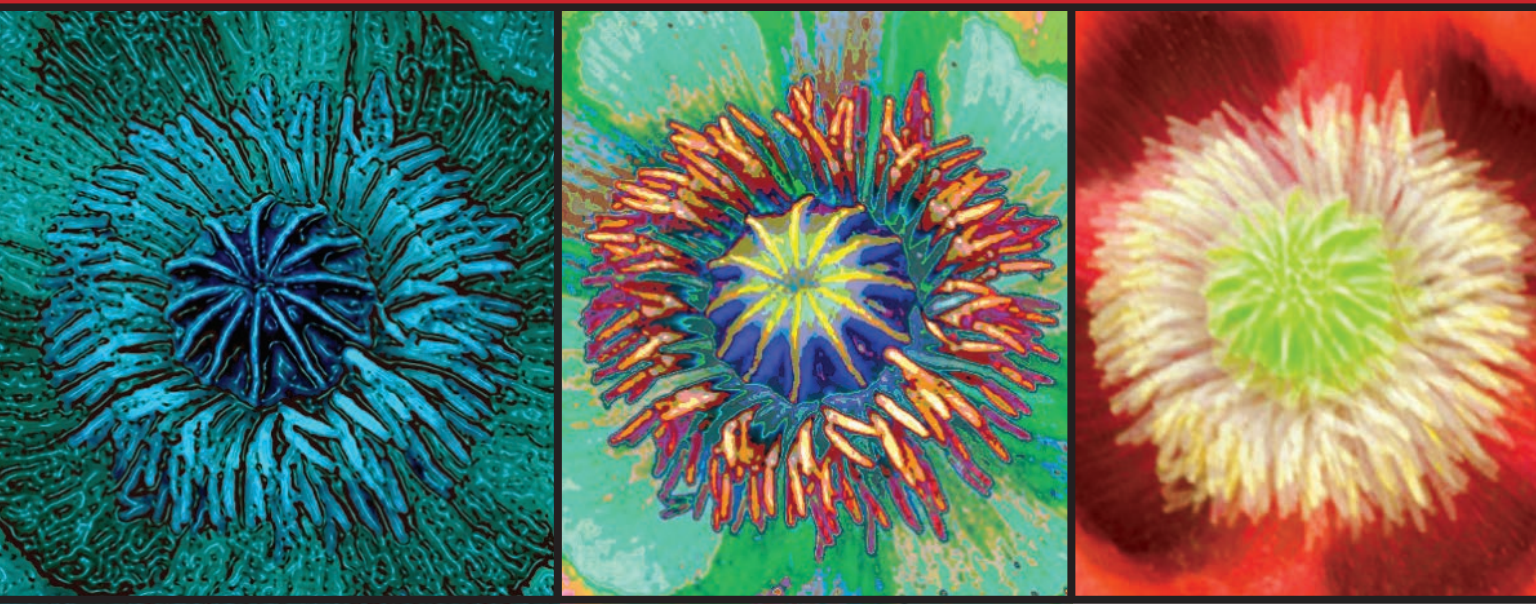
CHAPTER THREE



Drugs and the Nervous System

What Do You Think? True or False?

Answers are given at the end of the chapter.

___ 1. Certain cells in the nervous system have the unique ability to communicate with each other.

___ 2. The effects of drugs always involve naturally occurring physiological processes.

___ 3. Some drugs may act by mimicking a neurotransmitter.

___ 4. All drugs have the same basic effect on a cellular level; that is, they all block neural firing.

___ 5. The brain is shielded from many toxic substances by a protective barrier.

___ 6. The two main branches of the nervous system are the peripheral nervous system (PNS) and the autonomic nervous system (ANS).

___ 7. The brain and the spinal cord make up the peripheral nervous system.

___ 8. The brain is firmly attached to the inside of the skull by tough membranes known as the meninges.

___ 9. The autonomic nervous system is responsible for regulating food and water intake.

___10. Animals will work for the electrical stimulation of certain parts of the brain.

Every feeling or emotion you have—in fact, all psychological experience—is based on brain activity. The fact that this physical entity, the brain, is the basis of conscious experience is the key to understanding how the chemical agents we call drugs alter psychological processes.

One feature all psychoactive drugs have in common is that they produce their effects by acting in some way on nervous system tissue; this chapter is concerned with these physiological actions of drugs. Most of these actions occur at the level of the brain. As recent discoveries in neuroscience have led to a greater understanding of how the brain works, parallel advances have taken place in our understanding of drug actions. These developments have led to some radically new ways of thinking about drug effects and drug problems such as addiction. Before we discuss how drugs act on the brain, however, we must first cover some of the fundamentals of just how the brain works.

The Neuron

neurons ('nü-'rän) Individual nerve cells that are basic building blocks of the nervous system.

dendrites ('den-'drīt) Spiny branchlike structures that extend from the cell body of a neuron, typically contain numerous receptor sites, and are thus important in neural transmission.

axon ('ak-'sän) A long cylindrical extension of the cell body of the neuron; conducts an electrical charge from the cell body to the axon terminals.

The basic building blocks of the nervous system are cells called **neurons**. Neurons are similar to other cells in the human body, such as blood cells or muscle cells, but they have the unique feature of being able to communicate with one another. The structural properties of neurons provide us with some clues to the nature of the neural transmission process.

Notice that the neuron depicted in Figure 3.1 has a cell body similar to those of any other cell. The cell body includes a nucleus that contains the genetic material for the neuron and other processes that control the metabolic activities of the cell. Extending from the cell body of the neuron are a number of small spinelike or branchlike structures called **dendrites** and one long cylindrical structure called the **axon**. These structures are unique to the neuron and are responsible for some of its remarkable properties.

Axons vary in length but are usually much longer than shown in the illustration—sometimes thousands of times longer than the diameter of the cell body. The axon

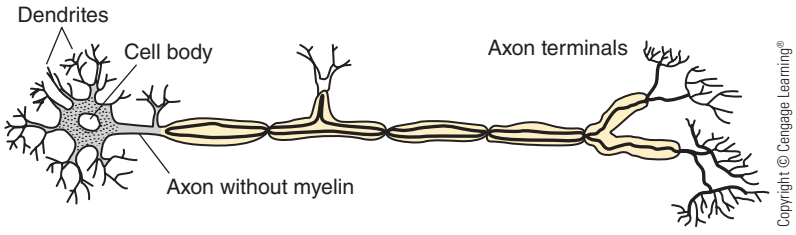


FIGURE 3.1
Diagram of a Neuron

depicted in Figure 3.1 is enclosed within a sheath of a white, fatty substance called **myelin** (not all axons are covered by myelin sheaths; "unmyelinated" axons are gray). Myelin provides insulation for the axon, similar to insulation for a wire. The comparison is fitting because the principal function of the axon is to conduct electrical current. The axon transmits information by conducting an electrical signal from one end of the neuron to the other. Generally, information is gathered by dendrites and the cell body and transmitted along the axon in the form of an electrical signal called the **action potential**.

myelin ('mī-ə-lən)
A fatty white substance that covers the axons of some neurons.

action potential
The electrical impulse along the axon that occurs when a neuron fires.

The action potential does not work in precisely the way that electricity travels along a wire. Rather it is produced by the flow of charged particles called ions through channels in the membrane that covers the axon. When the neuron is at rest, the concentration of positively charged sodium ions is greater outside the axon membrane, whereas negatively charged protein and chloride ions are concentrated within the axon. When the neuron is stimulated, certain ion channels open, permitting positive ions into the axon, and some depolarization of the axon will occur. If the level of stimulation becomes high enough, a threshold of excitation is reached, and a massive depolarization of the axon membrane occurs as positively charged sodium ions rush into the axon. This rapid depolarization that produces a change of about 110 millivolts is also termed the *action potential.* The action potential travels rapidly along the axon like a wave and is said to be "all or none," in that the axon is either "firing" with the full voltage charge or at rest. Once the neuron has fired, sodium ions are pumped out of the axon, channels close, and the neuron returns to its resting potential.

Neural Transmission

The branches at the end of the axon shown in Figure 3.1 terminate in small button-like structures known as **axon terminals** or **terminal buttons**. These axon terminals hold the key to an important puzzle: how the electrical message actually gets from one neuron to another. When advances in microscopy made possible the viewing of neurons as they are seen here, a surprising finding was that most axon terminals of one neuron do not come into direct contact with the dendrites of the neighboring neuron as had been supposed; instead, the junction between two neurons, the **synapse**, is generally separated by a gap called the synaptic cleft (see Figure 3.2). The question is: How does one neuron communicate with another without direct contact between them? It is now known that, when an action potential reaches the axon terminal, chemical substances stored in the terminal button are released into the synapse, and these chemical substances, called **neurotransmitters**, actually trigger activity in the adjacent neuron.

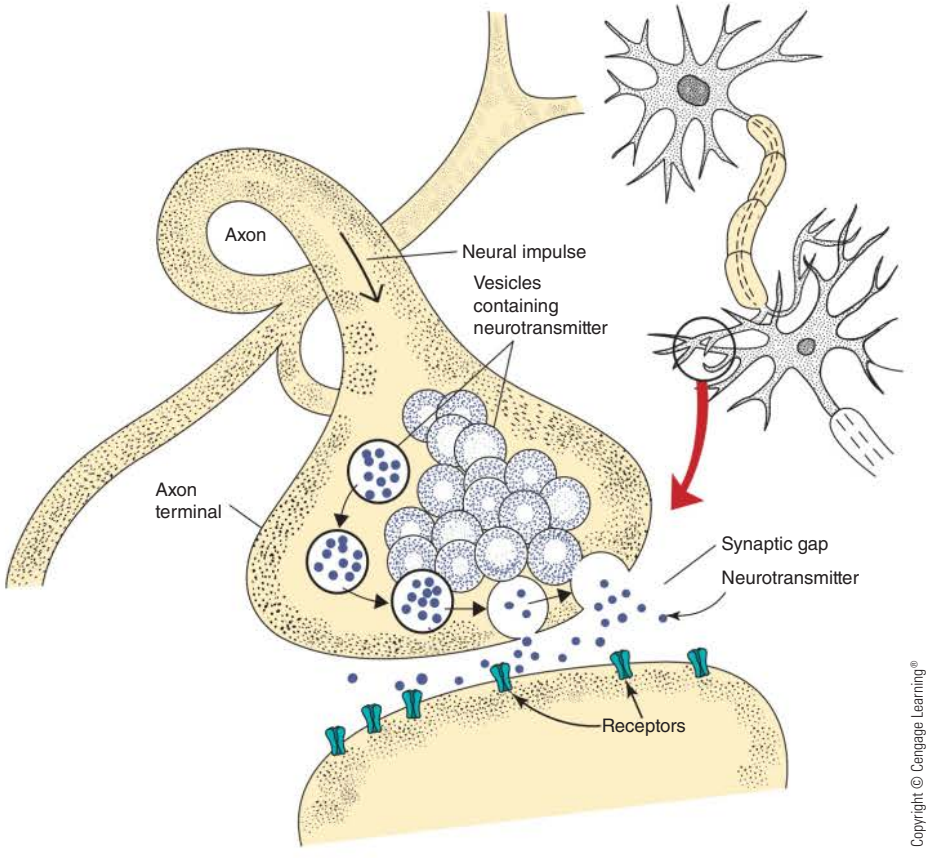
axon terminals (or terminal buttons)
Enlarged buttonlike structures at the ends of axon branches.

synapse ('si-'naps)
The junction between neurons.

neurotransmitters
Chemical substances stored in the axon terminals that are released into the synapse when the neuron fires. Neurotransmitters then influence activity in postsynaptic neurons.

Thus, neural transmission may be thought of as an electrochemical event—electrical along the axon and chemical at the synapse. This is of some importance for our purposes; it suggests that drugs may interact with the nervous system at the synapse

FIGURE 3.2
Diagram of a synapse showing an enlarged axon terminal with vesicles containing neurotransmitter molecules



because that is where chemical transmission takes place. In fact, we now know that most psychoactive drugs produce their important effects by action at the synapse (see Valenstein, 2005, for an account of the discovery of neurotransmitters and synaptic transmission). Therefore, more detailed analysis of the chemical processes that occur at the synapse is required.

receptor sites
Specialized structures located on dendrites and cell bodies for neurons that are activated by neurotransmitters.

A lock–key analogy is useful for depicting the neural transmission process. Scattered along the dendrites and cell body are special structures known as **receptor sites**, or receptors. Receptors are large protein molecules located on the surface of the neuron, and these structures may be viewed as locks that must be opened before the neuron fires. To fire, the receptors must be "unlocked," which is accomplished by the neurotransmitter substances released at the terminal button. The neurotransmitter molecules may be thought of as keys. The idea is illustrated in Figure 3.2. Receptor sites protrude from the membrane of the postsynaptic neuron like golf tees with a circular depression, and neurotransmitters are depicted as circles being released from the axon terminal. The notion is simple: The key must fit the lock to trigger an event such as neural firing.

In fact, neurotransmitter molecules and receptors have chemical structures that are considerably more complex than is illustrated, and the lock–key analogy does not completely explain the process. Transmitters and their receptors are said to have an affinity for one another; that is, the transmitter is attracted to the receptor site, and when a transmitter key occupies a receptor lock, it briefly becomes attached in a process called binding. When a neurotransmitter molecule binds to a receptor, changes occur in the neuron that may make the neuron more or less likely to fire. The two major mechanisms for these changes are ionotropic and metabotropic.

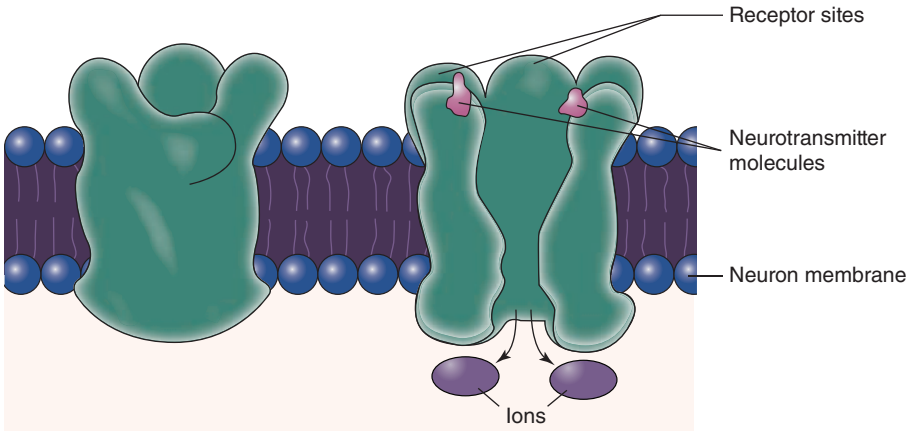


FIGURE 3.3
An ionotropic receptor is situated within the neuron membrane and consists of an ion channel (shown in the cutaway) and receptor sites. Receptor activation may open or close the ion channel, allowing ions into the neuron (Adapted from Prus, A. (2014). An introduction to drugs and the neuroscience of behavior. Belmont, CA: Wadworth, Cengage Learning.)

Ionotropic receptors are directly coupled to the ion channels that regulate the number of charged molecules inside and outside the neuron (see Figure 3.3). Note that when a transmitter binds to the receptor site, it causes the channel to open and allows charged particles to enter or leave the cell. If the receptor opens a channel that allows more positively charged ions into the neuron, then the neuron will be more likely to fire. If enough of these channels are opened, the neuron will generate an action potential, and such receptors are referred to as *excitatory*. At other synapses, when the neurotransmitter binds to a receptor, it may open ion channels that result in more negative ions entering the neuron, and this will hyperpolarize the neuron and make it *less* likely to fire. Because activating such a receptor actually makes it more difficult to produce an action potential, this is referred to as *inhibitory* neurotransmission. Ionotropic receptors are sometimes termed "*fast*" *receptors* because the entire process is completed in just a few milliseconds.

ionotropic receptors
Receptors that are coupled to ion channels and affect the neuron by causing those channels to open.

In contrast, another class of receptors, **metabotropic receptors** (see Figure 3.4), are said to be "*slow*" *receptors* because they produce changes in the neuron that are

metabotropic receptors
Receptors that act through a second messenger system.

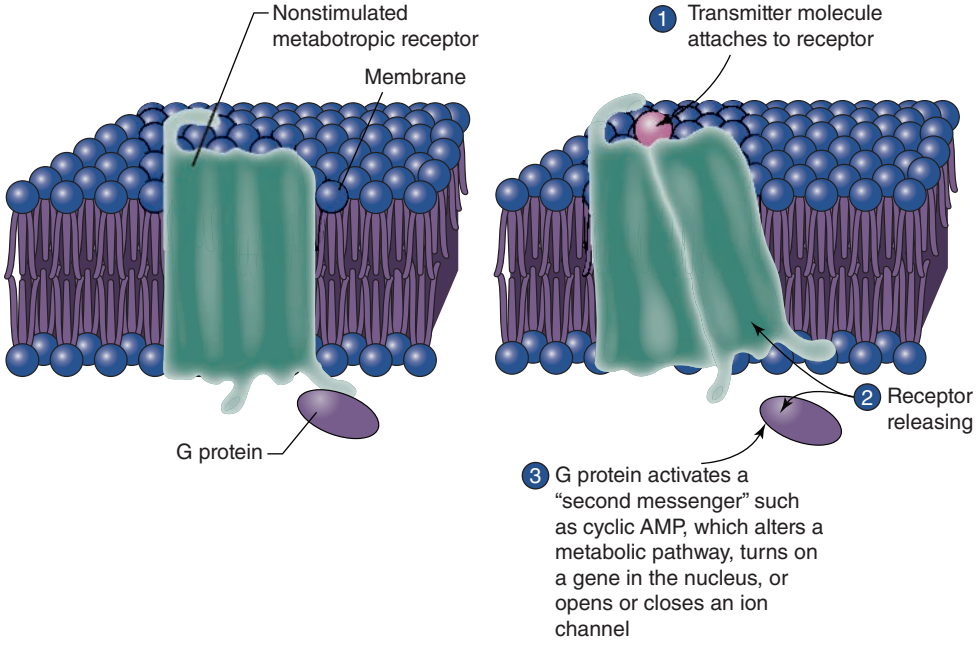


FIGURE 3.4
A metabotropic receptor. The left panel shows a nonstimulated receptor and the right panel depicts a neurotransmitter binding to the receptor and releasing the G protein (From Kalat, Biological Psychology, 11E. © 2013 Cengage Learning)

slightly delayed (by a few hundred milliseconds) and that can be relatively long lasting. Metabotropic receptors are not directly coupled with ion channels, but rather cause the release or activation of specialized molecules called G proteins. The G protein may then cause a number of effects within the neuron. The G protein may act much like ionotropic receptors and open ion channels somewhere in the neuron. Also like ionotropic receptors, some metabotropic receptors increase the likelihood of neural firing (excitatory), and others may decrease firing (inhibitory). G proteins may also initial the synthesis of other chemicals (such as cyclic adenosine monophosphate [AMP]), which are often referred to as second messengers. These second messengers may produce metabolic changes or activate genes within the neuron with a variety of consequences that may continue over a fairly extended period of time.

Drugs and Neural Transmission

There are many different types of neurotransmitters and many corresponding receptor sites. We now understand that the brain is chemically coded with different pathways that respond to different neurotransmitter chemicals and these hold the key to understanding drug effects. Several ways that drugs can interfere with synaptic transmission may have already occurred to you. For example, suppose the chemical structure of some drug is similar to the structure of a naturally occurring (endogenous) neurotransmitter. If the similarity is close enough, the drug molecules might bind to the receptor sites, thus duping the receptor into reacting as if the natural transmitter is present and stimulating the neuron. Just such a process actually does occur with some drugs. For example, morphine and heroin are now thought to act by mimicking natural neurotransmitters called endorphins.

Mimicry is an obvious mechanism of drug action, but drugs can influence neural transmission in numerous other ways as well. A sampling of these mechanisms is listed in Table 3.1. Neurotransmitters must be manufactured from simpler building blocks, or precursor molecules. Transmitters are usually manufactured in a cell body or axon terminal, but if the substance is manufactured in the cell body, it must still be transported to the terminal before it is functional. Some drugs interfere with transmitter production or transport. Neurotransmitter molecules are stored in small packages called **vesicles** located in the terminal buttons. Some drugs affect the ability of the vesicles to store neurotransmitter substances. For example, the drug reserpine, once used to treat high blood pressure, causes certain vesicles to become leaky, and then the transmitters involved are not effectively released into the synapse. Alternatively, other drugs can enhance the release of neurotransmitter substances into the synapse; this is one of the ways stimulants such as amphetamines are thought to act.

Another important rule of neural transmission is that neurotransmitters, once released, must be deactivated to terminate cell activity. Neurotransmitters are deactivated in two ways: **enzyme breakdown** and **reuptake**. Certain chemicals called enzymes act both to build the complex molecules of neurotransmitters and to break down neurotransmitters to inactive form. These processes are complex and reveal one reason that identifying and isolating the functions of neurotransmitters in the brain are difficult. The brain contains many different chemicals, and they are constantly changing form. Consider the processes involved in the production and destruction of **acetylcholine**, one of the better-known neurotransmitters. The precursor molecule choline is acted on by an enzyme (choline acetyltransferase) to make acetylcholine. Acetylcholine itself is broken down by a different enzyme—acetylcholinesterase—to yield two metabolites: choline

vesicles ('ve-si-kəl)
Tiny sacs in axon terminals that store neurotransmitters.

enzyme breakdown
One process by which neurotransmitters are inactivated. Chemicals called enzymes interact with the transmitter molecule and change its structure so that it no longer is capable of occupying receptor sites.

reuptake
One process by which neurotransmitters are inactivated. Neurotransmitter molecules are taken back up into the axon terminal that released them.

acetylcholine (-'se-tl-'kō-lēn)
A neurotransmitter linked with cognitive processes and memory that is found both in the brain and in the parasympathetic branch of the autonomic nervous system.

TABLE 3.1 Neurochemical Mechanisms of Drug Action

Drug effects can be produced by altering the following neurochemical systems:

1. *Neurotransmitter synthesis.* A drug may increase or decrease the synthesis of neurotransmitters.
2. *Neurotransmitter transport.* A drug may interfere with the transport of neurotransmitter molecules to the axon terminals.
3. *Neurotransmitter storage.* A drug may interfere with the storage of neurotransmitters in the vesicles of the axon terminal.
4. *Neurotransmitter release.* A drug may cause the axon terminals to release neurotransmitter molecules into the synapse prematurely.
5. *Neurotransmitter degradation.* A drug may influence the breakdown of neurotransmitters by enzymes.
6. *Neurotransmitter reuptake.* A drug may block the reuptake of neurotransmitters into the axon terminals.
7. *Receptor activation.* A drug may activate a receptor site by mimicking a neurotransmitter.
8. *Receptor blocking.* A drug may cause a receptor to become inactive by blocking it.

and acetate. By the way, enzymes are named by the stem of the chemical that they influence and always have an "-ase" ending. A drug can alter neural transmission by affecting enzyme activity. For example, some antidepressant drugs alter brain levels of the neurotransmitters norepinephrine, dopamine, and serotonin by inhibiting the activity of monoamine oxidase, the enzyme that breaks down these compounds.

A second mechanism for removing neurotransmitters from the synapse is called reuptake. Neurotransmitters are taken back up into the terminal button after they have been released—hence, the term *reuptake*. This is an economical mechanism of deactivating transmitters because the neurotransmitter molecule is preserved intact and can be used again without the expense of energy involved in the manufacture of new transmitters. Some drugs (notably cocaine) exert some of their action by blocking the reuptake process.

As noted, an important site of drug action is directly at the receptor. Some drugs directly affect the receptor by mimicking the activity of natural neurotransmitters—similar to a duplicate key that fits into and opens a lock. Other drugs seem to act as if they fit into the lock but then they jam the lock and prevent the neuron from firing. Such a drug is called a *blocking agent*. In general, any chemical—natural or otherwise—that fits a receptor lock and activates it is said to be an **agonist** of that receptor. Any compound that occupies a receptor and does not activate it, but rather prevents other compounds from activating the receptor, is said to be an **antagonist** (see Table 3.2). For example, naloxone is an antagonist of the receptors on which opiate drugs (such as heroin) work. If naloxone is promptly administered to a patient who has just taken a potentially lethal dose of heroin, the patient will survive and will rapidly be brought to a state in which it appears as if the heroin had never been taken. In fact, all effects of heroin and other opiates are blocked completely or reversed by naloxone. Thus, naloxone is called an opiate antagonist. These examples describe direct agonists or antagonists: drugs that produce their actions by binding directly to the receptor. The terms *agonist* and *antagonist* may also be used more generally to refer to drugs that enhance (agonist) or inhibit (antagonist) the activity of a particular neurotransmitter system without binding to the receptor for that transmitter. Such drugs are often referred to as *indirect* agonists or antagonists. For example, cocaine does not bind to dopamine receptors, but does enhance dopamine transmission by blocking reuptake, and so is considered an indirect dopamine agonist.

agonist ('a-g-nist)
A substance that occupies a neural receptor and causes some change in the conductance of the neuron.

antagonist
A substance that occupies a neural receptor and blocks normal synaptic transmission.

TABLE 3.2 Major Neurotransmitters With Representative Agonists and Antagonists

Neurotransmitter	Agonist	Antagonist
Acetylcholine	Nicotine	Atropine
Dopamine/norepinephrine	Cocaine/amphetamines	Chlorpromazine
Serotonin	LSD	Chlorpromazine
Endorphins	Morphine	Naloxone
GABA	Barbiturates	Bicuculline
Glutamate	Aspartic acid	Ketamine

Up to now, we have considered only the acute effects of drugs on neural transmission, that is, effects that occur during a single use of the drug. When drugs are used more regularly, long-lasting changes in neurotransmission can occur that are important in the development of drug tolerance and dependence. For example, chronic use of some drugs can result in a long-term reduction of the amount of neurotransmitter produced and released in affected neurons. Alternatively, the number of available receptor sites can be reduced. Such changes result in the affected pathway becoming less sensitive to the drug and thus illustrate neural mechanisms of tolerance development. Depending upon the functions of the affected pathway, these changes may alter responsiveness to nondrug environmental stimuli as well. If the user stops taking the drug, the loss of stimulation in these pathways may result in withdrawal symptoms (see Nestler, 2009).

We have seen a number of ways that drugs can act to influence neural transmission (see Prus, 2014, for a more detailed review). A point to remember, however, is that although drugs can interact with the brain in many different ways, the effects of the drugs always involve naturally occurring processes. That is, some systems in the brain or body with defined natural functions are made more or less active by the drug. The different effects of various drugs are coming to be understood in terms of which transmitter systems they influence and exactly how they influence them. Therefore, we next take a brief look at the neurotransmitter systems of the human brain and note some of their known functions.

Major Neurotransmitter Systems

More than 100 different chemicals are now thought to act as neurotransmitters in the human brain. We discuss a few of these that are known to be important in modulating drug action.

Acetylcholine

neuromuscular junction Junction between neuron and muscle fibers where release of acetylcholine by neurons causes muscles to contract.

One of the first neurotransmitters to be discovered was acetylcholine, probably because it is found in the more easily studied neurons located outside the brain. Acetylcholine resides in the axon terminals of neurons that activate the skeletal muscles. At sites where nerves meet muscles, there is a space similar to the synapse called the **neuromuscular junction**. When the neurons that synapse with muscle fibers fire, they release acetylcholine into the neuromuscular junction, and the muscle contracts. Some muscle disorders are related to problems with this process. For example, myasthenia gravis, a

disease characterized by severe muscle weakness and fatigue, is caused by a blockage of acetylcholine at the neuromuscular junction. A related similar process is the basis for one of the deadliest toxins known: botulinum. One gram of botulinum toxin (about the weight of a dollar bill) is enough to fatally poison more than 3 million people (Meyer & Quenzer, 2013). Botulinum toxin is produced by a bacterium that grows in oxygen-free environments such as improperly prepared canned goods, and as you might well imagine, is a major concern with respect to biological warfare and terrorism. The basis for botulinum toxicity is that it blocks the release of acetylcholine at the neuromuscular junction, resulting in muscle paralysis and, in sufficient doses, death by asphyxiation. Interestingly, a carefully prepared form of botulinum toxin is now being marketed and used cosmetically under the brand name Botox. When Botox is injected into one of the facial muscles, it causes that muscle to become partially paralyzed; this can produce a temporary smoothing of certain types of facial wrinkles and lines.

As a point of terminology, if the name of a neurotransmitter is to be used as an adjective, simply take the stem of the name (e.g., *choline*) and add the suffix "-ergic." Thus, neurons that contain acetylcholine are *cholinergic* neurons, and drugs that block acetylcholine, such as atropine, are *anticholinergic* drugs. Nicotine is an example of a cholinergic drug because it is an agonist at acetylcholine receptors. Interestingly, nicotine does not bind to all acetylcholine receptors, but only a subtype referred to as nicotinic receptors. Other acetylcholine receptors are structurally somewhat different than nicotinic receptors, and because a compound called muscarine binds to them, they are referred to as muscarinic receptors. The discovery that acetylcholine binds to more than one receptor is important because it turns out that most neurotransmitters have multiple receptor subtypes as well. Receptor subtypes often occur in different brain regions and regulate different neurotransmitter functions. These features have made them important targets in drug discovery because of the possibility that a drug might affect a receptor subtype that produces a desirable effect, while not affecting a subtype related to an undesirable side effect.

Alzheimer's disease ('älts-'h ī-mrz-)
One of the most common forms of dementia among the elderly; involves a progressive loss of memory and other cognitive functions.

Acetylcholine is an important neurotransmitter in the brain as well as at the neuromuscular junction, but like most neurotransmitters, its function in the brain is not thoroughly understood. Acetylcholine is thought to be important in sensory processing, attention, and memory. In fact, there is substantial evidence that **Alzheimer's disease**, a progressive loss of memory function that occurs in the elderly, is related to the loss of neural function in some of the brain's cholinergic pathways. Much current research on Alzheimer's disease is attempting to determine just what might be going wrong in these pathways and to develop ways of correcting or preventing the problem. Drugs such as Aricept (donepezil) and Exelon (rivastigmine) reduce the symptoms of Alzheimer's disease by elevating levels of acetylcholine in the brain through inhibition of the enzyme acetylcholinesterase. The problem of Alzheimer's disease underscores an important point: When neurotransmitter systems malfunction, disease states are a likely consequence, and drugs that target the affected system may provide effective treatments. These ideas have been critical to contemporary theories of the biological basis of mental illness, which are considered in the next section.

David Woo/Dallas Morning News/Historical/Corbis

Late President Ronald Reagan retreated from public life after it was revealed that he suffered from Alzheimer's disease.

Monoamines

norepinephrine ('no·r-'e-p-'ne-frn) A neurotransmitter in the brain that is also involved in activity of the sympathetic branch of the autonomic nervous system.

dopamine ('dō-pə-'mēn) A neurotransmitter in the brain that is involved with movement and reward.

serotonin ('sir-ə-tō-nən) A neurotransmitter in the brain that is involved with sleep and mood.

monoamines ('mä-nō-ə-'mən) A class of chemicals characterized by a single amine group; includes the neurotransmitters norepinephrine, dopamine, and serotonin.

Parkinson's disease A disease that primarily afflicts the elderly and involves a progressive deterioration of motor control.

L-dopa ('el-'dō-pə) A chemical precursor of dopamine used in the treatment of Parkinson's disease.

blood-brain barrier The system that "filters" the blood before it can enter the brain.

Three important neurotransmitters—**norepinephrine** (noradrenaline), **dopamine**, and **serotonin**—are collectively known as the **monoamines** because the chemical structure of each contains a single amine group. Like acetylcholine, norepinephrine was discovered early because it is found outside the brain. It serves as a key chemical to mediate the physical changes that accompany emotional arousal. Norepinephrine is also found in the brain as a neurotransmitter, where it seems to be important in the regulation of hunger, alertness, and arousal. Serotonin is found throughout the brain and has been shown to be important in the regulation of sleep. Dopamine is a key neurotransmitter in the pathways that regulate coordinated motor movements. This discovery led to the hypothesis that dopamine insufficiency may be the basis of **Parkinson's disease**, a disorder characterized by progressive loss of fine motor movements, muscle rigidity, and tremor primarily afflicting elderly people.

The dopamine deficiency hypothesis of Parkinson's disease led to new treatment approaches involving the administration of **L-dopa**, a precursor of dopamine. L-dopa was administered to patients in hopes of correcting the dopamine deficiency and proved to be dramatically effective in relieving the symptoms of this disease. Dopamine itself is not effective because it does not enter the brain from the bloodstream. The brain is protected from toxic compounds that might enter the bloodstream by a **blood-brain barrier** that screens many chemicals, including dopamine. But L-dopa does penetrate the barrier, and once it reaches the brain, it is converted to dopamine (Deutsch & Roth, 2009). Using L-dopa in the treatment of Parkinson's disease is a dramatic example of the value of new knowledge about neurotransmitters for the treatment of disease. Although L-dopa does not cure the disease process (dopaminergic neurons continue to be lost and eventually even L-dopa cannot correct the loss), it has brought years of productive living to many whose lives would otherwise have been prematurely ended by Parkinson's disease.

In addition to these functions, the monoamine neurotransmitters norepinephrine, dopamine, and serotonin have been closely linked to mood states and emotional disorders. In fact, drugs that influence the monoamine systems have revolutionized modern psychiatry. For example, considerable evidence shows that severe clinical depression may have a biological basis. Current theories propose that clinical depression is associated with dysregulation of monoamines, particularly norepinephrine and serotonin. This monoamine theory of depression originated with the finding that certain drugs that depleted monoamines seemed to produce depression. Reserpine, once used to treat high blood pressure, makes monoaminergic vesicles leaky (as we noted earlier), and the transmitters are then destroyed by enzymes, resulting in a depletion of norepinephrine, serotonin, and dopamine. This process often causes depression in people whose mood states were normal before treatment (as you may have guessed, it also produces Parkinson's symptoms due to dopamine depletion, and this side effect led to the use of L-dopa previously mentioned). Evidence of abnormal monoamine activity in clients who suffer from depression has been reported; for example, numerous studies have linked deficient serotonin activity to suicidal behavior (Arango & Mann, 2009). Finally, the drugs that are useful in the treatment of depression (e.g., Prozac) generally influence either norepinephrine or serotonin transmission or both, which further supports this monoamine-dysregulation hypothesis. Increased knowledge of neurochemical processes linked to depression is suggesting new and promising approaches to the understanding and treatment of depressive disorders (Berman et al., 2009—see Contemporary Issue Box 3.1).

Monoamines, particularly dopamine and serotonin, appear to be important as the biochemical basis of another important mental illness: schizophrenia. Schizophrenia involves a major loss of contact with reality, characterized by false beliefs or delusions,

CONTEMPORARY ISSUE BOX 3.1

You Are Never Too Old to Make New Neurons: Adult Neurogenesis and Depression

Until very recently, it was almost universally accepted that the birth of new neurons—neurogenesis—ended very early in development. Young adults were considered to possess all the neurons they would ever have. It was believed that cells lost due to stroke, injury, or drug abuse could never be replaced. However, in the 1990s, it was discovered that new neurons were born in certain brain regions in adult rats (Gould et al., 1999). These findings were subsequently confirmed in adult humans, and it is now believed that neurogenesis may occur in the hippocampus and certain other brain areas throughout adulthood. As yet, little is known about the functions of adult neurogenesis, but the possibilities for treatments of neurological disease are enormous if the process can be harnessed. The role of neurogenesis in mental health has become a major research emphasis. One of the most exciting early developments in this research is the possible linkage between neurogenesis and depression. A number of studies have shown that various types of stress can suppress production of new neurons (Duman, 2009). Stress is also linked to depression, and there is evidence of reduced hippocampus size in patients with depression, which may indicate less neurogenesis (Jacobs, 2004). We noted earlier that antidepressant medication generally elevates levels of the neurotransmitter serotonin, and several studies now indicate that elevated serotonin levels increase neurogenesis. Importantly, it requires several weeks for new neurons to become integrated into functional neural pathways, and this corresponds well with the time course of antidepressant action. These drugs generally increase serotonin levels fairly rapidly, but it takes several weeks for the depression to lift, which suggests that it may be the increased birth of new neurons, rather than the elevation of serotonin per se, that is responsible for antidepressant action. If this new neurogenesis theory of depression is correct, it could lead to new and more effective treatments for this serious disorder (see Duman & Aghajanian, 2012, for a review).

hallucinations, social withdrawal, and distortions of emotionality. Strong evidence ties these symptoms to high levels of monoamine activity. First, all the drugs that are effective in the treatment of schizophrenia also block monoamine transmission. In fact, it has long been known that a close correlation exists between the clinical potency of the various drugs used and their ability to block dopamine receptors (Snyder, Burt, & Creese, 1976). Another interesting piece of evidence is that stimulant drugs such as cocaine and amphetamines increase monoamine activity in the brain. Although low or moderate doses of these stimulants enhance mood, overdoses often lead to paranoid delusions and a loss of reality contact that strongly resembles some symptoms of schizophrenia. When the drug wears off and monoamine activity returns to normal, these symptoms generally dissipate—a finding that further supports the link between abnormal monoamine activity and schizophrenia (see Sawa & Snyder, 2002). Although complex disorders such as schizophrenia and depression cannot be understood completely without considering a host of psychological and

Reuters NewsMedia Inc./Corbis

Boxing legend Muhammad Ali pretends to punch actor Michael J. Fox. Both suffer from Parkinson's disease.

social factors, the biological approaches just noted have certainly improved our understanding and treatment of them. We consider the use of drugs to treat these and other disorders in more detail in Chapter 13.

Endorphins

During the late 1970s, compounds were discovered in mammalian brain tissue that were functionally similar to opiate drugs such as morphine and heroin. Unlike acetylcholine and the monoamines, these compounds were large molecules in the peptide family. Because they appeared to be, in effect, a naturally occurring morphine, they were named **endorphins**—a contraction of *endogenous morphine*. We now understand that the effects of opiate drugs are mediated through endorphinergic activity. The natural functions of the endorphins themselves are still far from clear but they certainly modulate pain relief. The endorphins are explained in more detail in Chapter 10.

endorphins (en-'do·r-fənz)
Neurotransmitters in the brain that are mimicked by opiate drugs.

Amino Acid Neurotransmitters

Two additional neurotransmitters are the amino acids gamma-aminobutyric acid, commonly referred to as **GABA**, and **glutamate**. GABA is among the most abundant of the known neurotransmitters in brain tissue, and it is the most significant inhibitory transmitter of the brain. That is, GABA opens negatively charged chloride ion channels that do not cause the neuron to fire but rather hyperpolarize the membrane and impede neural firing. If a neuron has a GABAergic receptor site that is activated, a larger quantity of the excitatory transmitter is required for the neuron to fire. A number of drugs are now thought to act on the GABA system; as you might guess, they are the classic depressant drugs: barbiturates, tranquilizers such as Valium (diazepam) and Xanax (alprazolam), and alcohol. Glutamate is among the most abundant of the excitatory neurotransmitters and is known to be important in learning and memory processes. Some hallucinogenic drugs (PCP and ketamine) act on glutamate receptors in some parts of the brain (see Chapter 12).

GABA
Short for gamma-aminobutyric acid; the most abundant inhibitory neurotransmitter in the brain.

glutamate
An excitatory amino acid neurotransmitter.

Other Transmitters

The development of more sophisticated research techniques has led to the recognition that many more neurotransmitters await discovery. A thorough discussion of recent advances in neuropharmacology is beyond the scope of this text, but some developments have already had a substantial impact on our understanding of psychoactive drug actions. Indeed, many neurotransmitters have been discovered beyond those previously mentioned, and no doubt many more remain to be found. We have much to learn about the brain's chemical code. Often the discovery of a new neurotransmitter increases our understanding of drug action. For example, one of the most recently discovered neurotransmitters is a lipid called **anandamide**. It is of considerable interest because the active chemical in marijuana appears to act by mimicking anandamide.

anandamide
A lipid neurotransmitter mimicked by marijuana.

The Nervous System

We have been focusing on a microscopic view of the nervous system as we considered how drugs might act at the level of the single neuron. We now turn to the larger picture and consider a macroscopic view of the nervous system. The structure of the nervous system is outlined in Figure 3.5. The major distinction is between the **central nervous system (CNS)** and the **peripheral nervous system (PNS)**.

central nervous system (CNS)
The brain and the spinal cord.

peripheral nervous system (PNS)
Sensory nerves, motor nerves, and the automatic nervous system.

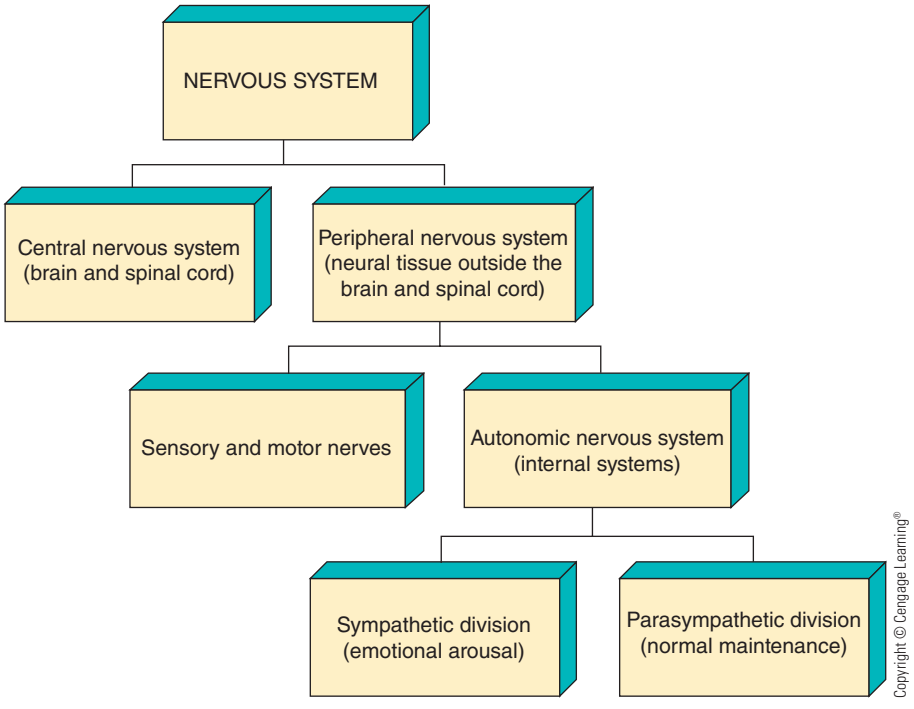


FIGURE 3.5
Organizational structure of the nervous system

The CNS includes the brain and spinal cord. All nervous tissue outside (or peripheral to) the CNS is part of the PNS. The PNS includes nerves (nerves are simply bundles of axons) that send input from the senses to the brain (sensory nerves) and nerves that send output from the brain to muscles (motor nerves).

The PNS also includes an important regulatory system known as the **autonomic nervous system (ANS)**. The ANS regulates various nonconscious or automatic functions and is divided into two parts. The **sympathetic branch** of the autonomic nervous system is activated during emotional arousal by a release of epinephrine and norepinephrine from the adrenal glands. This branch is responsible for the physiological changes that characterize the "fight-or-flight" reaction. During sympathetic arousal, heart rate increases, blood pressure increases, respiratory rate increases, sweating increases, pupils dilate, the mouth becomes dry, and changes occur in blood flow as blood is shunted away from the internal organs and to the brain and large muscle groups. These physiological effects are important to keep in mind because some psychoactive drugs mimic sympathetic arousal. Such drugs are said to be **sympathomimetic**; they include cocaine, amphetamines, and some hallucinogens such as LSD. Another group of drugs blocks a type of norepinephrine receptor in the sympathetic nervous system called "beta-noradrenergic" receptors. These beta receptors regulate blood pressure, and the so-called **beta-blockers** (drugs such as propranolol) are widely used in the treatment of hypertension.

The other branch of the autonomic nervous system is the **parasympathetic branch**, which in general balances the actions of the sympathetic branch by exerting opposite effects. Parasympathetic activity reduces heart rate, blood pressure, and so on. In contrast to sympathetic neurons, parasympathetic synapses are primarily cholinergic.

autonomic nervous system (ANS)
Part of the PNS; has two branches: sympathetic and parasympathetic.

sympathetic branch
Branch of the ANS that is activated during emotional arousal and is responsible for such physiological changes as increased heart and respiratory rate, increased blood pressure, and pupil dilation.

sympathomimetic
Drugs such as cocaine and amphetamines that produce the physiological effects of sympathetic activity.

beta-blockers
Drugs that block beta-adrenergic receptors of the sympathetic system and thus act to relieve high blood pressure.

parasympathetic branch
Branch of the ANS that is responsible for lowering heart rate and blood pressure.

The Brain

The key organ of the nervous system is the brain (see Figure 3.6). Covered with tough membranes called the *meninges,* the brain floats within the skull in a liquid known as cerebrospinal fluid. Although weighing just a few pounds, the human brain is an extremely complex structure. We have just examined the processes involved when a single neuron fires. Now consider that the human brain contains literally billions of neurons. Many of the brain's neurons synapse with several thousand other neurons because of an elaborate branching of axons. The complexity of billions of neurons and more billions of synapses is absolutely staggering and almost beyond comprehension. Despite the enormity of the task, great strides have been made in understanding how this most complex of organs works. One fruitful approach is to consider the different parts of the brain separately in an attempt to determine their individual functions.

The major divisions of the human brain are the **hindbrain**, **midbrain**, and **forebrain**. If a voyage through the brain began at the spinal cord and moved up, the first part of the brain encountered would be the hindbrain.

hindbrain
The lower part of the brain, including the medulla, pons, and cerebellum.

midbrain
Part of the brain that includes the inferior and superior colliculi and the substantia nigra.

forebrain
The largest part of the human brain; includes the cerebral cortex, thalamus, hypothalamus, and limbic system.

medulla oblongata (mə-'də-lə-'ä-bl·oŋ-gä-tə)
The lowest hindbrain structure of the brain; important in the regulation of breathing, heart rate, and other basic life functions.

cerebellum ('ser-ə-'be-ləm)
Hindbrain structure important in motor control and coordination.

pons ('pänz)
Hindbrain structure important in the control of sleep and wakefulness.

reticular activating system
Pathway running through the medulla and pons that regulates alertness and arousal.

The Hindbrain

The hindbrain consists of three main components: the **medulla oblongata**, the **cerebellum**, and the **pons** (see Figure 3.7). The medulla is located just above (and is really a slight enlargement of) the spinal cord. A highly significant structure for the regulation of basic life functions, the medulla controls breathing, heart rate, vomiting, swallowing, blood pressure, and digestive processes. Normal functioning of the medulla is critical, and when drugs begin to affect the medulla, the person is often in danger due to respiratory or cardiovascular failure. When toxic chemicals reach high levels in this area, the vomit center is often triggered to purge the body, which may be why drinking large quantities of alcohol often causes nausea and vomiting. Farther up the hindbrain is an enlarged section called the pons. In addition to providing the pathways for input up and output down from the spinal cord, the pons plays a role in the control of sleep and wakefulness. Running along the pons and through the medulla is a pathway (not visible in Figure 3.7) known as the **reticular activating system**, which is critical for alertness and arousal. Drugs that lower arousal and induce sleep (such as barbiturates and tranquilizers) are thought to act in this region of the brain.

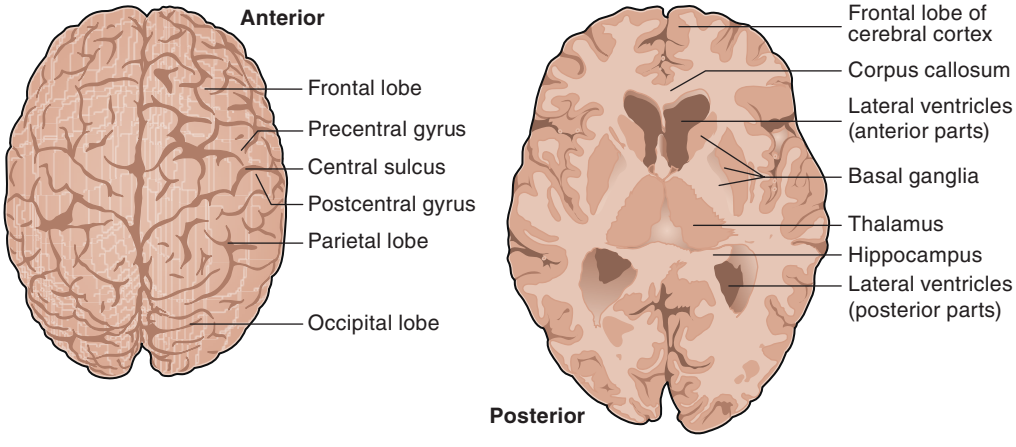


FIGURE 3.6
A dorsal view (from above) and a cross section of the human brain (From Kalat, Biological Psychology, 11E. © 2013 Cengage Learning)

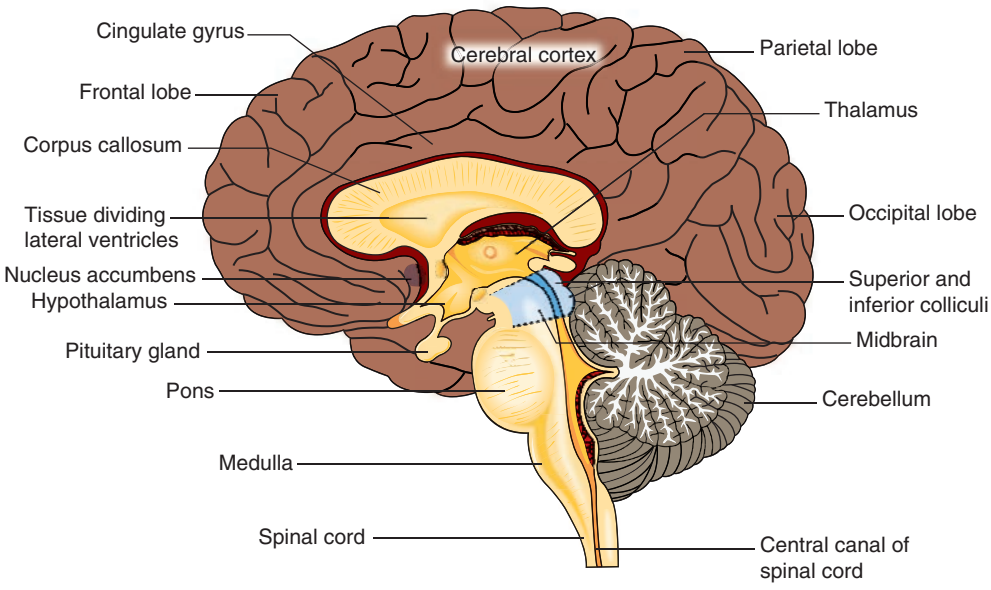


FIGURE 3.7
A sagittal (inside) view of the human brain (From Kalat, Biological Psychology, 11E. © 2013 Cengage Learning)

The cerebellum, the last major organ of the hindbrain, is a highly complex structure containing several billion neurons itself. The cerebellum is critical for motor control. Activities of the cerebellum are largely unconscious but do involve balance, coordinated movement of all kinds, and speech. The loss of motor control and balance produced by drugs such as alcohol may be caused by their action on the cerebellum.

The Midbrain

The midbrain consists of a number of structures, including the **inferior colliculi**, the **superior colliculi**, and the **substantia nigra** (not shown). The inferior colliculi form part of the auditory system. The superior colliculi function in localization of visual stimuli. These structures are specifically involved with localization of stimuli and mediation of reflexes. The actual recognition and interpretation of visual and auditory stimuli take place elsewhere in the brain (see the section on the cerebral cortex).

Parkinson's disease involves damage to the substantia nigra and the nigrostriatal motor pathway. Specifically, Parkinson's disease develops when nerve cells in this brain region begin to degenerate. The substantia nigra produces dopamine, which is transported through this motor pathway, and as the substantia nigra deteriorates, less and less dopamine is available for neurotransmission. Parkinson's symptoms do not appear until about 80% of the substantia nigra is destroyed. Although the causes of Parkinson's disease are not completely understood, some toxins, including some "designer drugs," appear to be capable of killing neurons in the substantia nigra and triggering the disorder (see Chapter 10).

inferior colliculi (ko-'lik-yū-lī)
Midbrain structures that control sound localization.

superior colliculi
Midbrain structures that control visual localization.

substantia nigra (səb-'stan(t)-shē-ə-'nī-grə)
Literally "black substance," this basal ganglia structure is darkly pigmented; produces dopamine. Damage to this area produces Parkinson's disease.

The Forebrain

The most important brain regions from the perspective of interpreting complex human behavior are in the forebrain, particularly the cortex, but also including the **thalamus** and **hypothalamus** (see Figure 3.7).

thalamus ('tha-lə-məs)
Forebrain structure that organizes sensory input.

hypothalamus ('hī-pō-tha-lə-məs)
Forebrain structure that regulates eating, drinking, and other basic biological drives.

The Thalamus and Hypothalamus

The thalamus is often referred to as a relay station because it receives incoming sensory stimuli and then "relays" that information to relevant centers throughout the brain. The hypothalamus is a critical structure in the motivation of behavior. It contains areas that appear to be involved in the regulation of eating and drinking, and the control of body temperature, aggression, and sexual behavior. Worth noting is that information about the particular function of a given brain region has not been easily determined and remains somewhat controversial. Historically, the methods for analyzing brain structures were primarily lesions and stimulation. Lesioning a structure involves performing surgery on an animal subject and causing localized damage to the structure in question. When the animal has recovered from surgery, changes in behavior are then attributed to the damaged structure. For example, lesions in one part of the hypothalamus result in greatly reduced food intake, whereas if another part is damaged, overeating and obesity occur. Thus, the hypothalamus contains at least two sites that appear to be important in the regulation of food intake. One area seems to inhibit eating (because its loss results in overeating) and the other seems to excite hunger (because its loss results in less eating). The effects of electrical stimulation of a brain region generally are the opposite of the effects of lesioning or removing that region.

A note of caution accompanies these findings. When cells in the brain are lesioned or stimulated, the effects extend beyond those specific cells, and indeed entire pathways may become damaged or stimulated. Thus, rather than speaking of the hunger or satiety *centers,* a more appropriate term is hunger or satiety *pathways.* However, even this may be an oversimplification because some researchers have noted that the role of these pathways may not be as specific to hunger as we first thought. That is, these pathways could affect motor movements, the sensation of taste, or more general motivational variables, and much current research is devoted to these effects. However, there is general agreement that the hypothalamus is an important structure in the regulation of hunger, thirst, and other basic biological motives (Kalat, 2013).

The Neural Basis of Reward

Despite the difficulties of such research, electrical stimulation of brain regions led to one of the most significant discoveries in the quest to understand the relationship of brain, behavior, and drugs. During the 1950s, the psychologist James Olds was trying to map the effects of stimulation on the rat brain by implanting electrodes into various regions. The rat seemed to enjoy the electrical stimulation in some areas of the brain. Here is how Olds describes his serendipitous discovery:

> I applied a brief train of 60-cycle sine wave electrical current whenever the animal entered one corner of the enclosure. The animal did not stay away from the corner, but rather came back quickly after a brief sortie which followed the first stimulation and came back even more quickly after a briefer sortie which followed the second stimulation. By the time the third electrical stimulus had been applied the animal seemed indubitably to be "coming back for more." (Carlson, 2001, p. 457)

mesolimbic dopaminergic pathway Pathway that is rewarding when stimulated.

Following up on this finding, Olds and Milner (1954) discovered that when electrodes are implanted in some brain areas, particularly in a region called the **mesolimbic dopaminergic pathway**, rats could actually be trained to press a lever to electrically stimulate themselves. The mesolimbic dopaminergic pathway includes a small subcortical area called the nucleus accumbens and travels through the ventral tegmental area all the way to the frontal cortex. When rats have been trained to self-stimulate this area, they often respond with great vigor (more than 1,000 responses per hour), and the potency of the reinforcement related to this center led Olds and others to refer to it as

the "pleasure center." The notion is that the region may represent the final common pathway for pleasurable stimulation and reward. It has been argued too that this brain region is of significance in understanding the rewarding properties of drugs. The nucleus accumbens is rich in dopamine, and some investigators have suggested that dopamine is a critical chemical in producing the rewarding properties of drugs (Koob & Le Moal, 2006; Nestler, 2009). Indeed, some have viewed this region of the brain as critical to drug addiction: "There is now a wealth of evidence that [the mesolimbic dopaminergic pathway] is a crucial substrate for the acute rewarding effects of virtually all drugs of abuse and for the derangements in reward mechanisms that contribute to drug addiction" (Nestler, 2009, p. 777). As Dackis and Gold (1985) once put it, addicts can be seen as individuals who have "tampered chemically with endogenous systems of reward and lost control of this shortcut to pleasure" (p. 476).

It is true that many pleasurable events result in the release of dopamine in this pathway—good-tasting food (especially chocolate), sex, and indeed many drugs such as cocaine, heroin, and nicotine (Goldstein, 2001). However, the idea that dopamine release in this pathway always translates into the psychological experience of pleasure appears to be an oversimplification. For example, events that are surprising or arousing but not especially pleasurable (like an electrical shock) seem to release dopamine in the nucleus accumbens, so perhaps activity in this pathway reflects events that have motivational significance or are "attention-getters" (Salamone & Correa, 2012; Salamone et al., 2012).

The Limbic System, Basal Ganglia, and Cerebral Cortex

The forebrain also includes three complex systems: the **limbic system**, the **basal ganglia**, and the **cortex**. The aspects of behavior that are most uniquely human, such as complex reasoning, memory, logic, speech, and planning, are largely derived from these structures.

limbic system
Forebrain structures including the amygdala and hippocampus.

basal ganglia ('bā-səl-'gaŋ-glē-ə)
Forebrain structures important for motor control; include the caudate nucleus, the putamen, and the globus pallidus.

cortex
The outermost and largest part of the human brain.

hippocampus ('hi-pə-'kam-pəs)
A structure of the limbic system thought to be important in the formation of memories.

The limbic system includes several structures in the interior of the forebrain. One limbic structure, the amygdala, seems to be important in mediating certain types of aggression, fear, and other emotional experiences. Another important limbic structure is the **hippocampus**, which appears to be critical in memory storage. People with damage to the hippocampus can remember things that occurred in their lives prior to the damage but, for the most part, are unable to store new memories. In other words, their long-term memories are intact, but they have difficulty in forming new permanent memories. The basal ganglia include the caudate nucleus, the putamen, and the globus pallidus. These structures are critical for motor movements.

One feature that distinguishes the human brain from those of most other animals is the greatly enlarged cerebral cortex. Indeed, many of the complex psychological functions that are characteristically human are thought to involve the cortex. The occipital lobe is at the back of the brain and is often referred to as the visual projection area (see Figure 3.6). Stimulation of the eye is eventually perceived as a visual stimulus when the signal reaches the occipital cortex. The temporal lobe is similarly specialized for auditory stimulation and also appears to be important in language. Damage to the left temporal lobe results in severe impairment of language abilities (at least for most right-handed individuals). Right temporal lobe damage often results in dysregulation of emotions. This relationship between right and left temporal lobe mediation of language and emotions is reversed in some cases (e.g., left-handed individuals). The frontal lobe is important in the initiation of movement and is involved with emotionality, intelligence, and personality. Tactile stimuli are registered in the parietal lobe (see Figure 3.6).

Because most nonhuman species do not share the enlarged cortex of humans, using animal models to study the functions of the cortex is more difficult. Much of

Monkey Business Images/Dreamstime.com

A technician monitors a patient during a CAT scan.

what we know about the cerebral cortex then has come from unfortunate accidents and diseases such as strokes and tumors, which in effect produce lesions in the patient's brain that may result in some loss of psychological function. Upon autopsy, the nature of the psychological impairment can be matched to the site of the damage. For example, consider the tragic but instructive example of Phineas Gage. Gage was a 25-year-old railroad worker in 1848, when an accidental explosion drove an iron rod through his head. Remarkably, Gage not only survived but after a recovery period was able to walk, talk, and remember as well as he had before the accident. It was clear, however, that Gage's personality had changed. His friends said that he was no longer himself. Before the accident, he was regarded as a mild-mannered, well-adjusted, friendly man, but his brain damage left him impulsive, ill-tempered, and unreliable. He was apparently unable to execute or stick to even the simplest plans. His skull was preserved, and nearly a century and a half later, a reconstruction of the trajectory of the rod showed that the likely area of damage was the frontal lobe, which is now recognized to be important in the ability to plan, to control impulses, and generally to consider the long-term consequences of behavior (Damasio, 1994). Some researchers have suggested that frontal lobe abnormalities may be caused by exposure to some drugs of abuse such as cocaine (e.g., Kalivas & Volkow, 2005).

Imaging the Human Brain

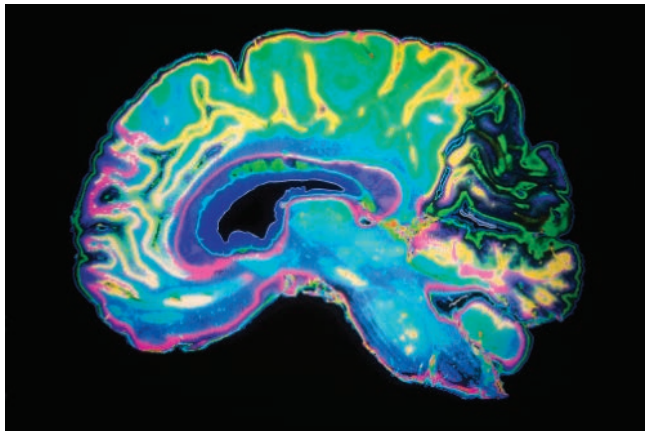
Although much of what we know about the brain comes from a combination of research with animals and autopsy data from humans, new imaging technologies in recent years have opened new windows on the human brain. These technologies are teaching us much about the functional neuroanatomy of the normal brain. They also provide us with more sophisticated answers to questions that come up whenever chronic effects of drugs are discussed: the issue of drug-induced brain damage. We discuss this problem throughout the text as we consider individual drugs, but now, after this lengthy discussion of the brain, a few general comments are warranted. Detecting brain damage caused by drugs is often very difficult. Rarely do psychoactive drugs produce such dramatic long-term effects as those seen with Phineas Gage, for example, so we must rely on specialized methods to determine whether damage has occurred. Various neuropsychological tests are available that can be used to detect impairment in memory, perceptual motor skills, language, and other functions that may be influenced by chronic drug use. More direct analysis of brain tissue may be accomplished through **electroencephalography (EEG)**. This technique involves measuring the brain's electrical activity through the scalp. These brain waves change in predictable ways with sleep or various kinds of arousal, and abnormalities in EEG patterns can reveal gross brain damage.

electroencephalography (EEG)
Technique used to measure electrical activity in the brain.

computerized axial tomography (CT)
Technique that produces a three-dimensional X-ray image of the brain.

A more recently developed and more sensitive measure of brain impairment is **computerized axial tomography**, better known as the CT or CAT scan. The CT scan involves passing X-rays through the head in a circular pattern to get a three-dimensional image of the brain. The focus can be changed to different depths of the brain to detect internal tumors, enlarged spaces or ventricles, and other internal abnormalities.

CT scans provide a picture of the brain but reveal nothing about its functioning. However, a technique called the PET scan may greatly increase our ability to detect brain activity. **Positron-emission tomography (PET)** involves injecting weak radioisotopes into the brain. Radioactive glucose or oxygen or even radioactive neurochemicals are then measured by sensitive detectors that can determine where the isotopes are absorbed, their rate of absorption, and so on. Then changes in activity in various brain regions can be assessed, including changes induced by drugs. Techniques like the PET scan and the closely related SPECT (single-photon emission computed tomography) scan promise to greatly increase our ability to determine where in the brain damaging drugs produce their effects.



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An MRI image of the brain

Another sophisticated and sensitive technique used to image the brain is **magnetic resonance imaging (MRI)**. With this technique, a strong magnetic field is passed through a person's head. Radio waves are then generated, which cause the molecules of the brain to emit energy of different frequencies, depending on their properties. This technique creates a localized and detailed brain image and eventually may greatly improve our ability to detect and understand brain dysfunction (Uttal, 2001). A modification of MRI technology called functional MRI (fMRI) has been developed; fMRI permits very rapid imaging and enables us to measure oxygen levels in blood vessels of the brain. Oxygen levels are correlated with the metabolism of a particular brain region

positron-emission tomography (PET)
Technique used to measure activity in selected brain regions.

magnetic resonance imaging (MRI)
Technique that creates a high-resolution, three-dimensional image of the brain.

CONTEMPORARY ISSUE BOX 3.2

Drug Craving and the Brain

Drug abusers often report experiencing strong reactions when they are exposed to environmental stimuli associated with drug use. For example, being in a place where they have frequently used drugs or with friends who use them can evoke drug craving, excitement, and even physical symptoms such as elevated heart rate. Using some of the sophisticated brain-imaging tools described in the text, researchers are now able to characterize how the brain reacts to drug-related stimuli. In an early study, Childress et al. (1999) used the PET scan to compare the reactions of cocaine users (not using at the time of the study) with those of control subjects who had never tried cocaine. Subjects in both groups watched two videos in the laboratory while measurements were taken. One video showed an individual purchasing, preparing, and smoking crack cocaine; the other video was a nature film unrelated to drugs. The cocaine users, but not the control subjects, reported strong craving after watching the crack video. The PET scans revealed increased activity in the limbic region of the brain, particularly the amygdala and a limbic structure called the anterior cingulate, that correlated with cocaine craving. That is, the cocaine users exhibited limbic activity while watching the crack video but not the nature video.

The nonusers did not show limbic activation during either video. Subsequent studies have replicated these findings with fMRI technology, and also shown increased brain activity throughout the brain's reward system (mesolimbic dopaminergic pathway) when alcoholics, cigarette smokers, and cocaine and methamphetine users experience craving as well (Lim et al., 2005; Myrick et al., 2004; see Volkow et al., 2012 for a review). Brain-imaging techniques have the potential to identify the brain regions involved with the psychological experiences, such as craving, that are thought to be important aspects of drug dependence.

and are taken as an index of brain activity in that region. Thus, fMRI images obtained while a subject is engaged in some psychological activity (e.g., doing mental arithmetic) can be used to make inferences about the brain regions that were most active during the activity. These various imaging techniques are increasingly being used to learn about the neural mechanisms of drug action and dependence (see Contemporary Issue Box 3.2), as well as to evaluate changes in the brain after long-term exposure to drugs.

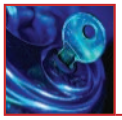
Summary

- All psychoactive drugs produce their effects by action on the nervous system—primarily by altering normal brain function.
- The brain is composed of specialized cells called neurons. Neurons transmit information by conducting electrical currents along their axons and releasing chemical substances called neurotransmitters into the synapse. Most drugs act by altering this chemical phase of neural transmission.
- Neurotransmitters work through a lock–key mechanism. The transmitter substance is like a key, and specialized areas on the neuron, called receptor sites, are like locks. Neurotransmitter chemicals must occupy the receptor sites for the neuron to fire.
- Drugs alter neural transmission in several ways. For example, a drug may mimic a natural or endogenous neurotransmitter by activating receptor sites. Alternatively, a drug may block a receptor site. Drugs can also affect the deactivation or release of neurotransmitters.
- Dozens of different chemicals have been proposed to act as neurotransmitters in the human brain; several are known to be related to drug effects. These include acetylcholine, anandamide, dopamine, endorphins, GABA, glutamate, norepinephrine, and serotonin.
- The nervous system is divided into two main sections. The central nervous system includes the brain and spinal cord. The peripheral nervous system includes the sensory nerves, motor nerves, and the autonomic nervous system.
- The autonomic nervous system is divided into two branches. The sympathetic branch produces the physiological effects that accompany emotional arousal, and the parasympathetic branch controls the body when at rest.
- For convenience of description, the brain is divided into three divisions: the hindbrain, the midbrain, and the forebrain.
- The evolutionarily primitive hindbrain includes the medulla, the pons, and the cerebellum.
- The midbrain includes the superior and inferior colliculi and the substantia nigra.
- The forebrain includes the cerebral cortex, the thalamus, the hypothalamus, the basal ganglia, and the limbic system.

Answers to "What Do You Think?"

1. Certain cells in the nervous system have the unique ability to communicate with each other.
   T *Neurons are able to communicate with each other through an electrochemical process known as neural transmission.*
2. The effects of drugs always involve naturally occurring physiological processes.
   T *Drugs act by making defined natural functions of the brain or body either more or less active.*
3. Some drugs may act by mimicking a neurotransmitter.
   T *Some drugs bind to receptor sites just as natural transmitters do.*
4. All drugs have the same basic effect on a cellular level; that is, they all block neural firing.
   F *Although some drugs, called antagonists, do block receptor sites and prevent activation of the receptor, other drugs, called agonists, activate the receptor.*

5. The brain is shielded from many toxic substances by a protective barrier.
   T *The brain is protected from toxic compounds that might enter the bloodstream by a blood-brain barrier that screens many, but not all, chemicals.*
6. The two main branches of the nervous system are the peripheral nervous system (PNS) and the autonomic nervous system (ANS).
   F *The two main branches of the nervous system are the central nervous system (CNS) and the peripheral nervous system (PNS).*
7. The brain and the spinal cord make up the peripheral nervous system.
   F *The brain and the spinal cord make up the central nervous system.*
8. The brain is firmly attached to the inside of the skull by tough membranes known as the meninges.
   F *The brain floats within the skull in a liquid known as cerebrospinal fluid.*
9. The autonomic nervous system is responsible for regulating food and water intake.
   F *Food and water intake appears to be regulated by the hypothalamus, a structure found in the brain.*
10. Animals will work for the electrical stimulation of certain parts of the brain.
    T *The mesolimbic dopaminergic pathway is sometimes called the pleasure center of the brain.*



Key Terms

acetylcholine (ə-ˈse-tᵊl-ˈkō-lēn)
action potential
agonist (ˈa-gə-nist)
Alzheimer's disease (ˈälts-ˈhī-mərz-)
anandamide
antagonist
autonomic nervous system
axon (ˈak-ˈsän)
axon terminals (or terminal buttons)
basal ganglia (ˈbā-səl-ˈgaŋ-glē-ə)
beta-blockers
blood-brain barrier
central nervous system (CNS)
cerebellum (ˈser-ə-ˈbe-ləm)
computerized axial tomography (CT)
cortex
dendrites (ˈden-ˈdrīt)
dopamine (ˈdō-pə-ˈmēn)
electroencephalography (EEG)
endorphins (en-ˈdo·r-fənz)
enzyme breakdown
forebrain
GABA
glutamate
hindbrain
hippocampus (ˈhi-pə-ˈkam-pəs)
hypothalamus (ˈhī-pō-tha-lə-məs)
inferior colliculi (ko-ˈlik-yū-lī)
ionotropic receptors
L-dopa (ˈel-ˈdō-pə)
limbic system
magnetic resonance imaging (MRI)
medulla oblongata (mə-ˈdə-lə-ˈä-bl·oŋ -gä-tə)
mesolimbic dopaminergic pathway
metabotropic receptors
midbrain
monoamines (ˈmä-nō-ə-ˈmēn)
myelin (ˈmī-ə-lən)
neuromuscular junction
neurons (ˈnü-ˈrän)
neurotransmitters
norepinephrine (ˈno·r-ˈe-pə-ˈne-frən)
parasympathetic branch
Parkinson's disease
peripheral nervous system (PNS)
pons (ˈpänz)
positron-emission tomography (PET)
receptor sites
reticular activating system
reuptake
serotonin (ˈsir-ə-tō-nən)
substantia nigra (səb-ˈstan(t)-shē-ə-ˈnī-grə)
superior colliculi
sympathetic branch
sympathomimetic
synapse (ˈsi-ˈnaps)
thalamus (ˈtha-lə-məs)
vesicles (ˈve-si-kəl)

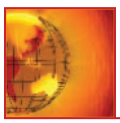
Essays/Thought Questions

1. Drugs produce psychological effects by chemical action on neurons. What implications does this mechanism have for the traditional distinction between mind and body?
2. Should addiction be viewed as a brain disease? Consider the implications of drug actions on the mesolimbic dopaminergic pathway.

Suggested Readings

Meyer, J. S., & Quenzer, L. F. (2013). *Psychopharmacology: Drugs, the brain, and behavior.* Sunderland, MA: Sinauer Associates.

Prus, A. (2014). *An introduction to drugs and the neuroscience of behavior*. Belmont, CA: Wadworth, Cengage Learning.



Web Resources

Visit the Book Companion Website at www.cengage.com to access study tools including a glossary, flash cards, and web quizzing. You will also find links to the following resources:

- Society for Neuroscience: The major international organization dedicated to brain research
- Neuroscience on the Internet: Presents various topics in neuroscience
- Whole Brain Atlas: Covers neuroanatomy and related materials
- Brain Science Podcast Archive: Podcasts of interviews with leading neuroscientists on various topics