate the existence and function of hormones. Berthold removed the testes of a rooster and found that the rooster no longer crowed; nor did it engage in sexual or aggressive behavior. Berthold then reimplanted one testis in the rooster’s body cavity. The rooster began crowing and displaying normal sexual and aggressive behavior again. The reimplanted testis did not establish any nerve connections, so Berthold concluded that it must release a chemical into the rooster’s circulatory system to influence the animal’s behavior. That chemical, we now know, is the hormone testosterone. The effect that Berthold produced by reimplanting the testis can be mimicked by administering testosterone to a castrated rooster, or capon. The hormone is sufficient to make the capon behave like a rooster with testes.

Until recently, there was little reason to associate hormones with drugs, except in the most indirect way. But now hormones, like other drugs, are used to treat or prevent disease. People take hormones as a replacement therapy because they have lost glands that produce those hormones. They also take hormones, especially the sex hormones, to counteract the effects of aging, and they take them to increase physical strength and endurance to gain an advantage in sports.

Hormones fall into three main groups. One group maintains a relatively constant internal environment in the body, a condition referred to as homeostasis. (The term homeostasis comes from the Greek words homeo, meaning “the same place,” and stasis, meaning “standing.”) These hormones control sugar levels in the blood and the absorption of sugar by cells. They also control the concentration of water in blood and cells, as well as the levels of sodium, potassium, and calcium in the body, and they play a role in a variety of digestive functions. A second group of hormones controls reproductive functions. They instruct the body to develop into a male or female, influence sexual behavior and the conception of children, and, in women, control the menstrual cycle, the birth of babies, and breast feeding. The third group of hormones, the stress hormones, is activated in emergency situations. They prepare the body to respond to and cope with challenges.
The Hierarchical Control of Hormones

Figure 6-22 shows that the control and action of hormones are organized into a four-level hierarchy consisting of the brain, the pituitary gland, the endocrine glands, and the target cells affected by the hormones. The brain, mainly the hypothalamus, produces releasing factors that instruct the pituitary gland to produce pituitary hormones. The pituitary hormones, in turn, influence the endocrine glands to release appropriate hormones into the bloodstream. These hormones then act on various targets in the body, also providing feedback about the need for more or less hormone.

Although many questions remain about how hormones produce complex behavior, they appear to do so by targeting the brain and activating neurons there. Testosterone’s influence on a rooster illustrates some of the ways that this hormone produces male behaviors. Testosterone may have neurotransmitter-like effects on the brain cells that it targets, but it also enters the neurons taking part in crowing, male sexual behavior, and aggression. In these neurons, it is transported into the cell nucleus, where it activates genes. The genes, in turn, trigger the synthesis of proteins needed for cellular processes that produce the rooster’s male behaviors. Sensory stimuli also are needed to elicit these behaviors: the rooster crows only at certain times, it is interested in sexual activity only if in the presence of hens, and it is aggressive only when it encounters another rooster. These sensory stimuli serve as signals to the endocrine system.

In addition to influencing behavior, testosterone also initiates changes in the size and appearance of the body. In a rooster, for example, testosterone produces the animal’s distinctive plumage and crest, and it activates other sex-related organs. This diversity of testosterone’s functions makes it clear why the body uses hormones as messengers. Their targets are so widespread that the best possible way of reaching all of them is to travel by the bloodstream, which goes everywhere in the body.

Figure 6-22
The control of hormones is hierarchical. (A) In response to sensory stimuli and cognitive activity, the brain influences the activity of the hypothalamus. The hypothalamus produces releasing factors that enter the anterior pituitary through veins and the posterior pituitary through axons. (B) On instructions from the releasing hormones, the pituitary releases pituitary hormones into the bloodstream and these hormones target endocrine glands. (C) In response to pituitary hormones, the endocrine glands release their own hormones into the bloodstream. Endocrine hormones target wide areas of the body, including the brain.
Homeostatic Hormones

The internal environment of our bodies needs to stay relatively constant in order for us to function. An appropriate balance of sugars, proteins, carbohydrates, salts, and water is required in the bloodstream, in the extracellular compartments of the muscles, in the brain and other body structures, and within all body cells. This constancy, or homeostasis, of the internal environment must be maintained regardless of a person’s age, activities, or state. As children or adults, at rest or in strenuous work, when we have overeaten or when we are hungry, a relatively constant internal environment is needed for survival. This makes the homeostatic hormones essential to life itself.

Insulin is an example of a homeostatic hormone. The normal concentration of glucose in the bloodstream varies between 80 and 130 milligrams per 100 milliliters of blood. One group of cells in the pancreas releases insulin, which causes blood sugar to fall by instructing the liver to start storing glucose rather than releasing it and by instructing cells to increase their uptake of glucose. The resulting decrease in glucose then stimulates the pancreatic cells to stop producing insulin. The disorder called diabetes mellitus is caused by a failure of these pancreatic cells to secrete insulin, resulting in a rise in blood-glucose levels and a failure of cells of the body to take up that glucose.

Reproductive Hormones

We are prepared for reproductive roles by the hormones that give us our sexual appearance and allow us to engage in sex-related behaviors. These sex hormones begin to act on us even before we are born and continue their actions throughout our lives. For males, sex hormones produce the male body and male behaviors. For females, they play a somewhat lesser role in producing the female body, but they control menstrual cycles, regulate many facets of pregnancy and birth, and stimulate milk production for breast-feeding babies.

Hormones also contribute to sex differences in cognitive behavior. Three lines of evidence, summarized by Elizabeth Hamson and Doreen Kimura (1992), support this conclusion. First, the results of spatial and verbal tests given to females and males in many different settings and cultures show that males tend to excel in the spatial tasks and females in the verbal ones. Second, the results of similar tests given to female subjects in the course of the menstrual cycle show fluctuations in test scores with various phases of the cycle. During the phase in which estradiol and progesterone are at their lowest levels, women do comparatively better on spatial tasks, whereas, during the phase when levels of these hormones are high, women do comparatively better on verbal tasks. Third, tests comparing premenopausal and postmenopausal women, women in various stages of pregnancy, and females and males with varying levels of circulating hormones all provide some evidence that hormones affect cognitive functions. These hormone-related differences in cognitive function are not huge. A great deal of overlap in performance scores exists between males and females. Nevertheless, the differences seem reliable. Similar influences of sex hormones on behavior are found in other species. The example of the rooster described earlier shows the effects of testosterone on that animal’s behavior. There are now a number of studies that demonstrate that motor skills in female humans and other animals improve at estrus, a time when progesterone levels are high.

Stress Hormones

Stress, a term borrowed from engineering, results from the action of a stressor, an agent that exerts a force and produces a stress response in the recipient. Applied to humans and other animals, stressors are events that have an arousing effect on us and
**stress responses** are behavioral and physiological processes that we use to cope with those events. Surprisingly, the response to stress is the same whether the stressor is an exciting event, a sad event, or a frightening event. Robert Sapolsky (1992) uses the vivid image of a hungry lion chasing down a zebra to illustrate this point. The chase for the two animals elicits very different emotional reactions, but their physiological stress responses are the same. Both are in a state of high arousal and are expending maximal energy.

The stress response begins when the brain perceives a stressor—some factor that triggers arousal. The response consists of two separate biochemical sequences, one fast and the other slow. Figure 6-23 shows that the hormone controlling the fast response is epinephrine, a chemical very similar to the neurotransmitter noradrenaline, whereas the hormone controlling the slow response is cortisol. The epinephrine response causes the “adrenaline” surge that we feel when we are frightened or before an athletic competition or some other important performance. The epinephrine pathway prepares the body for a sudden burst of activity. The cortisol pathway is activated more slowly, in minutes to hours. It prepares the body for longer-lasting adaptations, such as the restoration of cells and tissues after energy expenditure.

Cortisol has a wide range of functions, which include turning off all bodily systems not immediately required to deal with a stressor. For example, cortisol turns off insulin so that the liver starts releasing glucose, thus temporarily producing a homeostatic imbalance. It also shuts down reproductive functions and it inhibits the immune system. In this way, the body’s energy supplies can be concentrated on dealing with the stress.

**Figure 6-23**
The stress response activates one of two pathways. In the slow-acting pathway: (1) the hypothalamus releases corticotropin-releasing hormone (CRH) through veins into the anterior pituitary; (2) the pituitary releases adrenocorticotropic-releasing hormone (ACTH) into the bloodstream; (3) cortisol is released by the cortex of the adrenal gland into the circulatory system; and (4) cortisol activates body cells, endocrine glands, and the brain to reduce and control the stressor. In the fast-acting pathway: (1) the brain signals the spinal cord; (2) the sympathetic system of the spinal cord is activated; (3) epinephrine is released from the medulla of the adrenal gland; and (4) epinephrine activates body cells, endocrine glands, and the brain to reduce and control the stressor.
Cortisol is hydrophobic, but it travels in the bloodstream by attaching itself to a protein. When it leaves the blood, it sheds this protein, penetrates the membranes of cells, and induces gene transcription in the cells' DNA, resulting in the synthesis of new protein molecules. The newly made proteins contribute to mobilizing the body's resources and restoring the damage caused by both the stressor and the stress response.

Ending a Stress Response

Normally, stressors are short-acting events. The body mobilizes its resources, deals with the challenge, and then shuts off the stress response. Just as the brain is responsible for turning on the stress reaction, it is also responsible for turning it off. When it detects that the stressor is over, it instructs the hypothalamus to shut down the stress response.

Robert Sapolsky argues that the hippocampus plays an important role in turning off the stress response. The hippocampus contains a high density of cortisol receptors, and it has axons that project to the hypothalamus. Consequently, the hippocampus is well suited to detecting cortisol in the blood and instructing the hypothalamus to reduce blood-cortisol levels.

There may, however, be a more insidious relation between the hippocampus and blood-cortisol levels. When Sapolsky and his coworkers observed wild-born vervet monkeys that had become agricultural pests in Kenya and had therefore been trapped and caged, they found that some of the monkeys became sick and died of a syndrome that appeared to be related to stress. The animals that died seemed to have been subordinate ones housed with particularly aggressive dominant monkeys. Autopsies showed high rates of gastric ulcers, enlarged adrenal glands, and pronounced hippocampal degeneration. The hippocampal damage may have been due to prolonged high cortisol levels produced by the unremitting stress of being caged with the aggressive monkeys. Cortisol levels are usually regulated by the hippocampus, but, if these levels remain elevated because a stress-inducing situation continues, the high cortisol levels eventually damage the hippocampus. The damaged hippocampus is then unable to do its work of reducing the level of cortisol. This sets up a vicious cycle in which the hippocampus undergoes progressive degeneration and cortisol levels are not controlled. The circular relation between prolonged stress, elevated cortisol levels, and damage to the hippocampus is illustrated in Figure 6-24. Because stress-response circuits in monkeys are very similar to those in humans, the possibility exists that excessive stress in humans also can lead to damaged hippocampal neurons.
In Review

Endocrine glands produce hormones and distribute them through the bloodstream to targets throughout the body. Hormones are hierarchically controlled by sensory experiences, the brain, the pituitary gland, and the endocrine glands that secrete them. Hormones can be classified into three groups: homeostatic hormones, which regulate body nutrients and metabolic processes; reproductive hormones, which regulate sexual behavior, pregnancy, and child bearing; and stress hormones, which regulate the body’s responses to challenging events. Because these hormones often have such widespread targets, traveling through the bloodstream is an effective way for them to deliver their chemical messages.

SUMMARY

1. How do drugs enter the body, reach their target, and leave the body? Drugs, which are chemicals taken to bring about some desired change in the body, are administered in a number of ways, including by mouth, by inhalation, and by injection. To reach a target in the nervous system, a drug must pass through a number of barriers, including those posed by the digestive system, capillaries of the blood system, the blood–brain barrier, and the cell membranes. Drugs are diluted by the fluids of the body as they pass through these successive barriers until they reach their target cells. Drugs produce their effects by acting on receptors or chemical processes in the nervous system, especially on processes of neural transmission at synapses. They act either as agonists to stimulate neurons or as antagonists to depress neurons. Drugs are metabolized in the body and are excreted through feces, urine, sweat glands, and breath.

2. How do individual people respond to drugs? A drug does not have a uniform action on every person. Many physical differences, including differences in body weight, sex, age, and genetic background, influence the effects of a given drug.

3. How are drugs classified? Psychoactive drugs are classified into seven groups according to their major behavioral effects: sedative hypnotics and antianxiety agents, antipsychotic agents, antidepressants, mood stabilizers, narcotic analgesics, psychomotor stimulants, and stimulants that have psychedelic and hallucinogenic effects. Each group of drugs contains many natural or synthetic drugs or both, and they may produce their actions in different ways.

4. How does the repeated use of drugs and their use in different contexts affect behavior? A common misperception of drugs is that they have relatively specific and constant actions. The body and brain rapidly become tolerant to many drugs, and so the dose must be increased to produce the same effect. Alternatively, people may also become sensitized to a drug, and so the same dose produces increasingly greater effects. Learning also plays an important role in what people do when they are under the influence of a drug.

5. Why do people become addicted to drugs? Addiction develops in a number of stages as a result of repeated drug taking. Initially, the drug-taking act produces pleasure or liking. With repeated use of the drug, however, the act of taking it becomes conditioned to associated objects, events, and places. Eventually, those cues acquire incentive salience, causing the drug user to seek them out, which leads to
more drug taking. The subjective experience associated with prominent cues and drug seeking is wanting the drug. As addiction proceeds, the subjective experience of liking decreases while that of wanting increases.

6. Does the effect of a drug depend on the drug-taking situation? The influence of drugs on behavior varies widely with the situation and as a person learns appropriate drug-related behaviors. Some drugs, such as alcohol, can produce myopia such that a person’s behavior is primarily influenced by prominent cues in the environment. These cues may encourage the person to behave in ways that he or she would not normally behave.

7. Can the repeated use of drugs produce brain damage? The use of alcohol can be associated with damage to the thalamus and hypothalamus, but the cause of the damage is poor nutrition rather than the direct actions of alcohol. Cocaine can harm the brain’s circulation, producing brain damage by reduced blood flow or by bleeding into neural tissue. The drug “ecstasy,” or MDMA, can result in the loss of fine axon collaterals of serotonin neurons. Marijuana and LSD are associated with psychotic behavior, but it is not clear whether this behavior is due to the direct effects of the drugs or to the aggravation of preexisting conditions.

8. What are hormones? Hormones are substances that are produced by glands in the body and circulate in the bloodstream to affect a wide variety of targets. Homeostatic hormones regulate the balance of sugars, proteins, carbohydrates, salts, and other substances in the body. Reproductive hormones regulate the physical features and behaviors associated with reproduction and the care of offspring. Stress hormones regulate the body’s ability to cope with arousing and challenging situations. Hormones are under the hierarchical control of sensory events, the brain, the pituitary gland, and the endocrine glands, which all interact to regulate hormone levels.

KEY TERMS

- addiction, p. 216
- alcohol myopia, p. 220
- antianxiety agent, p. 201
- cellular tolerance, p. 213
- cross-tolerance, p. 201
- glutamate analogue, p. 222
- incentive salience, p. 217
- incentive-sensitization theory, p. 218
- metabolic tolerance, p. 213
- physical dependence, p. 216
- psychomotor activation, p. 216
- sensitization, p. 213
- substance abuse, p. 216
- substance dependence, p. 216
- withdrawal symptoms, p. 216

REVIEW QUESTIONS

1. What problems are encountered in making a drug a “magic bullet”?
2. Describe how the blood–brain barrier works.
3. Describe the seven categories of drugs.
5. Distinguish between the disinhibition, time-out, and alcohol-myopia explanations of behavior under the effects of drugs.
6. Describe the hierarchical control of hormones.
7. Describe the relation among stress, cortisol, and the hippocampus.
FOR FURTHER THOUGHT

A traditional view of drugs is that they cause people to do certain things. Discuss contemporary views of how drugs can influence our behavior.

Because many drugs work by affecting the function of synapses, the effect that they produce must be similar to some naturally produced behavior. Discuss this idea in relation to a drug of your choice.

RECOMMENDED READING


Sapolsky, R. M. (1994). Why zebras don't get ulcers. New York: W. H. Freeman and Company. A readable popular summary of everything you would like to know about stress. The theme of the book is that stress affects the brain and contributes to a great many medical conditions—including heart disease, depression, sexual and reproductive problems, and hormonal disorders—to aging, and to death; finally, of course, it affects zebras.